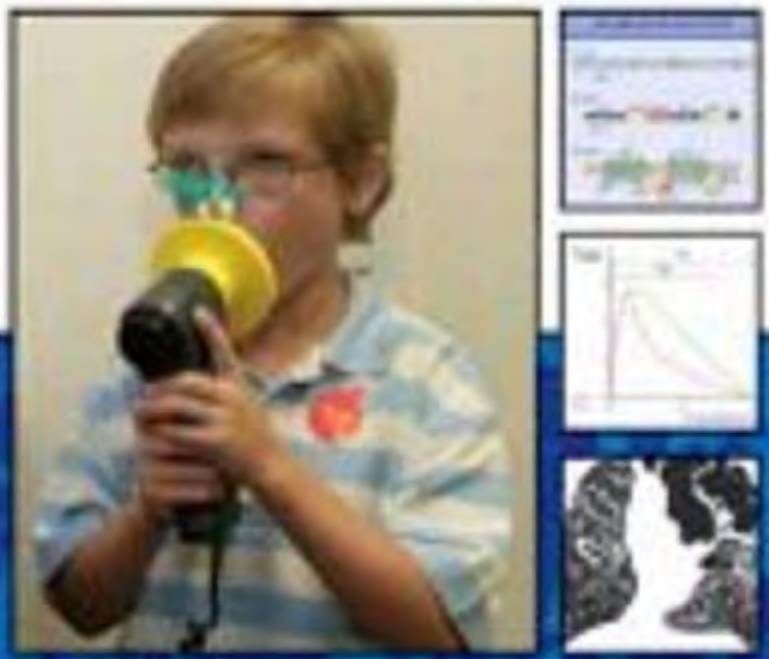
Pediatric Respiratory Medicine

SECOND EDITION



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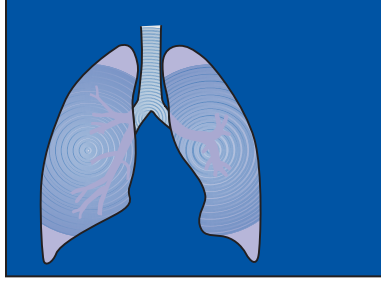

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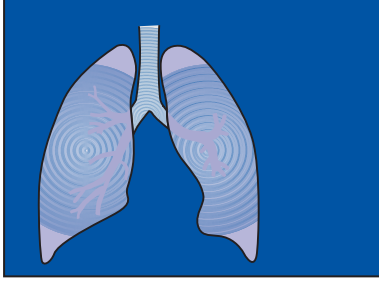
To the Landau, Le Souëf, Martinez,

Morgan, Sly, and Taussig families

for their love, encouragement,

patience, and understanding.



Foreword

"The needs of children should not be made to wait."
John F. Kennedy, 1963

It is reported that the Kahun papyrus, written around 1825 B.C., proposed some specific treatments for what was then considered obscure childhood disease. For example, chewing a field mouse was the recommended remedy for teething pain!

Thereafter, it took quite some time to establish pediatric medicine as a specialty. The incentive to concentrate on problems of children developed in the 18th century in Germany and France; in the United States, a German native, Abraham Jacobi (1830-1919), gave the field such impetus that he is hailed as the father of American pediatrics.

Since that time, pediatrics has become a vibrant specialty, thriving on the basis of fundamental and clinical research, which gained extraordinary momentum in the years following World War II. For example, during the 1960s and 1970s, pioneer researchers in the United States uncovered the mechanism of neonatal respiratory distress syndrome; this led to the development of effective therapeutic interventions, resulting in an amazing decrease in deaths from this condition. Another example is the research that led to our understanding of the immune system; this, in turn, enabled development of modern vaccines that have revolutionized the control of childhood infectious diseases. Also noteworthy is the tremendous progress we have witnessed in asthma treatment and control as a result of outstanding research in pediatric medicine.

These examples well illustrate the immense value of biomedical basic and clinical research. However, effective communication is needed to bring the outcomes of this research work to the practice of medicine and the benefit of public health.

Pediatric Respiratory Medicine—the encyclopedia of respiratory health and illness in children—accomplishes just that. This new edition offers the reader an updated review of ongoing pursuits in basic sciences and clinical principles. Moreover, 75 chapters authored by more than 130 well-known experts discuss specific clinical conditions from which children can suffer. The authors represent twelve different countries and many of the major U.S. medical centers.

A treatise of such dimension is a major educational contribution to the field, but its significance depends on whether the readers can, or will, improve their practice of pediatrics. Clearly the editors, Drs. Lynn M. Taussig and Louis I. Landau, and their associate editors had this in mind when they selected contributors highly skilled in translating the science base into information that can readily be applied in the daily practice of pediatric medicine. The result will undoubtedly help the readers in their efforts to meet the needs of children with respiratory illness.

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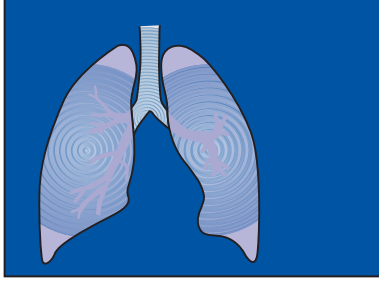
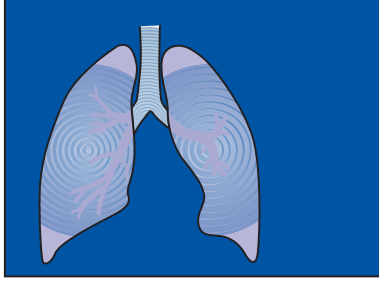


From the Foreword to the First Edition

Welcome to a new textbook, *Pediatric Respiratory Medicine*, authored by authorities from around the world. We might ask what is so special about an international perspective in this age of telecommunication and frequent world congresses. Practices do differ, and insight into approaches based on varied experiences can be thought provoking and enriching.

I cannot think of a better way for the student of pediatric pulmonology to acquire an authoritative overview of the state of the specialty than to refer to this book over and over again.

MARY ELLEN AVERY, MD
Thomas Morgan Rotch
Distinguished Professor of Pediatrics
Harvard Medical School
Boston, Massachusetts



Preface

From its inception, *Pediatric Respiratory Medicine* was to be an international textbook. This second edition broadens that international perspective. The tremendous advances in communication, the expansion of professional societies globally, and the interactions among clinicians and scientists on different continents make it essential that medical textbooks be international in scope, summarizing different geographic and social approaches to advance the understanding of health and disease.

A number of major influences contributed to the evolution of pediatric pulmonology as a distinct pediatric subspecialty. These included the following:

- Growing interest by pediatricians in childhood respiratory problems, especially asthma and pneumonia
- Growth of adult pulmonology, which provided training for pediatricians and spawned an expanded interest in the research, clinical, and educational aspects of pediatric pulmonary disorders
- The establishment of cystic fibrosis centers
- Increasing interest by pathologists in the growth and development of the lung
- Increasing technologic and epidemiologic research in respiratory disease
- Increased interest in childhood tuberculosis in the 1950s and dramatic changes in the worldwide patterns of this disease, particularly with the presence of HIV infection
- Development of neonatology as a discipline and heightened interest in respiratory problems of the newborn and subsequent chronic lung disease
- Growth of academic departments of pediatrics and the desire and need for research and teaching in the pediatric subspecialties
- Establishment of pediatric intensive care units
- Increasing publication of books and journals focusing on various respiratory illnesses of infants and children

As the discipline grew, there was progressive recognition by funding and certifying agencies. This culminated in the establishment of certification examinations in a number of countries, enhanced funding of research programs for pediatric respiratory disorders by governmental agencies, increased focus on pediatric respiratory problems by academic societies, and proliferation of training programs.

The breadth and depth of clinical and research interests encompassed in this discipline have increased markedly over the past five decades. However, major challenges still face our children. The global burden of disease falls disproportionately on children, especially those living in developing countries. Environmental conditions play a major role in disease initiation and severity in children, not just in the traditional infectious diseases but in the so-called "lifestyle" diseases such as asthma, obesity, and type 2 diabetes. These chronic diseases are posing threats to children's health in developing countries as well as those in high-income developed countries. Emerging issues such as the impact of climate change on children's health are going to become important.

Although no book can cover all issues of current and future interest, this book attempts to meet these varied concerns. The chapters have been written to provide more epidemiologic, anatomic, biochemical, pharmacologic, physiologic, cellular, and molecular information for those interested in these areas while also increasing discussion of the clinical aspects of both common and rarer presentations and diseases for the clinicians caring for the millions of children who suffer from respiratory disorders. Thus we trust that the book will be of benefit to students at all levels of training as well as experienced pediatric respiratory and primary care physicians. The major purpose of this textbook is to provide a relatively quick and concise overview of a topic, thereby allowing the reader to have a better foundation as he or she reads current articles that focus on more specific aspects of the subject. This edition is published in a new format for greater ease of use of content and graphics, with recommended selected readings, and access to an extensive collection of references on the accompanying web site, www.pedrespmedtext.com.

Many thanks are in order. First, to our publisher, Elsevier, and especially to Dolores Meloni, Karen Carter, Anne Snyder, and Michael Goldberg, for advice, patience, persistence, guidance, and encouragement. Second, to all of our contributing authors, some the same as for the last edition and some new, for their enormous contribution of time and effort. We also acknowledge the great support of our wives and families. Finally, to the children with respiratory illnesses and their families, who have helped us to better understand and manage these conditions and shown us courage in the face of adversity.

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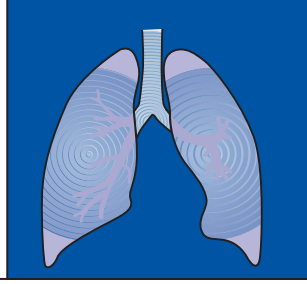

CHAPTER 1

Early Childhood Origins and Economic Impact of Respiratory Disease Throughout Life

Louis I. Landau and Lynn M. Taussig

TEACHING POINTS

- Much respiratory disease throughout life is programmed during pregnancy and/or early life as evidenced by associations with birth weight, lung function, and immunologic studies in the first year of life.
- Manifestations of respiratory disease are usually a result of a combination of gene(s) expression and the timing and dose of exposure to environmental factors such as microbes, allergens, diet, and toxins.
- Bacterial lower respiratory infections remain a major cause of morbidity and mortality globally.
- The global burden of the short- and long-term effects of respiratory illnesses in childhood is at least $1 trillion annually.
- Improved nutrition, immunization, decreased smoking, reduced pollution, new approaches to immune modulation, and the development of new drugs could dramatically reduce this burden.

Epidemiologic studies are increasingly reporting that a tendency to respiratory disease throughout life is programmed during fetal life and the early years after birth. The evidence now justifies further causality, mechanistic and interventional studies to better define the gene-environment interactions responsible for this early programming. Appropriate population-based education and therapeutic interventions may then significantly affect the considerable burden of respiratory disease on the individual, health services, and the community. This chapter will provide an overall worldwide perspective of these issues, with greater detail provided in the individual chapters.

Epidemiologic studies frequently have a temporal or geographic base within which the independent (explanatory) variables are used to explain the dependent (response) variables. Response variables have changed with time from indices such as mortality and hospitalization to morbidity and quality of life.

Considerable differences in disease patterns persist between developing and developed countries. The cycle of poor housing, poor sanitation, malnutrition, and infections continues to underlie the major causes of death and disability in developing countries—aggravated, particularly in Africa and Asia, by the emergence of human immunodeficiency virus. Improved standards of care have led to an increase in the median life expectancy for inherited disorders such as cystic fibrosis and acquired conditions such as chronic neonatal lung disease—both conditions now requiring long-term adult care. The changes in the environment, with improved socioeconomic status, have led to both a reduction in microbes in the home and, in many societies, an increase in exposure to pollutants such as tobacco smoke, pesticides, preservatives, and other chemicals. These independently or together are associated with new morbidity, particularly atopy and other inflammatory disorders.

The characterization of the human genome is leading to the promise of a better understanding of the genetic and molecular basis for most diseases. However, the substantial variation in the phenotypic expression for single gene disorders, the important contributions of multiple genes to common disorders, the recognition of epigenetic influence of modifier genes, and the impact of environmental factors such as diet on gene expression are highlighting the important role of environment-gene interactions in the disease spectra in both developing and developed countries.

Environmental factors may affect the outcomes in genetically predisposed individuals with different affects early or late in pregnancy, perinatally, during infancy, and later childhood. The outcome will depend on the timing and sequence of environmental insults during development from conception to maturity. Exposure to an infection at one stage in development under certain conditions may lead to a reduction in atopy while, at another stage with different conditions, may potentiate the emergence of atopic features. Both low and high birth weight may be associated with increased risk for the development of the metabolic syndrome (obesity, cardiovascular disease, diabetes), and higher birth weight is sometimes reported in association with subsequent atopy and asthma.[1] Excessive weight gain after birth, especially if born small, may be associated with more severe manifestations of the metabolic syndrome[2] and the development of asthma.

Chronic lung disease in adulthood has been associated with lower respiratory illnesses in childhood.[3,4] Do the

symptoms in early life identify the at-risk individual who continues to have problems in adult life or does illness in early life cause lung damage that predisposes to progressive lung disease? There are studies that support each hypothesis. Factors common to both hypotheses include active and passive smoking, family history of atopy and/or respiratory disease, social conditions, and gender.

GENETICS

Numerous candidate genes have been identified that affect atopic status and airway function.[5] Asthma appears to be the result of expression of a number of these genes that are influenced by environmental factors. No single genomic region has been linked in all studies and no individual genetic marker has been found to account for more than 10% of the asthma phenotype. Studies in twins suggest that more than 50% of variance for all cytokines is genetically determined, being particularly high for interleukin (IL)-1 beta and IL-10. Some of the potentially relevant genes identified include those for atopy, such as CD14 (159T) and GM-CSF (117T); for asthma, CC16 (A38G), tumor necrosis factor-alpha (TNF-α) (308G), LTC4 synthase (A444C), and IL-10 (-571C); and for asthma severity, beta 2R (Arg16,Gln27) and IL-4 (-589T).

The gene for cystic fibrosis—the cystic fibrosis transmembrane conductance regulator (CFTR)—was identified in 1989. Since then, more than 1000 mutations of this gene have been identified with varying phenotypic expressions and disease manifestations.[6] Substantial variations of the disease have been noted within the same CFTR genotype—suggesting modification by factors that could be related to diet and the environment or to modifier genes coinherited with the CFTR polymorphism. However, definitive modifier genes for cystic fibrosis remain to be identified.

Primary ciliary dyskinesia is a multisystem disorder characterized by recurrent respiratory tract infections, male subfertility, and, in 50% of cases, with situs inversus (Kartagener syndrome). The disease phenotype is caused by ultrastructural defects of cilia in the mucosa of the respiratory tract, sperm, and other organs. It is a heterogenetic disorder, usually inherited as an autosomal recessive trait. Mutations in some human genes have been shown to cause the disease by alterations in the coding for ciliary proteins such as those in the dynein arms.[7] Tissue-specific expression of mutant genes at different stages of ontogenesis lead to varying clinical presentations.

Severe alpha-1 antitrypsin deficiency is one proven genetic risk factor for chronic obstructive pulmonary disease (COPD) in adult life. Apart from manifesting as liver disease in early life, COPD develops at an age when a patient may have commenced smoking and lung disease rapidly develops. The World Health Organization has recommended that all patients with chronic lung disease and all adolescents and adults with asthma be tested. Homozygous alpha-1 antitrypsin deficiency PiZZ occurs in 1 in 5000 to 1 in 500 whites. Argument has been made for neonatal screening to identify those at risk before they are likely to be exposed to cigarette smoke. This must be balanced against the issues of psychological consequences, impact on insurance, and the effectiveness of antismoking programs.[8]

It is suggested that sudden infant death syndrome (SIDS) is a result of polygenic inheritance which, in combination with environmental risk factors such as mild infection, prone posture, non-breastfeeding, exposure to environmental tobacco smoke, and preterm delivery, predisposes infants to sudden unexpected death. The genetic component of SIDS can be divided into two components[9]: mutations that lead to disorders that cause rapid death and those that predispose infants to death in critical situations. Those that may cause death themselves include mutations in the medium chain acyl-CoA dehydrogenase gene (A985G) causing MCAD deficiency but is seen in less than 1% of SIDS; polymorphisms associated with severe hypoglycemia; and mutations in genes such as KVLQT1 and SCNA5, which encode for cardiac ion channels and are associated with the long QT syndrome.

Those with predisposing polymorphisms for death in critical situations include partial deletions of the "complement component 4" gene and "interleukin 10" gene promoter (ATA/ATA) which impair the immune response to infection. Others affect the serotonin transporter gene which may have an important autonomic regulatory role. In spite of some genetic component, the recurrence risk is not high.

Toward the end of gestation, the fetal lung prepares for the transition to air breathing at birth. Respiratory epithelial cells synthesize lipids and surfactant proteins that are necessary for alveolar stability with air breathing. The components of surfactant are developmentally regulated. SP-B and SP-C are detectable in early gestation. Type 2 cells appear around 20 to 24 weeks when SP-A and DP-D synthesis is noted. Numerous, usually isolated, genetic disorders have been reported in these processes leading to perinatal morbidity and death related to respiratory distress syndromes, as well as alveolar proteinosis and familial lung fibrosing disorders in later life. These abnormalities include genetic variations of surfactant proteins and Foxa2-regulated expression of genes mediating surfactant protein and lipid synthesis.[10,11]

DEVELOPMENTAL ORIGINS OF RESPIRATORY HEALTH AND DISEASE

Prenatal

It has been assumed that the womb is a warm and safe place, but it has been clearly documented that the placental barriers can be breached by infectious agents such as syphilis, cytomegalovirus (CMV), *Toxoplasma* and rubella; allergens; toxins; metabolites such as maternal phenyl ketones; radiation; hyperthermia; tobacco smoke; alcohol; nutritional agents such as folate; and antioxidants with major impact on the developing fetus, including the developing respiratory and immune systems, which affect long-term respiratory health and disease.

The impact will be influenced by the time in gestation when the insult occurs. Periconceptually, metabolites and growth regulators influence placentation and morphogenesis. Maternal age and age of menarche of the mother may influence fetal development and maturation, possibly associated with variance in hormonal levels. Later age of menarche has been reported to be associated with lower rates of atopy but not asthma.[12] Later in gestation, insults will influence placental and fetal growth and maturation of organ systems. Birth

weight has been reported as a surrogate for fetal insult and low birth weight has been reported to be a predictor of subsequent cardiovascular and respiratory health.

Many have now suggested subsequent ill health may be associated with either low or high birth weights, this being evident for cardiovascular disease, diabetes, and asthma associated with high IgE/atopy. The low birth weight babies may be those whose cerebral development has been protected to the detriment of other systems, impacting on immunologic maturation and the high birth weight babies may represent those with fetal adaptation to a compromised placenta that allowed transplacental movement of allergens or mediators. Excessive catch-up growth during infancy for low birth weight babies has been reported as a more important factor for the development of obesity, cardiovascular disease, and asthma than the low birth weight itself. Xu and colleagues[13] reported that at age 31 years, those born small, with rapid postnatal weight gain and body mass index (BMI) above the 95th percentile had the highest risk for asthma (OR 3.27:1.32 to 8.11).

In fetal life, there is a skew to a Th2 immune response to prevent maternal rejection of the foreign placenta and fetus. Those primed to develop asthma and/or atopy have evidence of immaturity of both their Th1 and Th2 immune systems at birth with a propensity to Th2 as reflected by cytokine levels (high IL-4/IFN gamma ratios) and cord blood mononuclear cell proliferation studies.[14] Low IFN gamma levels are associated with increased infections in early life and with increased atopy in later life.

Cord blood IgE and cytokines suggest that in-utero priming of the fetoplacental unit by allergens or mediators crossing the placenta or absorbed from swallowed amniotic fluid via the fetal gut may result in allergic sensitization but is unlikely to be significant when it is the sole factor.[15] Lung function measured soon after birth suggests that airway structure and function have also been affected by factors leading to these immunologic changes as well as by other stimuli such as exposure to maternal cigarette smoking before birth, thus predisposing to the development of respiratory symptoms in later life.[16]

Many authors have reported lower prevalences of atopy with increasing birth order.[17] Turner and coworkers[18] have found that the lower prevalence in those not first born is transient and is lost by 11 years of age. The effect of birth order on immunologic development may be related to different hormonal levels, reduced transplacental allergens or IgE, variation in nutritional status during subsequent pregnancies, or to the different microbial exposures after birth likely to occur with contact with other young children in the household.

Maternal smoking is associated with elevated cord blood IL-4, lower IFN gamma, altered responses of IL-5, IL-9, and IL-13 production to stimulation of cord blood cells and abnormal lung function soon after birth.[19] Nicotine causes growth dysfunction of the airways with increased airway branching and increased airway wall thickness and reduced alveolar elastin in animal models. Humans demonstrate an association of prenatal smoking with transient wheezing during infancy, increased sudden infant death syndrome, and continuing reduced lung function but the associations with asthma, atopy, and persistent wheezing are less consistent.[20-22]

High vitamin E levels in the maternal diet are associated with changes in cord blood macrophage proliferation, but this is not related to blood levels of vitamin E, suggesting that the dietary intake may be a marker of some other factor that influences immunologic development and atopic priming.[23] Lower levels of vitamin E in the maternal diet have been reported to be associated with increased atopy, wheeze, and elevated exhaled nitric oxide measured at 5 years.[24] A potential reduction in subsequent infant allergy has been seen with maternal supplementation with polyunsaturated fatty acids.[25]

Congenital abnormalities such as lung hypoplasia, diaphragmatic hernia, lobar emphysema, cystic adenomatoid malformation and sequestration may occur as a result of genetic predisposition or in utero insult. The impact on neighboring normal lung tissue may be caused by mechanical factors or nonmechanical influences such as vasoactive mediators or endothelin dysregulation.[26] Some early studies suggest that lung underdevelopment may be attenuated by dietary interventions such as vitamin A.[27]

Steroids given to a mother with the risk of impending premature delivery have contributed to major improvements in outcomes by accelerating maturation of airway surfactant production and function with subsequent reduction in severity of hyaline membrane disease. Steroids upregulate the SP-B and SP-C production at the transcription level.[28] The effect may be an explanation for a gender difference in response to steroids.

Some longitudinal cohort studies have reported that stressful delivery may be associated with respiratory illness and reduced levels of lung function later in life. Long duration of delivery has been reported to be associated with increased atopy.[29] This could be a result of stress hormones such as cortisol driving the immune response toward a Th2 profile.

Postnatal

Postnatally, commensal gut flora appear to be a strong stimulus for maturation of the immune status, particularly the Th1 response. There are more than 400 species of bacteria in the human gastrointestinal tract and these compete for adhesion receptors, stimulate antimicrobials and gut-associated lymphoid tissue. Kalliomaki and Isolauri[30] reported that probiotics (lactobacillus) given to the mother and infant was associated with a 23% prevalence rate of eczema compared with a 46% rate in controls. Probiotics have been demonstrated to promote IL-2, IFN gamma, TGF beta production and inhibit IL-4, IL-5 and IL-13 production, as well as improve gut barriers and reduce gut permeability.

Some house dust mite studies have reported that attempts to reduce exposure pre- and postnatally may reduce subsequent asthma and atopy, but these results are inconsistent and many other studies have shown that reduced exposure may, in fact, lead to increased sensitization in later childhood. Perzanowski and colleagues[31] have found that exposure to cat fur in early infancy may induce tolerance with higher levels of protective IgG4. Those living on farms with grass exposure and those in Africa sleeping on grass mattresses show relative protection from grass sensitization.[32]

Attendance at day care, larger families, and living on farms with increased exposure to animals in the houses have been

associated with protection from atopy and it is argued that this may be due to stimulation of a Th1 response by microbes, lipopolysaccharides, or endotoxins.[33,34] The lipopolysaccharides could affect innate immunity via TLR2, TLR4 and CD14, and there may be genetic predispositions in different polymorphisms of these receptors. This imbalance of Th1/Th2 activity oversimplifies the complexity of T cell function and the hypotheses do not explain the contemporaneous rise in Th1-based conditions such as diabetes. The explanation is more likely to be complex because the Th1/Th2 paradigm is not so explicit with Th1 cells able to increase some Th2 mediators and the influence of factors including exposure dose and timing.

The development of atopic disease and asthma should be considered in a number of discrete phases: induction, progression, and exacerbations of acute episodes. During the induction phase, the underlying inflammatory response and airway hyper-reactivity are induced by environmental agents affecting a genetically predisposed host. Once induced, environmental agents will then trigger exacerbations and/or progression of inflammation and airway reactivity—usually resulting in clinical symptoms. The impact of the same environmental agent can be different in these phases. Microbes and high levels of allergens may be protective during induction but responsible, in smaller doses, for heightened responses resulting in progression/exacerbations in those already induced. The sequence of exposure to either microbes or allergens may affect the response to the other.

Breastfeeding has a variable effect on atopy. Most studies show no significant decrease in atopy. Wright and coworkers[35] and others have reported reduced lower respiratory illnesses with breastfeeding but subsequent increased atopy if the mother is atopic.

Indirect measures of airway development by lung function testing soon after birth relate variably to the presence or absence of asthma, the severity of asthma, or the presence of transient wheezing. Reduced lung function, suggesting reduced airway size, may be a result of changes in the mucosa (epithelium, mucus glands, submucosal tissue), muscle, lung elastic properties, or airway compliance in addition to airway growth. The mucosa is a source of cytokines, growth factors, nitric oxide, epithelial-derived peptides, and adhesion molecules, which may contribute to these changes.

The rapid thoracic compression technique has allowed measurements of maximum flow at functional residual capacity (FRC) in early infancy, and low levels have been associated with maternal smoking during pregnancy, wheezing illnesses, continuing low lung function (tracking) and bronchial hyper-responsiveness in later life. Most studies show associations of reduced infant lung function with transient wheezing of infancy[36,37] and some,[36] but not all, with persistent wheezing. Many studies also find that reduced lung function in infancy and early childhood is associated with lower lung function and asthma in adolescence.[36] Persistent bronchial hyper-responsiveness in early life is also associated with abnormal lung function and asthma in later life,[38] but measurements of airway responsiveness may reflect different processes, with increased responsiveness in infancy being associated with airway structure and in later childhood and adult life with current asthma.

Chronic neonatal lung disease/bronchopulmonary dysplasia is found increasingly with the improved survival of extremely low birth weight babies. It appears to be a result of the impact of high pressure ventilation and high inspired oxygen on immature lungs. Genetic predisposition, maternal smoking, use of steroids prenatally, and a family history of asthma have all been reported to influence the development and severity of the lung disease. The family history of asthma appears to relate to severity rather than prevalence.[39]

Intrauterine chorioamniotic infection may do harm (lead to acute and chronic neonatal lung disease) or be advantageous (promote alveolar maturation).[40,41] Its role in the evolution of chronic neonatal lung disease and subsequent lung growth is uncertain. Many cord blood cytokines and mediators such as IL-6, IL-8, soluble TNF-1, E-selectin, and matrix metalloproteinases[42,43] have been reported to be associated with the development of chronic neonatal lung disease.

Following chronic neonatal lung disease, recurrent wheezing illness is common in early childhood, but tends to become less problematic with age, although impairment of lung function—varying from very subtle to severe—persists into later childhood and adult life.[44]

Early Childhood

Lower respiratory illnesses in early childhood have been shown to be associated with chronic lung disease in adulthood,[3,4] either the symptoms in early life identifying at-risk individuals who continue to have problems in adult life or the illnesses in childhood causing lung damage. Lung damage can occur with organisms such as adenovirus and mycoplasma, and with irritants such as aspirated gastric contents and toxic inhalations, but the longitudinal cohort studies are suggesting that the predisposed infant who gets a serious lower respiratory tract illness with respiratory syncytial virus (RSV), rhinovirus, or meta-pneumovirus is already at risk for continuing respiratory disease.[45]

More than 30% of infants in the first 3 years of life will wheeze due to a number of underlying causes and more than one half of these will be transient wheezers.[37] Transient wheezing is seen with reduced airway function, respiratory viral infections, neonatal lung disease of prematurity, heart failure, foreign body aspiration, and maternal smoking. Persistent wheezing may be due to asthma, cystic fibrosis, or congenital abnormalities of the airways. Those who become persistent wheezers due to asthma are usually atopic, have frequent wheezing episodes, and are often admitted to hospital in the first year of life with more severe lower respiratory tract illness such as with RSV infection.[46] Those who commence wheezing after 2 to 3 years of age are more likely to have asthma or, if of sudden onset, may have an inhaled foreign body.

Viral infections, particularly those caused by RSV, metapneumovirus, and rhinovirus, occur frequently in infants and often cause wheezing. Those exposed to tobacco smoke, especially in utero, are more likely to develop severe symptoms requiring hospitalization.[47] Some studies would suggest that the virus interacts with the immune system in those genetically predisposed to initiate asthma. Sigurs and associates[48] and Welliver and Ogra[49] reported a high rate of asthma and atopy following RSV bronchiolitis. This was not con-

firmed in other studies. Most studies have followed those hospitalized with bronchiolitis, but those following community based cohorts have generally not shown that RSV infection per se predisposes to subsequent asthma.[50] It is likely that those with a genetic predisposition to atopy and asthma are more likely to have coexistent evidence of atopy and to respond differently to the RSV or other viruses, resulting in more severe symptoms requiring admission to hospital. It is the severity of response that is more likely the predictor, not the virus. Neutrophilia and elevated IL-8 and IL-9 are found in RSV bronchiolitis. Different phenotypes for these cytokines may predispose to more severe bronchiolitis and to asthma.

Helminthic infections are highly prevalent in many parts of the developing world, stimulate strong Th2 responses associated with high levels of polyclonal (non-antigen specific) IgE and eosinophilia, but are associated with lower prevalence of skin reaction to common allergens such as house dust mites.[51] It is suggested that the Th2 response to worms is protective for the host and is a mechanism to dampen potentially damaging inflammatory responses against the parasite. The downregulating mechanism responsible for the incongruity between the immune response to the helminths and other environmental allergens could be due to the non-antigen-specific nature of the IgE, dampening effects on dendritic antigen-presenting cells, on toll-like receptor innate immunity or to stimulation of regulatory T cells producing anti-inflammatory cytokines, such as IL-10 and TGF beta.[52,53] Anthelmintic treatment of chronically infected children is noted to result in increased atopic skin reactivity.[54]

It has been proposed that early identification of those with asthma and early use of inhaled corticosteroids may have a positive effect on the inflammatory process and prevent airway remodeling and disease progression. Studies so far have not shown any major benefit of early steroids, unless justified by symptoms, with no long-term impact on lung function or prevalence of persistent or more severe asthma.[55] They do lead to some reduction in somatic growth, although minimal, and mainly in the first year of use. There is a potential effect on immune maturation and alveolar septation with chronic high-dose usage in early life[56]; most septation occurs between birth and 2 years but continues until 7 years and to a lesser degree up to 20 years. This deleterious effect may be partially rescued by retinoic acid.[57]

A number of prospective cohort studies in childhood show a significant association between excess weight gain and asthma prevalence, especially in girls. The mechanistic relationship between an increase in BMI and asthma has yet to be defined, but there are a number of possibilities. The increased weight usually antedates the asthma and there is a dose-response effect. Overweight children breathe at a lower functional residual capacity with associated reduced load on the airway smooth muscle and airway narrowing which will result in increased airway responsiveness. These children also breathe at a faster rate with smaller tidal volumes, further reducing airway smooth muscle stretch. Increased BMI is also associated with a systemic inflammatory response with increased levels of potentially proinflammatory hormones such as leptin, adiponectin, and plasminogen activator inhibitor from adipose tissue and increased cytokines such as TNF-α and IL-6. The continuing increase in the frequency of overweight children, especially in developed countries, is a major public health issue not only for the impact on asthma but also on cardiovascular disease, diabetes, cancer, and psychological health.[58]

The prevalence of tuberculosis (TB) is still a major global health problem. In spite of dramatic advances through the 20th century when the prevalence of childhood TB fell from 100/100,000 to 60/100,000 in the 1950s and then to 5/100,000 following the introduction of national tuberculosis programs, it is predicted that there are currently more than 1 million new childhood cases of tuberculosis each year (10% of all cases). Prevalence is currently highest in Asia and the Indian subcontinent, and when seen in developed countries, it is often in the immigrant population.[59] Mortality was initially an accurate guide to disease because there was a constant relation between infection, disease, and death. Once this relationship was broken by highly effective treatment, it was necessary to use other indices, such as the tuberculin test, to determine the prevalence of infection. In the 19th century, the mortality was highest in young adults infected in childhood, but following the introduction of chemotherapy, it is now highest in the very young and in the elderly. In 1950, more than 40% of 14-year-old children in the United Kingdom were tuberculin positive, and this rate has fallen to nearly 1%.[60] Infection with human immunodeficiency virus is putting a new group of younger people at risk for tuberculosis.

The control of tuberculosis resulted from a combination of public health initiatives to identify cases and contacts by effective screening processes, effective chemotherapy administered according to standardized regimens, directly observed therapy, and chemoprophylaxis for those with infection reflected by positive Mantoux tests without evidence of active disease (clinical or radiologic), which prevents disease that would otherwise evolve in 1% to 2%. The bacille Calmette-Guérin vaccination is widely used even though considerable controversy about its effectiveness (0% to 80%) persists. The potential benefit certainly declines as infection rates decline, so that in developed countries it is used only in high-risk groups.[61]

On a global scale, respiratory infections remain a major cause of morbidity and mortality in developing countries. The annual incidence of new cases of pneumonia has been estimated at about 150 million., of which 11 to 20 million require hospitalization.[62] Approximately 20% (around 2 million) of all childhood deaths in developing countries can be attributed to acute respiratory infections. Many are related to conditions preventable by immunization such as pertussis, measles, diphtheria, pneumococcus, *Hemophilus influenzae*, and tuberculosis. The relative rate of bacterial versus viral lower respiratory tract illness in developing countries is difficult to determine because of the lack of sensitivity and specificity for most tests available. The rate of lower respiratory illness with bacterial infections probably lies between 15% and 60% or more. Studies of lung aspirates in lower respiratory illnesses in developing countries have suggested that more than 60% are associated with bacterial infection, with 25% being viral alone.[63] The therapeutic approach to acute respiratory illnesses in developing countries cannot be extrapolated from that in developed countries. Implementation of WHO guidelines for treating suspected bacterial

pneumonia is associated with dramatic falls in morbidity and mortality.

Non–cystic fibrosis bronchiectasis in childhood is still one of the most common causes of childhood morbidity and chronic adult lung disease in developing countries.[64] In New Zealand, the incidence of bronchiectasis, especially in Pacific Islanders, is double that of cystic fibrosis.[65] Bronchiectasis is particularly common posthospitalization in Australian indigenous children.[66] This is likely because of malnutrition, preterm delivery, and recurrent episodes of pneumonia. Breastfeeding has a protective effect. Bronchoscopic lavage analyses in infants with cystic fibrosis who are asymptomatic suggest that airway inflammation may start very soon after birth before clinical evidence of infection.[67] Better understanding of these findings will affect long-term outcomes for all causes of chronic suppurative lung disease.

Children and infants are among the most susceptible to ambient air pollution. Links have been reported between air pollution and preterm birth, low birth weight, infant mortality, respiratory symptoms, asthma emergency department visits and hospitalizations.[68] Pollutants clearly exacerbate asthma, but a specific influence on the induction of asthma has not been shown. Eighty percent of alveoli are formed postnatally and lung growth continues through adolescence. Children spending more time outdoors in communities with higher levels of urban pollution show deficits in the growth of lung function into adult life.[68]

Children are more vulnerable to air pollution levels because they have a higher relative minute ventilation, spend more time outdoors, and are more physically active. Pollutants that have an effect on the respiratory tract in children include ozone, sulfur dioxide, particulate matter, and nitrogen dioxide. Air pollution is also associated with increased health care utilization and school absences.

Ozone, formed from the action of sunlight on motor vehicle exhaust and industrial emissions, is associated with respiratory symptoms and asthma exacerbations in children and decreased lung function that continues into adult life. Children in Mexico City given antioxidants were less affected by pollutants than those who were not treated.[69] This effect needs to be further explored. Particulate matter (PM2.5) is emitted from engines, industrial sources, and wood burning. In children, particulate pollution affects lung growth and lung function and is associated with increased bronchial symptoms. Nitrogen dioxide is produced by high temperature combustion from engines and power plants. Nitrogen oxides cause respiratory symptoms and asthma exacerbations and have been shown to enhance the allergic response. Strong associations with hospital admissions for asthma have been reported.[70]

Indoor pollution is increased with gas burners, particularly unflued combustion heaters, dampness, and molds. The effect is most marked in children, both with and without asthma, who demonstrate increased risk estimates for wheezing and breathlessness.[71]

Altitude is known to have acute and long-term effects on the lungs, but this has been less well documented in children. Comparing one population group living at both low and high (4000 m) altitudes, it was found that those born at high altitude were smaller and weighed less, although economic factors could not be excluded as contributing factors.[72] Differences in altitude did not affect thoracic dimensions relative to stature. Lung volumes were higher, possibly reflecting the effect of hypoxia on alveolar growth. The Sa_{O_2} in children living at 4000 m is lower, at an approximate mean of 87%. Younger children were shown to have a lower Sa_{O_2}, falling further during sleep, suggesting physiologic adaptation to high altitude over time.[73]

Children demonstrate acute physiologic responses to exposure above 3000 m with increased respiratory rate, decreased end tidal CO_2, and reduced oxygen saturation—this reduction again being greater in infants. An inflammatory illness, such as a viral respiratory tract infection, may contribute to the development of high altitude pulmonary edema in children.

Allergen avoidance at high altitude has been reported to lead to reduced clinical symptoms, improved lung function, and reduced responses to specific and nonspecific bronchial challenges in asthmatic children. However, others have found that children with atopy and asthma living in a high altitude mite-free environment still have major morbidity with sensitization to other allergens.[74]

Children with chronic lung disease such as bronchopulmonary dysplasia and cystic fibrosis may develop significant hypoxia at high altitudes during flight or on vacation. The level cannot be easily predicted from baseline lung function, and a laboratory hypoxic challenge may be wise so that appropriate advice can be given.[75]

ECONOMIC BURDEN OF RESPIRATORY DISEASE

Respiratory illness throughout life is a global burden on individuals, families, health care services, and societies. The impact includes direct health service costs, family functioning and social costs, years of life lost, loss of productivity from days off work or school absenteeism. There are at least 200 million children with asthma worldwide. Taking an estimated cost of $100 to $10,000[76-78] per year for mild to severe disease respectively, this would result in an average total burden of around $200 billion per year. The economic impact for adults continuing from childhood with asthma, with fewer numbers but more severe disease, would be at least $50 billion per year.

Smoking rates in various countries range from more than 60% to less than 1%. Most start to smoke during childhood or adolescence. Taking an average of 10% heavy smokers (400 million) and assuming a burden of $1000 per smoker per year, would suggest a total cost of $400 billion per year in health care related costs. However, this is much less than predicted from assessment of adult disease costs in Germany, with a population of 82 million and 33% male and 20% female smokers, where the annual costs are estimated to be 16.6 billion EURO,[79] which could extrapolate to a global burden of $1 trillion for all adult diseases resulting from smoking. In Korea, with 66% male and 3.3% female smokers, the total annual cost of smoking-related illnesses in adults was between $6.79 and $9.86 million per 100,000 population,[80] extrapolating to a global burden of $200 to $400 billion. The annual avoidable direct health care costs associated with exposure to tobacco smoke in children from birth to 12 years in Hong Kong, with 990,972 children to 12 years

of age, ranged from $0.34 to $3.34 million,[81] which would extrapolate to between $676 million and $6 billion annually and *only* for direct costs. Therefore a total global burden of the effects of smoking throughout life of $402 billion annually seems consistent with these data.

Worldwide, there would be at least 3000 children newly diagnosed with cystic fibrosis each year, with costs varying from $1000 to $1 million per year. Taking an average cost of $10,000 per year, the total burden for all cystic fibrosis patients would be around $1 billion per year.

One hundred and fifty million children with pneumonia and 15 million with tuberculosis, living mostly in developing countries, generate a potential cost of at least $1000 per child per year.[82-84] This would result in a minimum burden of $165 billion annually.

Excessive weight in childhood is reaching levels of 30% in developed countries, with at least 5 million children in these countries having health problems that could be estimated to cost at least $1000 annually, resulting in a burden of $5 billion. Overweight-associated annual hospital costs for 6- to 17-year-old youth in the United States in 1997 to 1999 were $127 million.[85] This would extrapolate globally to $2.5 billion for overweight-related hospital costs alone. Asthma and sleep apnea were among the more common primary diagnoses when obesity was listed as a secondary diagnosis.

Pollution has been considered to affect 1% of children, with direct health costs relating to respiratory symptoms and medical consultation as well as lifelong quality of life affected owing to school absenteeism and chronic illness, to be at least $1000 per year and a burden of $20 billion annually.

These estimates are hypothetical and conservative, but they provide a perspective showing that many preventable causes of respiratory illness in children are currently resulting in a burden of at least $1 trillion per year globally—greater than the gross domestic product of many countries. Attention to prevention of these illnesses in early childhood is not at the forefront of policy, which is more often directed to those diseases affecting the elderly and the affluent.

Interventions that could significantly reduce this economic burden include improvement in health and nutrition for women of reproductive age and of young children, minimization of smoking, immune modulation by appropriate adjustments to the responses to the microbial and allergen exposures during pregnancy and early childhood, development of new drugs which will positively affect immunologic maturation, early prevention of progressive lung disease in those identified at risk, better regulation of pollution, improved immunization and other public health measures for prevention of infectious diseases. If these measures had a similar impact as the education on sleeping position, breastfeeding, and smoking have had on the prevention of sudden infant death syndrome, there would be, at reasonably modest cost, a reduction in the economic burden resulting from respiratory disease starting in early childhood of at least $300 to $500 billion per year.

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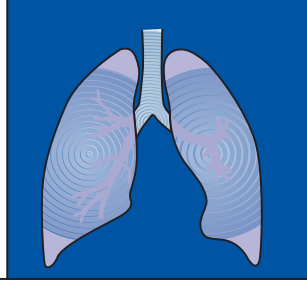

CHAPTER 2

Environmental Determinants of Childhood Respiratory Health and Disease

Fernando D. Martinez

TEACHING POINTS

- Environmental exposures in early life can drastically change developmental trajectories of the lung and airways in ways that predispose children to the development of respiratory diseases later in life.
- In cystic fibrosis, asthma, and other conditions in which genetic factors have an important role, environmental factors may change the expression of the phenotype in ways that are often specific for each exposure and for different critical periods during growth and development.
- Exposure to viral infections in early life may be associated with early expression of airway obstructive disease in predisposed individuals. Microbial burden during the growing years, on the other hand, can modulate the developmental patterns of the immune system and can protect against the development of allergies and asthma in susceptible individuals.

Although the phenotypic manifestation of the genetic material is the essence of biology, factors that are external to the genotype control its expression at all times. In its broadest sense, the "environment" is the lifetime accumulation of external effects on cellular configuration and gene expression. This definition provides a broader view of the environment than that usually attributed to this concept. In fact, the biological "environment" has been increasingly made synonymous with our physical surroundings: water, land, and atmosphere. This restrictive concept fails to consider the significance of the interaction between all body functions and flora and fauna (including viruses and bacteria) and the important role of the uterine milieu in determining the patterns (normal or abnormal) of fetal development.

ONTOGENIC SELECTION OF DEVELOPMENTAL PATTERNS

There is now strong evidence suggesting that the pathways followed by the lung and the immune system during the developmental phase are not mechanically determined by the genetic background of the individual alone. It has become increasingly apparent that both systems usually have the potential for alternative developmental pathways. There is little doubt that genetic factors limit these developmental choices, but for the great majority of individuals (i.e., those lying away from the extremes of the gaussian distribution of compounded polygenic influences[1]), the history of encounters with external influences determines to a large extent the final outcome. This property of phenotypic selection mediated by external influences is probably common to all organs, but should be expected to be particularly important for the immune and respiratory systems, which have among the widest and most active relations with the environment of all body systems.

It is reasonable to surmise that these choices between different developmental pathways can occur only early during ontogeny, when organs and their cell components are still in a more primitive, malleable form. It is also likely that, once a developmental pattern is selected, the potential for a shift back to other alternatives may be very limited. In a certain sense, "natural selection" of ontogenic pathways may behave much like natural selection of species as hypothesized to occur during evolution. If this were true, however, a mechanism would need to exist by which specific cell system selections occurring during the developmental phase would favor the individual's adaptation later in life. Although this could be an efficient mechanism of anticipated or "preemptive" adaptation, there is very little empirical evidence that such a mechanism exists. One of the best examples of developmental responses to external stimuli during fetal life is the induced early maturation of surfactant synthesis by corticosteroid administration to the mother.[2] This "environmental" induction of a vital metabolic function seems to be suspiciously useful: increased corticosteroid production occurs naturally in association with intrauterine stress, and stressful events in the perinatal period are often associated with premature birth and sure death in the absence of a surface-tension-reducing mechanism for lung and airways. It is possible to speculate that, during evolution, a variety of preemptive adaptive responses to specific external influences may have been selected that resulted in subsequent enhanced survival of those individuals who had the potential of developing those responses.

It can be deduced from the foregoing discussion that critical periods could be defined during which external stimuli can influence the development of the lung and the immune system in ways that would not be possible in other life periods. These stimuli may even give rise to irreversible changes in organ structure and function. An extraordinary example of this pattern of lung response to external stimuli was accidentally discovered by Dr. Thurlbeck and his coworkers.[3] These authors were interested in the effects of beta-amino-propionitrile on lung structure and function in suckling rats. They thus designed an experiment in which the active substance dissolved in saline was injected intraperitoneally to the experimental group and saline was injected by the same route to control animals. When subsequently studying the elasticity and microscopic anatomy of the lungs in these two groups, the investigators noted that the control group had abnormally larger alveoli and significantly fewer alveoli per unit volume than untreated animals. Saline-treated animals also had higher static lung compliance than expected. When saline-treated animals and untouched animals were sacrificed early during adult life (at 8 weeks of age), Thurlbeck and coworkers observed that the changes in lung structure in saline-injected animals had persisted up to that age. Other researchers[4] have shown that similar changes to those observed by Thurlbeck and colleagues in their "control" animals can be elicited in the lungs of animals receiving low doses of corticosteroids, but these doses need to be administered during a very precise developmental window: from postnatal day 4 to postnatal day 13. The same doses of corticosteroids, administered at any other time, produce no significant long-term changes in lung structure or function.

Studies by Barker and coworkers[5] have suggested that very long-term consequences of environmental influences on the lung may also occur in humans. They studied the relation between birth weight and subsequent level of lung function. They observed that birth weight was directly correlated with lung function up to 70 years later. More recently, Stern and coworkers[6] reported that maximal flows at functional residual capacity (VmaxFRC) measured shortly after birth are strongly and positively correlated with indices of airway function measured in the same subjects at age 22. There is little doubt that these two neonatal parameters (birthweight and airway function) are determined both by genetic and by environmental factors, including among the latter maternal nutrition, maternal age, and maternal exposure to noxious stimuli such as tobacco smoke. By altering developmental patterns of the respiratory system, these external stimuli may have consequences that can still be detected decades after their initial effects.

DEVELOPMENTAL TRAJECTORIES AND LUNG DISEASE

In this context, many chronic respiratory diseases can be considered deviations in the normal developmental design of the lung and immune systems that render the subject unable to adequately cope with the environment in which he or she is raised and lives. It is obvious that we are not dealing here with the environmental factors that determine acute diseases or even exacerbations of chronic lung ailments in children. These factors are so disparate and specific to each illness that it would be impossible to deal with them in a single, introductory chapter. What we are dealing herewith is the mechanism by which external influences determine the *inception* of long-term illnesses or create the conditions for the incidence of recurrent acute illnesses.

The paradigm of ontogenic "natural selection" that we are proposing also applies to "monogenic diseases" such as cystic fibrosis (CF). It is well known to all those involved in the care of CF patients that large phenotypic differences may exist between CF siblings who, by definition, have the same CF genotype. It is now clear that the CF phenotype is determined only partially (albeit substantially) by the CF genotype, and that other genes and an important environmental component determine the expression of the disease, particularly in the lungs.[7] Unfortunately, few studies of the natural history of CF have addressed this issue. Of interest is the fact that the long-term course of CF in children with meconium ileus (MI), a form of intestinal obstruction that occurs during the neonatal period in 15% to 20% of CF patients, seems to be different from that of children without MI. Specifically, MI children showed significantly worse lung function tests and shorter median times to the development of obstructive lung disease than children without MI.[8] Two potential explanations for these findings are that complications associated with surgical treatment of MI may affect lung development[9] or that MI may be associated with a developmental pattern that is globally different than that of children without MI. A recent study[10] showed that concordance for MI is very high (82%) among monozygotic twins and much lower (22%) in dizygotic twins with CF, suggesting that non-CF modifier genes play a major role in the development of MI in CF. However, a linkage study failed to identify a single modifier gene as responsible for these findings. It is thus possible that many genes may interact with the CF gene to cause MI, or that an environmental factor, interacting with one or more non-CF genes, may induce the expression of MI. In any of these scenarios, the developmental pathway would be affected in such a way that the long-term clinical outcome of the child would also worsen.

INCEPTION OF ASTHMA AND THE ENVIRONMENT

The case can be made even more convincingly for asthma. Results of twin studies have shown that up to one half of the susceptibility to asthma is inherited. Although this suggests a strong genetic component, it also indicates that the expression of the disease is modulated by the environment. Because the incidence of asthma is highest during childhood and up to three fourths of all cases develop during this age period,[11] it is reasonable to assume that the developmental paradigm we have described applies to asthma. Recent evidence strongly suggests that this may indeed be the case (see also Chapter 58).

Emerging data suggest that the developmental pattern followed by the immune system in early life may be strongly influenced by external stimuli. Initially, T-helper cells, which play a pivotal role in determining the nature of the immune response to external stimuli, are characterized by a primitive, multipotential program of cytokine production. When stimulated, these so-called Th-0 cells secrete cytokines that will

later be produced exclusively by one or the other *but not both* of the two main mature T-helper cell phenotypes, so called Th1 and Th2 subtypes. These two T-helper cell types are well characterized in the mouse, but appear to exist more as extreme developmental poles than as two unique T-helper cell types in humans. Th1-like cells produce mainly interferon-gamma and IL-2, whereas Th2-like cells produce (among other cytokines) IL-4, IL-5, and IL-13. Th1-like cells promote cell-mediated and IgG-mediated responses, and they also block the development of Th2-like responses to antigen. Conversely, Th2-like cells promote IgE-mediated responses to antigen and they may block Th1-like responses as well.

Role of Exposure to Microbial Products in Early Life

Studies of children raised on animal farms,[12] taken to day care as infants[13] or exposed to dogs in early life[14] have provided new insights into the potential role of environmental factors, interacting with genetic variants, in changing developmental trajectories in children. These three exposures were shown to be associated with decreased likelihood of developing atopic asthma and associated traits, such as allergic rhinitis and aeroallergen sensitization, and all were found to be associated with increased concentrations of endotoxin, a marker of microbial exposure, in house dust. These findings supported the hypothesis that the development of immune responses in early life is influenced by the microbial burden to which the child is exposed, and that the final result of these exposures is a decreased risk of Th2-like responses and atopic asthma. Studies in which both indices of microbial exposures and variants in genes encoding for components of the receptor system for these same exposures revealed that the considerable variance in responsiveness to these exposures in the population was determined, at least in part, by hereditary factors. For example, polymorphisms in the gene for toll-like receptor 2 (TLR-2) modulate the degree of protection against asthma and atopy conferred by a farm environment.[15] The most widely studied gene, however, has been that for CD14, a central player in the receptor system for endotoxin and other microbial products. A functional polymorphism at position -159 with respect to the transcription start site of the gene showed strong evidence of antagonistic interaction with microbial exposure in house dust in four separate studies.[16-19] This means that the same allele that protects against asthma and allergies at high levels of endotoxin exposure is a risk factor for asthma and allergies at low levels of exposure.

These results provide insights into the multidimensional influences on developmental trajectories that determine the inception of asthma. What emerges is a system that is sensitive to environmental influences, with great inter-individual variability in responsiveness to these influences.

Role of Exposure to Allergens in Early Life

The characteristics of the response to the first encounters with antigen in early life (and even during fetal life) may have a profound effect on the nature of subsequent responses to antigen. It has been suggested, for example, that exposure to allergens, when occurring at a particular period during infancy, could drive the immune system toward a persistent Th2-like response to these same allergens. Data by Holt and colleagues[20] showed that, in mice, development of immune tolerance is a normal phenomenon by which animals exposed to certain antigens initially develop IgE responses to those antigens, but later show no IgE responses when re-exposed to these same antigens. Interestingly, Holt and colleagues[21] observed that tolerance did not develop when animals were exposed to antigens during a very precise age interval during the newborn period; these animals in fact showed persistent production of specific IgE against these antigens when re-exposed during adult life. Because asthma is known to be strongly associated with high concentrations of circulating IgE against certain specific allergens during childhood, it was postulated that exposure to these allergens during critical periods in early life could block the development of immune tolerance to these allergens. This could thus predispose to persistent production of IgE against asthma-related allergens and to asthma.

This conclusion appeared to be reinforced by the finding of a relation between sensitization to certain seasonal allergens and being born during the season of highest allergen exposure.[22] In addition, an inverse relation was reported between bedroom exposure to house dust mites during the first 2 years of life and age at first episode of asthma in asthmatic subjects who were allergic to mites.[23] Finally, it was observed that asthmatic children who were strongly sensitized against house dust mites became symptom-free when transferred for somewhat prolonged periods of time to a mite-free environment in the Italian Alps.[24] It was thus proposed that a causal relation existed between early life exposure to house dust mite antigen and the development of asthma and that prevention of exposure could be a strategy for the primary prevention of the disease.[25] Moreover, it was recently suggested that a strategy of early activation of immune tolerance by administration of high doses of antigen could prevent sensitization to allergens,[26] with the implicit conclusion that it could also prevent the development of asthma. This proposed strategy implied the administration of antigen via the oral route, based on the assumption that this route is a much stronger inducer of tolerance, as demonstrated by the high incidence of tolerance to ingested allergenic foods such as egg or milk products.

This line of thought has had considerable influence on the design of strategies for the prevention and treatment of asthma in the last 10 years. Unfortunately, new evidence suggests that the factors determining the development of asthma are more complex than a simple cause and effect relation between certain exposures and asthma inception. Data from the inland desert districts of Australia[27] and from Arizona[28] and New Mexico,[29] two arid regions of the United States, have shown that childhood asthma is not less frequent in these areas than in the coastal regions of both countries. What is particularly intriguing about these findings is that house dust mites are found either in very low amounts or are simply absent from indoor environments in these arid regions. Asthmatic children were thus very unlikely to be sensitized to house dust mites in these regions, and sensitization to other allergens such as molds was more prevalent. Of particular interest are studies performed in the arctic regions of

Sweden, where none of the aeroallergens against which children with asthma are most often sensitized in lower latitudes were detected.[30] In these areas, the prevalence of childhood asthma is as high as that observed in Stockholm, but children with asthma are either sensitized against furred pets or not at all, in spite of having higher total serum IgE levels than their nonasthmatic peers.

Of great importance are two clinical trials, in which children at high risk for the development of asthma were randomized to either drastic (and ultimately quite successful) interventions to decrease exposure to house dust mites in areas with high infestation rates in homes or to a sham intervention.[31,32] These studies showed either similar prevalence of asthma in the early school years in the active arm as compared with the sham arm or paradoxical increased sensitization to house dust mites in the active arm. These data thus suggest that allergic sensitization to specific allergens has a complex, nonlinear association with the degree of exposure to those allergens in the environment.[33] Subjects predisposed to asthma seem to have the potential for becoming sensitized to many allergens, and especially to those present in their specific locales in early life.[34] It is likely that predisposition to asthma (and not primarily exposure to aeroallergens) may be the main risk factor for allergic sensitization in chronic asthma. This may explain the tendency of asthmatics to become sensitized to multiple aeroallergens,[35] including food allergens to which they rapidly become tolerant after infancy.[36] Conversely, sensitization among nonasthmatics (for example, among subjects with allergic rhinitis) may be much more strongly related to exposure, and symptoms may be more strongly related to exposure to these aeroallergens than that which is usually evident in asthma.

Role of Infection in Early Life

The role of infections in the inception of asthma has been one of the most intensely studied and debated issues in pediatric pulmonary medicine. Several reports starting in the early 1970s and into the 1980s suggested that bronchiolitis in infancy was associated with increased likelihood of subsequent bronchial hyper-responsiveness,[37-39] increased prevalence of wheezing,[40] and lower levels of lung function.[41] One possible explanation for these findings was that viral infections caused changes in the lungs and in the immune system that predisposed to the outcomes described earlier. This hypothesis was attractive because it offered the possibility of a prevention strategy for asthma aimed at avoiding or immunizing against viral respiratory infections in early life. It soon became clear, however, that most children become infected at least once during the first 2 years of life with the most common respiratory viruses such as respiratory syncytial virus (RSV).[42] It also became clear that certain predisposed subjects had a peculiar reaction to *infections* with RSV, and that this gave rise to specific *illnesses* such as bronchiolitis or wheezing respiratory illnesses.[43] This predisposition may also extend to responses to rhinovirus, because children infected with this virus, and who developed wheezing episodes in the first year of life, were more likely to still be wheezing at age 3.[44] The connection between these *illnesses* and the subsequent development of asthma would be not one of cause and effect, but would be attributable to a pattern of response to environmental stimuli that determine both the *illnesses* and the subsequent development of asthma. The nature of this connection is the matter of considerable debate, but it is most likely heterogeneous, involving different mechanisms in different individuals.[45]

Role of Other Environmental Factors

Unfortunately, very little is clearly established regarding the role of other environmental factors on the inception of asthma. Some studies have suggested that younger maternal age predisposes to the development of asthma in their children.[46] Maternal age is directly related to birth weight,[47] and it has been postulated that younger mothers may compete for nutrients with their children during pregnancy.[48] There is also some evidence of a direct relation between infant lung size and maternal age.[49] Difference in hormonal levels associated with the parity and with the age of the mother may influence the development of the fetal lung and immune system.

Diet in early life has been extensively investigated, but the evidence suggesting a protective role of prolonged breastfeeding on the development of asthma is not convincing. Breastfeeding may decrease the likelihood of developing wheezing in non-atopic preschool children,[50,51] but it has also been reported to increase the likelihood of developing asthma in the breastfed child when the nursing mother has asthma herself.[52] One study suggested protection by breastfeeding and food allergen avoidance on the development of asthma into the teen years,[53] but other studies have been unable to confirm this finding.[54] Observational studies had suggested that, when eaten regularly, certain foods such as fish may decrease bronchial responsiveness and the likelihood of developing asthma.[55] However, a clinical trial in which omega-3 fatty acids, to which this preventive effect was attributed, were added to the diet of high-risk children from birth showed no protective effect for asthma or allergies up to age 5 years as compared with placebo.[31]

The role of indoor and outdoor contamination has been extensively studied. The only indoor factor that has been clearly linked to the development of asthma is environmental tobacco smoke,[56] but the issue is still controversial.[57] Other indoor contaminants such as nitric oxides have not been shown to be associated with an increased incidence of asthma. Paradoxically, an inverse relation has been reported between the use of coal or wood for heating and the prevalence of bronchial hyperresponsiveness and allergies.[58] Recently, studies of children living close to major highways suggested that lung function growth during childhood may be negatively affected by exposure to traffic-related contaminants.[59] In addition, children living in areas with high outdoor exposure to ozone reported increased asthma-like symptoms if they exercised outdoors as compared with children living in the same areas who did not exercise outdoors.[60]

CONCLUSIONS

Many external factors regulate the expression of genotype as a specific phenotype. The paradigm that these external factors contribute to the selection of developmental pathways for the respiratory and immune system in utero and during early

life, in a complex interaction with genetic variants that regulate responses to these factors, offers a framework for the understanding of the complex role of the environment on the development of most childhood respiratory illnesses and especially of asthma.

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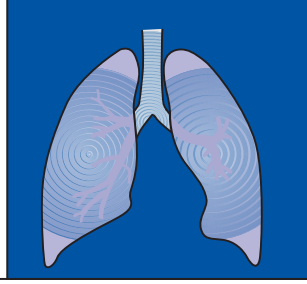

CHAPTER 3

Developmental Anatomy and Physiology of the Respiratory System

Claude Gaultier and André Denjean

TEACHING POINTS

- Immaturity of the upper airways can lead to obstructive apneas during sleep in infants.
- Immaturity of the respiratory muscles, combined with high chest wall compliance, can cause ventilation asynchrony and promote respiratory fatigue.
- Branching and septation are essential to the development of the conducting airways and alveoli, respectively.
- Alveolization is incomplete at birth and continues during the first 2 postnatal years.
- Numerous factors contribute to the control of lung morphogenesis. They include epithelium-mesenchyme interactions, growth factors, cell-cell interactions, extracellular matrix, and intercellular adhesion molecules.
- Vasculogenesis, angiogenesis, and intussusception are the mechanisms of pulmonary vascular development, which is closely associated with airway growth.
- Cell proliferation and apoptosis occur in combination throughout lung development and maturation.
- Lung mechanics, lung volume, and gas exchange in infants are closely dependent on complete and harmonious processes of fetal and neonatal lung development.
- Maturation of respiratory control is dependent on development and plasticity of the brain stem respiratory network, which are controlled and influenced by many neurotrophic factors and neurotransmitters.

In the first year of life, major maturational changes occur in the respiratory system and its control mechanisms, and respiratory disorders are particularly common and severe. Lung immaturity contributes substantially to the morbidity and mortality associated with prematurity. Chest-wall immaturity limits the ability of infants to adapt to increased breathing loads related to respiratory disorders, especially during sleep. Respiratory control immaturity is involved in the pathophysiology of apnea of prematurity, apparently life-threatening events, and sudden infant death syndrome (SIDS). Importantly, respiratory system development occurs as one component of a broader maturation process that modifies respiratory effectors, respiratory control, behavioral states, and metabolic demands.

Research into respiratory system development has moved from developmental anatomy and physiology to developmental molecular biology. Environmental insults during early respiratory-system maturation may alter developmental programming, leading to respiratory system abnormalities that may persist in infancy and even into adulthood. Recent studies in newborn mice with targeted gene deletions have shown links between the expression of specific genes and the development of individual respiratory system components. Improved knowledge of the underpinnings of developmental processes will help to prevent antenatal and postnatal exposure to insults and to devise effective treatment strategies.

UPPER AIRWAYS

Developmental Anatomy

The configuration of the upper airways changes with growth.[1,2] In the newborn, the epiglottis is large and can cover the soft palate, forming a low epiglottic sphincter and encouraging nasal breathing. A horizontal position of the tongue and an elevated position of the hyoid bone and laryngeal cartilage are other specific features. Over the first 2 years of life, changes in upper airway anatomy lead to the formation of a dynamic velolingual sphincter that permits buccal respiration and speech. The epiglottis, larynx, and hyoid bone move downward. The posterior portion of the tongue becomes vertical during late infancy. The facial skeleton grows vertically during late infancy, and the mandible lengthens from front to back.

Recent studies using magnetic resonance imaging have investigated the growth relationships of the bone and soft tissues surrounding the upper airways in normal children (47% males; age range, 1 to 11 years).[3] The results indicate that (1) the lower facial skeleton grows linearly in the sagittal and axial planes from the 1st to 11th year; and (2) the soft-tissue structures, including the tonsils and adenoids, grow proportionally to the skeletal structures during the same period. Family aggregation of upper airway soft tissue structures was recently shown, suggesting that genetic determinants may predispose to obstructive sleep apnea syndrome.[4]

Developmental Physiology

FUNCTION

Human newborns and infants have difficulty breathing through their mouths when their nasal passages are occluded. Although nasal breathing is considered obligatory in the

newborn and infant, mouth-breathing can occur when the nose is blocked. Oropharyngeal structures have been examined using fluoroscopy during nasal occlusion in healthy infants.[5] Infants can breathe through the mouth by detaching the soft palate from the tongue, thus opening the pharyngeal isthmus. However, the time required to establish mouth breathing varies with age, state of alertness, or both, with younger and sleeping infants responding more slowly than older and awake infants.[6,7]

Few studies have investigated the upper airway dilator muscles during development. No phasic activity of the genioglossus muscle was found during quiet breathing in normal sleeping preterm infants[8] or normal children.[9,10] Interestingly, a delay in the genioglossus muscle response at early inspiration relative to the diaphragm has been reported in preterm infants and may promote upper airway collapse.[8]

An early study documented pharyngeal dynamics at autopsy in infants.[11] The closing pressure was 0.82 cm H_2O on average and was lower than the opening pressure. Neck flexion raises the closing pressure, making the upper airway prone to collapse.[11] Another early study showed that pharyngeal collapsibility decreased gradually during development in infants.[12] Recent work further documented the developmental changes in pharyngeal collapsibility during infancy.[13] The static pressure–area relationship of the passive pharynx was endoscopically quantified under general anesthesia with complete paralysis, allowing an evaluation of pharyngeal properties without any influence of neuromuscular regulation of the upper airway muscles. Pharyngeal wall thickness increases significantly during development, and the resulting increase in passive pharynx stability helps to maintain airway patency. The prone position increases the collapsibility of the passive pharynx in infants.[14] A study of the static mechanical properties of the passive pharynx in anesthetized and paralyzed children showed that the closing pressure (P, close) was more negative than in infants (Fig. 3-1).[13] Thus, airway stability increases during childhood in terms of pharyngeal wall compliance and closing pressure.[15] One half of the children closed their airways primarily at the soft palate edges and one third closed their airways at the tongue base.[13] Closing pressure increased during adulthood to the level seen in infants, whereas compliance was lower in adults than in infants.[13] Lateral positioning increased the upper airway cross-sectional area and total upper airway volume compared with the supine position in sedated, spontaneously breathing children.[16] A study using respiratory-gated magnetic resonance imaging showed that changes in upper airway area were small during tidal breathing in mildly sedated children.[17]

Nasal resistance has been measured in white and black infants during the first year of life, using an adapted posterior rhinomanometric method. The percentage contribution of nasal resistance to airway resistance was significantly higher in the white than in the black infants (mean values, 49% and 31%, respectively).[18] Active anterior rhinomanometry was used to measure nasal airflow and resistance in a large group of white children and adolescents.[19] Nasal inspiratory airflow and nasal inspiratory airflow from the right and left nostrils increased significantly with body height and age. Total nasal inspiratory airflow resistance and inspiratory flow resistance for the right and left nostrils decreased as body height and age increased. No difference was found between boys and girls.

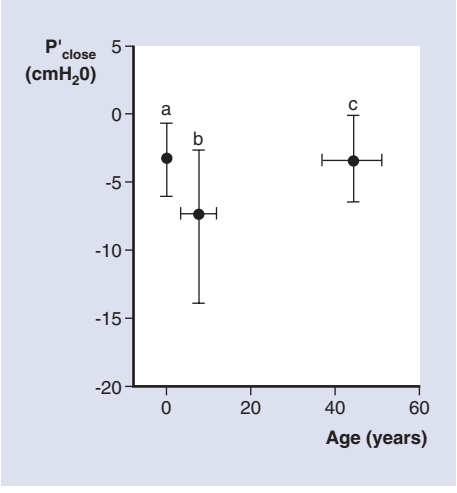

Figure 3-1 Differences in P'close (closing pressure, i.e., the pressure corresponding to zero of the measured cross-sectional area obtained under general anesthesia with complete paralysis) in healthy infants (a), children (b), and adults (c). *Closed circles* represent mean values; bars indicate standard deviation. (From Isono S, Tanaka A, Ishikawa T, Nishino T: Developmental changes in collapsibility of the passive pharynx during infancy. Am Rev Respir Crit Care Med 162:832-836, 2000.)

REFLEXES ORIGINATING IN THE UPPER AIRWAYS

The upper airway is less susceptible to collapse in the pediatric population than in adults. This difference may be related, at least in part, to differences in neuromuscular reflex responses. In adults, upper airway neuromuscular activity increases in response to subatmospheric pressure loading, but this response is blunted during sleep compared to wakefulness.[20] In contrast, reflex responses are strong in children, who are thus able to maintain upper airway patency despite increasing subatmospheric pressure loading during sleep.[21] The ventilatory drive during wakefulness is stronger in children than in adults.[22] Interestingly, the level of the upper airway response to subatmospheric pressure loading is significantly related to the level of ventilatory drive during sleep in children, and both levels decrease with age until adulthood.[21]

In human infants and newborn mammals, reflexes originating from the laryngeal mucosa can induce apnea and bradycardia.[23,24] In anesthetized puppies, the duration of apnea elicited by water instillation into the larynx decreased as age increased.[24] In nonsedated lambs, the inhibitory cardiorespiratory response was more pronounced in preterm than in full-term lambs.[25-26] In premature human infants, reflex apnea has been reported to occur after instillation of water or saline into the larynx during sleep.[27-29] Prolonged apnea in preterm infants may be an abnormal extreme that extends the normal spectrum of airway-protecting responses to upper airway fluids.[29] Studies in newborn animals showed that the degree of apnea and bradycardia elicited by the laryngeal chemoreflex was increased by respiratory syncytial virus infection,[30] a condition associated with central and obstructive apneas during sleep in human infants.[31] The apnea and bradycardia elicited by the laryngeal chemoreflex in human infants increase dramatically in the presence of hypoxemia, because of a cardio-inhibitory effect on peripheral

chemoreceptors during apnea with suppression of input from pulmonary stretch receptors.[32]

During the neonatal period, stimulation of other upper airway receptors can result in apnea. Activation of upper airway mechanoreceptors by negative pressure causes apnea in puppies.[33] In human infants, trigeminal airway stimulation can elicit a response similar to that seen during the diving reflex and can induce apnea and bradycardia. The ventilatory response to trigeminal stimulation became increasingly blunted during rapid eye movement (REM) sleep as infants matured.[34]

CHEST WALL

Developmental Anatomy

RIB CAGE

At birth, the ribs are composed mainly of cartilage and project at right angles from the spine. As a result, the rib cage is more circular than in adults[35-37] (Fig. 3-2) and lacks mechanical efficiency.[38] In adults, elevating the ribs increases the volume of the rib cage, whereas in neonates rib cage movements produce little change in volume.[38] Acquisition of the upright posture is the main factor leading to the change in rib orientation that occurs with age. The pull of gravity moves the ribs caudally, so that the thoracic cavity lengthens and changes in section from circular to ovoid.[36,37] The thoracic index, which is the ratio of the anteroposterior over the lateral diameter, decreases significantly during the first 3 years of life, and gradual ossification of the ribs occurs concomitantly.[37] These changes in shape and structure are important because they help to stiffen the rib cage.

RESPIRATORY MUSCLES

In the newborn, the diaphragm seems ill-suited to the heavy burden of respiratory work. The angle of insertion of the diaphragm is not oblique as in adults but almost horizontal, which results in decreased contraction efficiency. With its open angle of insertion and small area of apposition (Fig. 3-3),[39] the flat diaphragm of the newborn seems designed to suck the chest wall inward rather than to draw air into the chest cavity. Because of its almost horizontal insertion, the contracting diaphragm tends to pull the lower rib cage inward. For the same reason, the downward course of the contracting diaphragm is shorter, the abdominal pressure increase is smaller and, consequently, the rib cage expansion is less marked.

The immature diaphragm is composed chiefly of type IIC undifferentiated fibers, which are gradually replaced by type I and type IIB fibers.[40,41] Type IIC fibers coexpress fetal and adult myosin heavy chains (MHCs), whereas type I and type IIB fibers express only the adult MHC isoform. The fetal MHC isoform predominates between 16 and 24 weeks of gestation, after which transition to the adult isoform occurs, between 24 and 42 weeks.[42,43]

The enzymatic oxidative capacity of the diaphragm changes significantly with postnatal maturation.[44-46] Succinyl dehydrogenase activity is very low at birth, then increases dramatically between the first and sixth postnatal weeks, whereas

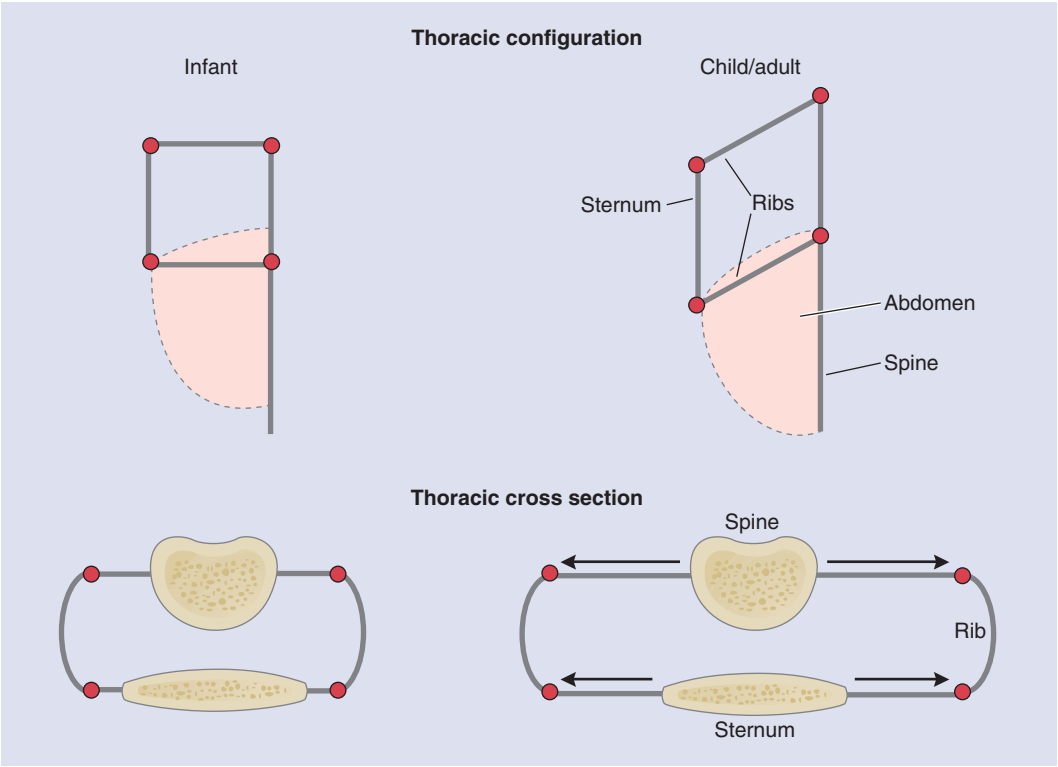

Figure 3-2 Changes in configuration and cross-sectional shape of the thorax from infancy to early childhood. (Redrawn from Openshaw P, Edwards S, Helms P: Changes in rib cage geometry during childhood. Thorax 39:624-627, 1984.)

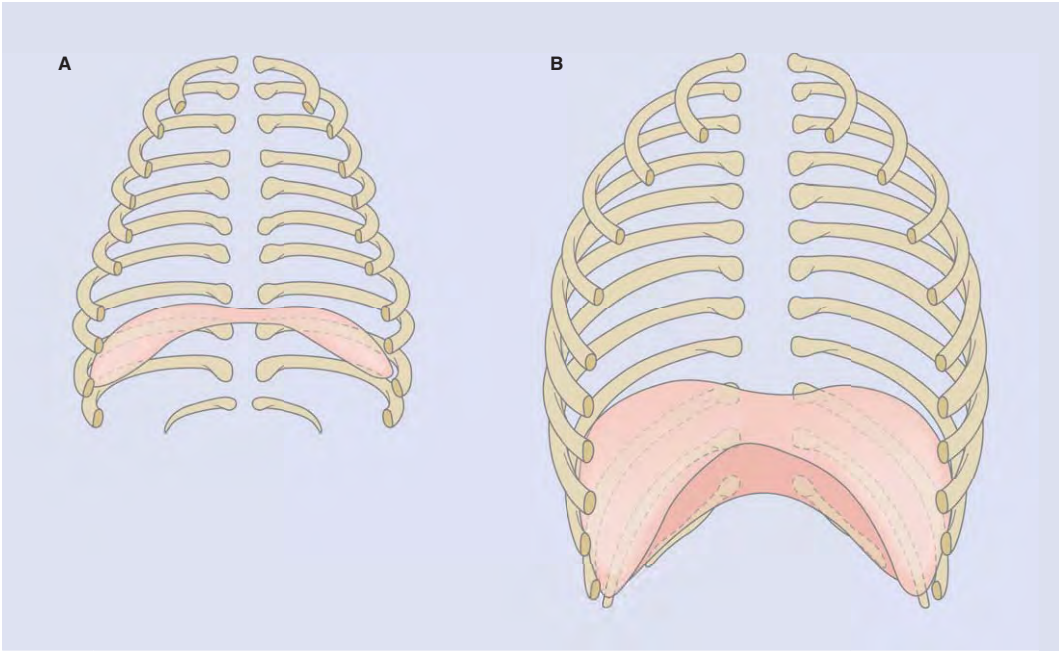

Figure 3-3 Area of costal apposition of the diaphragm in newborn **(A),** and adult **(B).** (Redrawn from Devlieger H, Daniel H, Marchal G, et al: The diaphragm of the newborn infant: Anatomic and ultrasonographic studies. J Dev Physiol 16:321-329, 1991.)

global oxidative capacity is higher at the first than at the eighth postnatal week.[46] The first postnatal month is also characterized by a considerable increase in ryanodine receptor (RyR1) expression in the sarcoplasmic reticulum, which is required for the maturation of the excitation-contraction coupling system.[47-49] Expression of the ryanodine receptor RyR3 occurs gradually during fetal development and reaches its peak after the second postnatal week in rats; RyR3 expression is higher in the diaphragm than in the other skeletal muscles.[49] Neuromuscular transmission undergoes postnatal maturation, with changes in the morphology of the neuromuscular junction and an increase in postsynaptic receptor density.[51,52] Finally, the phrenic motoneurons undergo morphologic changes after birth, increasing their cross-sectional area and their numbers of primary and secondary dendrites.[52]

These modifications in anatomy, morphology, contractile properties, and energetic capacity probably explain why the susceptibility to respiratory muscle fatigue changes with advancing age. Premature neonates cannot handle increases in respiratory demand.[53] However, the mechanisms underlying the susceptibility of premature infants to respiratory failure are probably complex and multifactorial. Thus, recent studies have established that the neonatal diaphragm is less susceptible to fatigue than the adult diaphragm, although the mechanisms underlying this age-related change remain unclear.[46,54-57]

Developmental Physiology

CHEST WALL COMPLIANCE

High chest wall compliance relative to lung compliance (with a 3:1 ratio) is an inherent characteristic of newborn mammals.[58] Few studies have investigated chest-wall mechanics in infants and children.[59-61] High chest wall compliance contributes to the respiratory vulnerability of preterm infants during early postnatal life,[61,62] as incomplete rib cage ossification and underdevelopment of the respiratory muscles predispose the chest wall to distortion. The high chest wall compliance relative to lung compliance results in a limited thoracic volume with a low functional residual capacity (FRC). By 2 years of age chest wall compliance is similar to lung compliance, which is the pattern seen in adults.

THORACOABDOMINAL MOTION

Developmental changes in thoracic properties over time influence the pattern of thoracoabdominal motion during infancy and early childhood. The contribution of the rib cage to tidal breathing increases with postnatal age, from 34% during non-rapid eye movement sleep (non-REM) sleep at 1 month to approximately 60% at 1 year.[63]

Chest wall muscle contractions help to stabilize the compliant infant rib cage, minimizing inward displacement of the ribs during diaphragmatic contractions. However, when the stabilizing effect of the intercostal muscles is inhibited (e.g., REM sleep), paradoxical inward motion of the rib cage occurs during inspiration (Fig. 3-4).[38,64] This is important because REM sleep accounts for more than one half the total sleep time in full-term infants and for an even larger proportion in preterm infants.[65]

Asynchronous chest wall movements during REM sleep are associated with a number of mechanical derangements in healthy newborns, including a decrease in FRC,[66,67] a decrease in transcutaneous partial pressure of oxygen,[68] and an increase in diaphragmatic work of breathing.[69] During REM sleep, a large proportion of the force of the diaphragm is wasted in distorting the rib cage and is, therefore, not available for inducing volume exchange. Furthermore, infants can use their abdominal muscles to optimize diaphragmatic length, but this

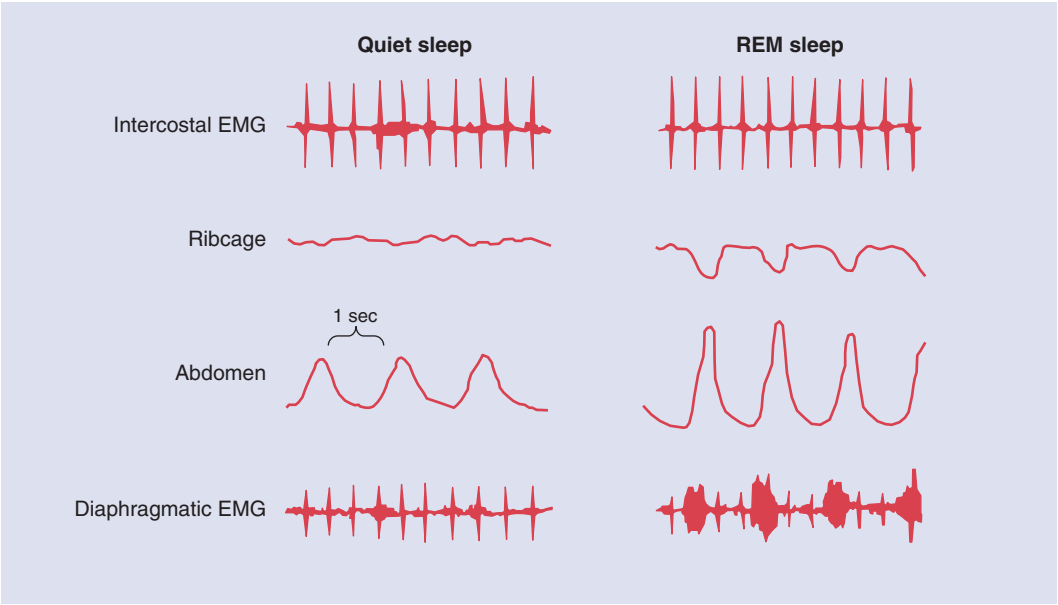

Figure 3-4 Movement of the rib cage and abdomen measured with magnetometers and electromyograms (EMG) using surface electrodes on the intercostal muscles and the diaphragm of a newborn during non-REM *(left)* and during REM *(right)* sleep. During REM sleep, there is marked inward distortion of the rib cage with increased outward movement of the abdomen; the intercostal electromyogram is decreased, and the diaphragmatic electromyogram is increased. (Redrawn from Bryan AC, Gaultier CL: The thorax in children. In Macklem PT, Roussos H [eds]: The Thorax, part B, New York, 1985, Marcel Dekker, pp 871-888.)

abdominal muscle activity is inhibited during REM sleep.[70] The increased diaphragmatic work of breathing in young infants represents a significant expenditure of calories and may contribute to the development of diaphragmatic fatigue and respiratory failure.

With the changes in rib cage geometry and chest wall compliance that occur with age, the time spent with paradoxical rib cage motion during REM sleep decreases, nearing or reaching zero after 3 years of age.[71] Recently, a study involving respiratory inductive plethysmography in 22 infants confirmed that inward rib cage movement during REM sleep decreased with age.[72] Paradoxical movements disappeared completely at 3.3 years of age. In adolescents, no paradoxical movements were observed.[73]

The mechanical properties of the chest wall have clinical implications for respiratory adaptation during sleep in infants who have respiratory disorders associated with increased resistive loads of breathing, such as upper airway obstruction and chronic lung disease. In young infants with such disorders, thoracoabdominal asynchrony occurs even during non-REM sleep.[74-76] As growth proceeds and the thoracic cage becomes less compliant, the increases in resistive load lead to heightened activation of the inspiratory thoracic muscles, which maintains inspiratory rib cage movement. However, the inspiratory intercostal muscles are inhibited during REM sleep, and the need for lower negative pressures during inspiration leads to paradoxical motion of the destabilized rib cage.[77]

PRESSURES GENERATED BY RESPIRATORY MUSCLES AND RESPIRATORY MUSCLE FATIGUE

Maximum pressures exerted by infants are surprisingly high compared to adult values, probably because of the small radius of curvature of the rib cage, diaphragm, and abdomen. According to the Laplace law, a smaller radius results in higher pressures. Esophageal pressures reaching –70 cm H_2O have been reported during the first breath.[78] Inspiratory and expiratory pressures of about 120 cm H_2O have been recorded during crying in normal infants.[79] During late childhood and adolescence, gradual increases in maximum static inspiratory and expiratory pressures occur, with substantial differences between males and females in all age groups.[80,81] Transdiaphragmatic pressure ($\bar{P}di$) measured using magnetic phrenic-nerve stimulation was significantly lower in preterm than term infants and was correlated with gestational age and postconceptional age.[82]

However, despite a relatively high maximum static inspiratory pressure, the inspiratory force reserve of respiratory muscles appears reduced during early infancy compared with adulthood because the inspiratory pressures are higher at rest.[22,83] The high pressure demand at rest in infants is due to the high minute ventilation and high metabolic rate normalized for body weight.[84] Occlusion pressure and inspiratory time measurements have been used to estimate the inspiratory pressure demand in children older than 4 years of age.[22] The ratio of mean inspiratory pressure to maximum static inspiratory pressure at FRC was 0.2 at 7 years of age (i.e., more than twice the value in adults).[83] It has been suggested that the tension-time index of the diaphragm in healthy newborns may be close to the fatigue threshold.[85]

Under all breathing conditions, two important parameters, i.e., pressure and time, determine the tension-time index, which allows the clinician to evaluate the position of the breathing pattern in relation to the critical level of muscle function or to the threshold of muscle fatigue (Fig. 3-5).[86-88] Their small inspiratory force reserve places young

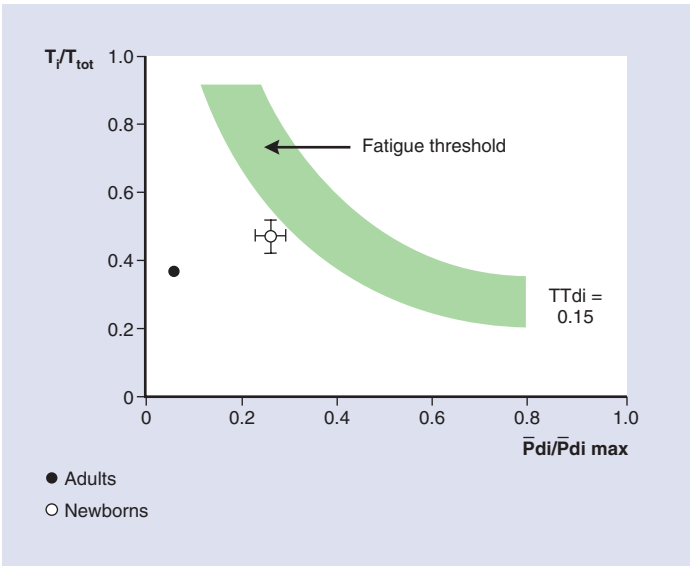

Figure 3-5 Relation between ratio of inspiratory time (T_i) over total duration of the respiratory cycle (T_{tot}) and mean transdiaphragmatic pressure used to breathe at rest over maximal transdiaphragmatic pressure ($\bar{P}$di max). The green area defines the diaphragmatic fatigue threshold and corresponds to the so-called tension-time index of the diaphragm (TTdi = 0.15). Breathing patterns below the fatiguing threshold can be obtained indefinitely. *Filled circle* refers to the average value for normal adults during resting breathing. *Open circle* is the estimated value for normal infants. Bars indicate 1 standard deviation. (Redrawn from Milic-Emili J. In Cosmi EV, Scarpelli EM [eds]: Pulmonary Surfactant System, Rome, 1983, Elsevier Science, pp 135-141.)

children closer to the diaphragmatic fatigue threshold than older children. All conditions characterized by prolonged muscle contraction or increased pressure demand may lead to respiratory muscle fatigue. Young children with croup or epiglottitis are at especially high risk for fatigue because obstructed and prolonged inspiration is combined with a need for high pressures to produce adequate ventilation. Thus, infants can develop ventilatory failure rapidly after small changes in mechanical loads. Infants can use other muscles to unload (rest) the diaphragm. When the respiratory drive is increased because of carbon dioxide breathing or increased upper airway resistance, infants and young children recruit their intercostal muscles, abdominal muscles, or both.[70] However, this muscle recruitment aimed at preventing an increase in diaphragmatic work of breathing and diaphragmatic fatigue is suppressed during REM sleep.

The paucity of fatigue-resistant type I fibers, high proportion of fatigue-susceptible type IIc fibers, and low oxidative capacity of the neonatal diaphragm suggest that the muscle may be relatively prone to fatigue. This hypothesis has been contradicted by in vitro[56] and in situ findings. However, an in vivo study in rabbits found that fatigue occurred more quickly in neonatal than in adult animals.[89] Thus, whether fatigability of the neonatal respiratory muscles is increased compared to adults remains controversial.

LUNGS

Developmental Anatomy

Lung development includes growth of lung structures and maturational cell differentiation processes. Alveolar development occurs both before and after birth and extra-acinar airway development is complete by week 16 of gestation. The development of extra-acinar arteries follows airway development and that of intra-acinar arteries follows alveolar development.[90] Figures 3-6 and 3-7 show the timetable of antenatal and postnatal lung development.[91,92]

Four processes are essential to lung development. They operate throughout the prenatal and early postnatal periods to create this organ essentially dedicated to exchanging gases through the blood-gas barrier. These processes include *branching* of the airways to form conducting and respiratory airways, *septation* to divide the airspaces and participate in *alveolization*, and formation of blood vessels, or *lung vascularization*, which accompanies the development of bronchi. These four essential processes, together with cell differentiation and maturation, contribute to lung formation and development.

ANTENATAL LUNG DEVELOPMENT

The antenatal development of the human lung can be subdivided into an early embryonic period, during which most organs are formed; and a fetal period, which includes several stages.[91-94]

Embryonic Lung Development

The lung appears around day 26 as a ventral bud of the esophagus at the caudal end of the laryngotracheal sulcus. The epithelial components of the lung are thus derived from the endoderm and the enveloping connective tissue from the mesodermal germ layer. The tracheal bud rapidly divides into two branches that develop into the two main bronchi. The future airways continue to grow and branch dichotomously into the surrounding mesenchyme. By the end of the sixth week, the lobar and segmental portions of the airway tree are preformed as tubes of high columnar epithelium. Simultaneously with the early stages of pulmonary organogenesis, vascular connections develop. The pulmonary arteries branch off from the sixth pair of aortic arches and descend to the newly developed lung buds, forming a vascular plexus in the surrounding mesenchyme. The pulmonary veins start to develop around the fifth week as a single evagination in the sinoatrial portion of the heart. Merging of the embryonic period into the fetal period is thought to occur on day 50. At that time, the lung resembles a small tubuloacinar gland, which is why the subsequent stage is called the *pseudoglandular stage*.

Fetal Period

The fetal period includes the pseudoglandular stage to week 16, the canalicular stage to weeks 24 to 26, and the saccular-alveolar stages to term.[90-94]

Pseudoglandular Stage. The extra-acinar bronchi and arteries develop during the pseudoglandular stage by continuous growth and branching. The proximal airways are lined with a high columnar epithelium (Fig. 3-8) and the distal airways with a cuboidal epithelium. The cytoplasm of airway epithelial cells is poorly differentiated and rich in glycogen. Differentiation of the airway wall occurs in a centrifugal direction, so that ciliated, nonciliated, and goblet cells first appear in the proximal airways. The luminal surfaces of the columnar cells have scarce microvilli with or without primary

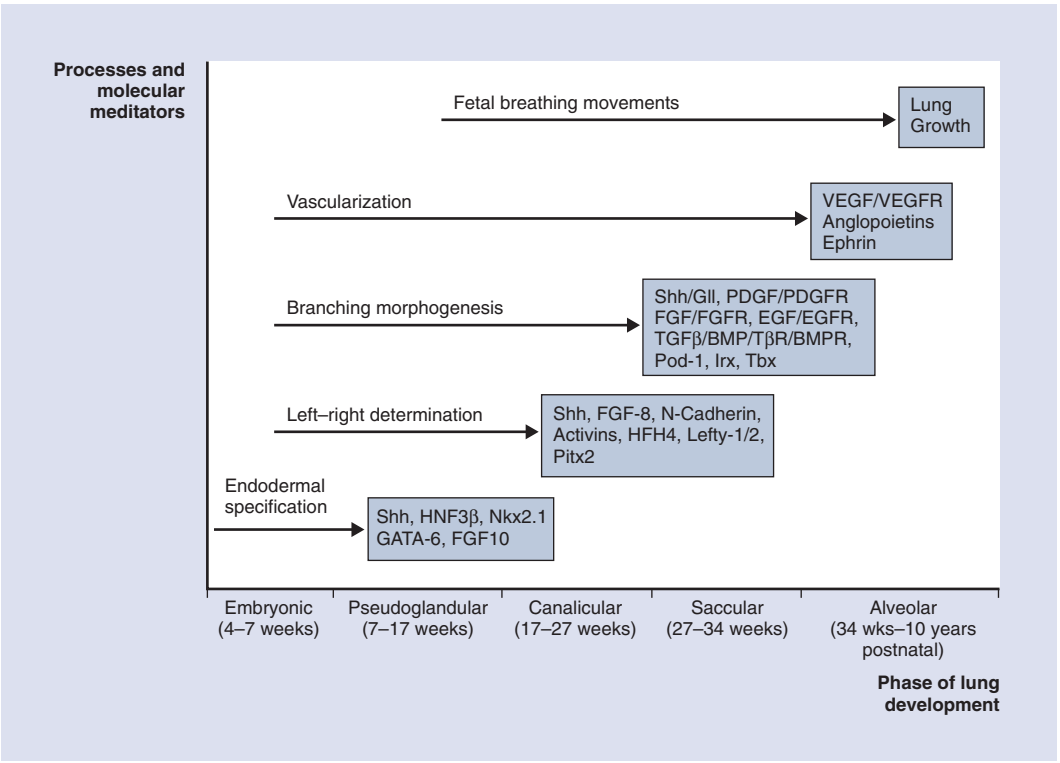

Figure 3-6 Regulatory factors implicated in the different phases of respiratory morphogenesis. Transcription factors: Nkx2.1, forkhead homolog hepatocyte nuclear family proteins (HNF3β, HFH4), GATA family of zinc finger transcription factors (GATA-6), basic helix-loop-helix (bHLH) proteins (öd-1), Gli zinc finger transcription factors (gli), Iroquois complex homeobox family members (Irx), and Tbox family proteins (Tbx). Growth factor signaling pathways: sonic hedgehog (Shh), fibroblast growth factors (FGF), platelet-derived growth factors (PDGF), transforming growth factors (TGFβ)/bone morphogenetic proteins (BMP), epidermal growth factor (EGF) proteins and vascular endothelial growth factor (VEGF) proteins. Receptors for growth factors: PDGFR, FGFR, TGFβR/BMPR, EGFR, VEGFR. (From Copland I, Post M: Lung development and fetal lung growth. Paediatr Respir Rev 5:S259-S264, 2004.)

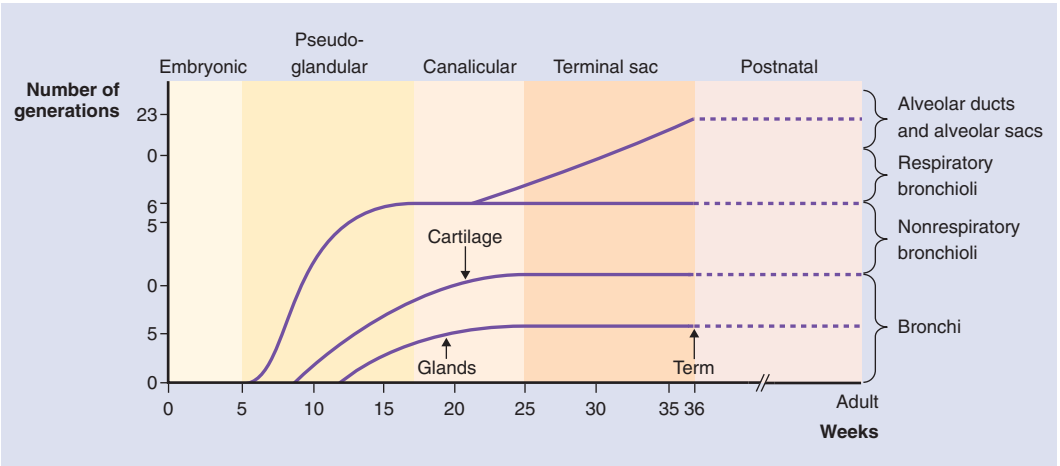

Figure 3-7 Timetable for development of the airway tree, its generations, and typical wall structures. Generation numbers are fitted to the average airway tree of Weibel's dichotomous branching model. (Redrawn from Burri P: Circulatory and nonrespiratory functions. In Fishman P, Fisher A [eds]: Handbook of Physiology, Section 3: The Respiratory System, vol 1: Bethesda, Md, 1985, Williams & Wilkins, pp 1-46.)

rudimentary cilia.[95] Precursors for neuroendocrine cells appear at this stage.[96] Mucus glands are also present.[97] Mesenchymal cells differentiate into chondrocytes[98] and smooth muscle cells.[99] Capillaries are randomly distributed in the mesenchyme (Fig. 3-9). As a rule, the arteries develop and grow according to the same pattern as the airways. In contrast to the airway system, which averages 23 generations in adults, the arterial system has 28 to 30 generations. By 34 days of gestation, the capillary network around each main bronchus connects both cranially and caudally with the aortic sac and

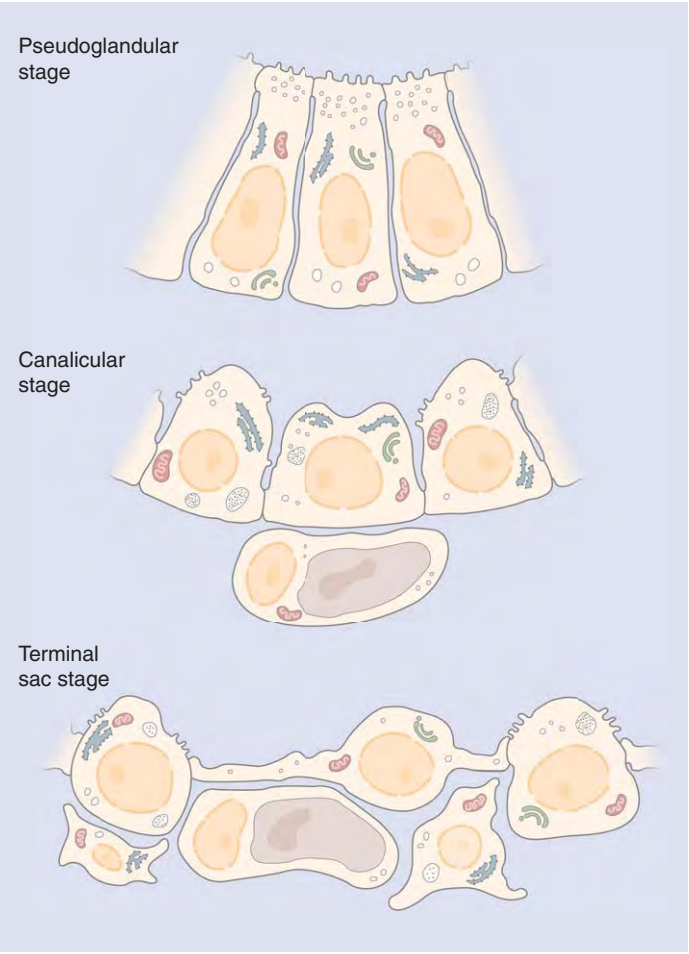

Figure 3-8 Phases of epithelial transformation. *Top,* Pseudoglandular stage: high columnar epithelium and cells rich in glycogen. *Middle,* Canalicular stage: epithelium beginning to differentiate into two cell types, secretory (type 2, containing lamellar body) and lining cells (type 1), and characterized by the low position of the junctional complex with neighboring cells and close contact with capillaries. *Bottom,* Terminal sac stage: differentiation of type 1 and type 2 cells. (From Burri P: Circulatory and nonrespiratory functions. In Fishman P, Fisher A [eds]: Handbook of Physiology, Section 3: The Respiratory System, vol 1: Bethesda, Md, 1985, Williams & Wilkins, pp 1-46.)

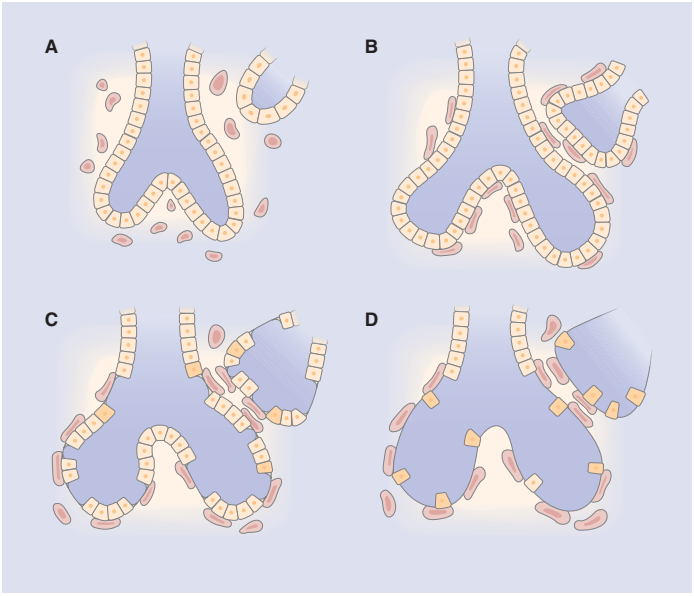

Figure 3-9 Development of the pulmonary capillaries. **A,** Pseudoglandular stage: Capillaries are randomly distributed in mesenchyme. **B,** Beginning of the canalicular stage: Capillaries start to arrange around the epithelial tubes. **C,** Capillaries establish close contacts to the lining epithelium, which flattens to form thin air-blood barriers. **D,** Saccular stage: Epithelium is differentiated in type 1 and type 2 cells. (Redrawn from Burri P: Circulatory and nonrespiratory functions. In Fishman P, Fisher A [eds]: Handbook of Physiology, Section 3: The Respiratory System, vol 1: Bethesda, Md, 1985, Williams & Wilkins, pp 1-46.)

the left atrium, respectively.[100] These capillaries coalesce to form small blood vessels alongside the airways. As each new airway buds into the mesenchyme, a new plexus forms and adds to the circulation, thus extending the arteries and veins. Arteries that follow the divisions of the airways are called *conventional arteries;* the smaller arteries with intermediate branchings that supply alveolar regions adjacent to airways are called *supernumerary arteries*.[101,102] By week 12, both types are present. The branching pattern of the veins matches that of the arteries.[103]

Canalicular Stage. Events during the canalicular stage include acinar anlage formation and epithelial cell differentiation with development of the air-blood barrier. Production of surfactant starts toward the end of the canalicular stage. The transition from the pseudoglandular stage to the canalicular stage is marked by the appearance of rudimentary acini. The acinus is generally defined as the unit of gas-exchanging tissue that is supplied by a terminal bronchus. The acinus margins become recognizable as a result of decreased density of the mesenchyme. At the end of week 17, the newly delineated acinus is composed of the anlage of the terminal bronchiole, two to four rudimentary respiratory bronchioles, and clusters of short tubules and buds. Over the following weeks, the clusters grow by further peripheral branching and by lengthening of each tubular branch. The epithelium differentiates into two cell types: secretory cells (type 2, containing lamellar bodies) and lining cells (type 1) characterized by low junctional complexes with neighboring cells and by close contact with capillaries (see Fig. 3-8). Peripheral growth is accompanied by an increase in capillaries, which begin to develop around the airspaces and subsequently establish close contact with the lining cells to form the future air-blood barrier (see Fig. 3-9).

Saccular-Alveolar Stage. The saccular-alveolar stage starts at weeks 24 to 26 of gestation. At this time, the fetal lung can theoretically function in air. However, because of a low level of surfactant synthesis, very premature babies are at high risk for respiratory distress syndrome. At the beginning of this stage, the airways end in clusters of thin-walled saccules, which produce the last generations of airways (i.e., alveolar ducts and alveolar sacs). Between weeks 28 and 36, there is a striking change in the appearance of the lung characterized by a marked decrease in interstitial tissue with thinning of saccule walls. Secondary crests divide the saccules into smaller units. The margins of the crests contain elastic fibers. The saccule walls retain their earlier double capillary

network. The formation of alveoli marks the beginning of the alveolar phase. According to recent studies, alveolar development starts between weeks 29 and 32.[104,105] The internal surface area of the lung increases rapidly after the onset of alveolar development, from 1 or 2 to 3 or 4 m^2 at full term. The number of alveoli present at birth is still controversial. Early studies[106,107] examining a single lung found numbers ranging from 17×10^6 to 24×10^6. More recently, larger mean numbers of 50×10^6 and 150×10^6 were reported.[104,105] Despite these discrepancies, there is no doubt that the number of alveoli is lower at birth than in adulthood (i.e., 300×10^6 to 600×10^6).[108] During the saccular and alveolar phases, intra-acinar blood vessels increase in width, length, and number.

POSTNATAL LUNG DEVELOPMENT

Alveolar Development

At full term, the in vitro lung volume at a transpulmonary pressure of 25 cm H_2O is 150 mL.[104] Alveolar multiplication continues after birth. Early studies suggested that postnatal alveolar multiplication might end at 8 years of age.[107] However, more recent studies showed that alveolar multiplication was complete by 2 years of age and possibly even earlier, between 1 and 2 years of age.[91,94,109] During postnatal alveolar multiplication, the capillary network of the septa is remodeled from the initial double pattern to the single pattern seen in adults.[110] This process continues after the end of alveolar multiplication, stopping between 3 and 5 years of age. At 2 years of age, the number of alveoli varies substantially among individuals. After 2 years of age, boys have larger numbers of alveoli than do girls. After the end of alveolar multiplication, the alveoli continue to increase in size until thoracic growth is completed.[109]

Airway Development

Airway size and structure in normal lungs of fetuses and infants have been described.[111] The mean airway lumen diameter from the main bronchi to the respiratory bronchi increases linearly with postconceptional age. Each type of airway shows a similar relative increase in diameter of 200% to 300% from birth to adulthood. The absolute amount of cartilage increases until 8 months of age. The area of the submucosal glands (expressed in relation to the lumen perimeter as millimeters squared per millimeter) increases linearly from birth to 8 months of age. The area of the hilar bronchi continues to increase until adulthood. At birth, submucosal glands are supplied by nerves containing peptides. Bronchial smooth muscle is present at birth, even in the respiratory bronchioles. Bronchial smooth muscle area increases from birth to 8 months of age in all airways from the main bronchi to the respiratory bronchioles. In proximal airways only, this area increases from 8 months of age to adulthood. In premature infants, airway size is appropriate for postconceptional age and the airways contain increased amounts of bronchial smooth-muscle and goblet cells. At birth, the smooth muscle is supplied by nerves containing peptides (neuropeptide-tyrosine, vasointestinal peptide, substance P, neuropeptide Y, somatostatin, and gene-related peptide).[112] Smooth-muscle innervation appears to change with age, as the relative number of peptide-containing nerves within the respiratory unit decreases from infancy to adulthood. No developmental changes in myosin chain isoforms have been demonstrated in human airway smooth muscle.[113]

Arterial Development

Pulmonary vascular resistance falls rapidly at birth as a result of dilation of the small muscular arteries and a reduction in the amount of vascular smooth muscle in the lungs.[114] Postnatal adaptation of the pulmonary circulation is thought to be related to changes in endothelial cell function, including increased capabilities for synthesis and release of the endothelium-derived relaxing factor nitric oxide.[115,116] Ultrastructural studies found evidence of postnatal smooth muscle maturation, with changes in contractile myofilaments and in cytoskeletal protein types.[117] The number of arteries increases rapidly during the first 2 months of life.[118] Subsequently, arteries multiply at the same rate as alveoli, and the alveolar-arterial ratio remains fairly constant. Arterial growth is most marked during the first 2 months of life but remains substantial during the first 4 years.

Studies of the structure of the arteries that accompany the peripheral airways have demonstrated that the respiratory bronchiolar arteries acquire a muscle coat as they increase in size during the first year of life. From birth to 6 months of age, the mean number of arteries surrounded by muscle cells is 58% among arteries accompanying terminal bronchioli versus only 23% among arteries accompanying alveolar ducts. These mean proportions reach 92% and 40%, respectively, between 1 and 4 years of age and increase further to 96% and 71%, respectively, after 5 years.[118]

Remodeling of the arterial wall within the acinus is accompanied with an increase in the nerve supply to the arterial wall during childhood.[119] Many respiratory unit arteries do not have accompanying nerve fibers in infants 1 to 4 months of age. The proportion of innervated vessels increases with age. In all age groups, the vasoconstricting neuropeptide tyrosine is the predominant neuropeptide associated with perivascular nerves. In infants with pulmonary hypertension, respiratory unit arteries are prematurely innervated by sympathetic-like nerve fibers. In both the normal and the pulmonary hypertensive lung, sympathetic innervation seems to develop in parallel with an increase in the amount of smooth muscle in peripheral arteries.[119]

FACTORS CONTROLLING LUNG MORPHOGENESIS

Lung morphogenesis is controlled by numerous factors, including transcription factors, growth factors, extracellular matrix molecules, integrins, and intercellular adhesion molecules. These factors can also interact on gene networks responsible for lung branching morphogenesis, septation, vascularization, and response to mechanical stress. A schematic representation of some of the numerous molecular factors involved in the different stages of lung development is given in Figure 3-10.[92]

Lung Branching Morphogenesis

Epithelium-mesenchymal interactions play a key role in regulating lung growth and branching pattern. Transplantation

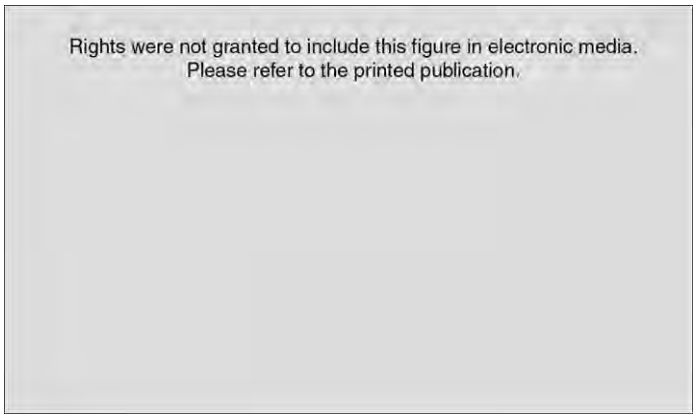

Figure 3-10 Examples of interactions between transcription factors, growth factors, and components of extracellular matrix. (1) Overexpression of Foxa2 decreases VEGF expression; (2) lungs of mice with deleted RAR? have reduced elastin content; (3) Foxa2 modulates expression of TTF-1; (4) exogenously added FGF2 decreases elastin transcription in cultured type II cells; (5) TGFβ hampers activity of TTF-1 and Foxa2 in cytoplasm; (6) blockade of TGFβ signaling pathway favors response to EGF and PDGF activity; (7) integrins modulate transcription factor signaling; (8) proteoglycans form tertiary structures with growth factors, modulating their activity; (9) fibronectin interferes with cell-cell and cell-matrix adhesion properties. (From Roth-Kleiner M, Post M: Similarities and dissimilarities of branching and septation during lung development. Pediatr Pulmonol 40:113-134, 2005.)

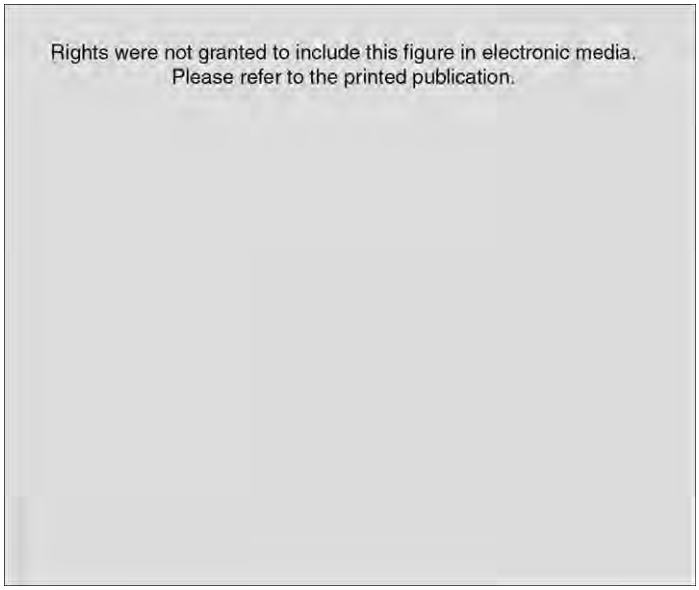

Figure 3-11 Branching morphogenesis in lung. **A,** FGF10 is the driving force for outgrowth of bronchial endbuds. Penetration of surrounding tissue is facilitated by thinned-out basal membrane and increased expression of MMP2. FGF10 stimulates Shh production in epithelium of endbud. **B,** Increasing expression of Shh and BMP4 lateralizes FGF10 activity, which induces outgrowth of new endbuds. At branch point, increased epithelial expression of fibronectin and mesenchymal expression of laminin5 enhance cleft formation. (From Roth-Kleiner M, Post M: Similarities and dissimilarities of branching and septation during lung development. Pediatr Pulmonol 40:113-134, 2005.)

experiments have shown that the mesenchyme is directly responsible for the branching pattern in the lung.[120] The branching process depends on interactions between cell-substrate adhesion molecules and underlying extracellular matrix (ECM) and intercellular adhesion molecules.[121,122] Epidermal growth factor may be an important mediator of this process.[123] The mechanisms responsible for the mesenchymal influences have not been fully elucidated but have been shown to depend on the synthesis of proteoglycans, collagen, laminin, and fibronectin.[124] Cellular attachment to the ECM is mediated by integrin receptors.[124] Branching is decreased in the presence of monoclonal antibodies against integrin receptors.[125] Integrin receptors appear to interact with fibronectin within the clefts that mark the branching points.[126] Transforming growth factor-β_1 co-localizes with fibronectin within these clefts and may regulate fibronectin deposition, thereby indirectly affecting branch formation.[127]

Reduced pulmonary branching was demonstrated in chimeric GATA-6 null mice.[127,128] Thyroid transcription factor-1 (TTF-1) expression occurs in the epithelial cells of dividing lung buds and decreases with advancing gestation.[129] Early branching is impaired in TTF-1 knockout mice.[130] Foxa2 overexpression impairs airway branching, whereas deletion of this factor does not affect lung morphogenesis.[131] Retinoic acid (RA) exerts key effects in regulating heterodimerized transcription factors, retinoic acid receptors (RAR family), and retinoic X receptors (RXR family). RA signaling is active early in lung morphogenesis,[132] and its absence leads to lung agenesis or hypoplasia.[133,134] Fibroblast growth factors (FGF) are expressed in the developing lung. FGF-10 signaling via its receptor (FGFR-2) is crucial to early lung development and branching.[135] In addition to FGF-10, sonic hedgehog (Shh) is essential for early branching and is markedly expressed by the epithelium at the tips of the endbuds.[136] Shh-null mice exhibit reduced lung epithelial branching early in development.[137] Vascular endothelial growth factor (VEGF), which plays a key role in vasculogenesis and angiogenesis, is also expressed in airway epithelial cells and involved in branching morphogenesis.[138,139] Transforming growth factor-beta (TGFβ) is another group of growth factors that is crucial to lung development. Both TGFβ1 and TGFβ2 inhibit airway branching in vitro, whereas inhibition of the TGFβ signaling pathway by downregulation of the receptor TGFβR-II expression stimulates lung branching in vitro.[140,141] This effect of TGFβ is indirect, being mediated by the transcription factors Smad proteins, interactions with matrix proteins and related enzymes, and effects on TTF-1 and Foxa2.[142-144]

The ECM is under the control of the matrix metalloproteases, which are proteolytic enzymes. Inhibition of major ECM molecules (elastin, fibronectin, proteoglycan, laminin, and integrin) leads to branching failure, as does overexpression of matrix metalloproteases.[145-151]

Lung Septation and Growth of the Peripheral Lung

Septation is the formation of secondary septa that divide primary saccules into smaller units, the alveoli. Septation takes place during the alveolar stage of lung development. It is initiated by interactions between smooth muscle cells, elastic fibers, and collagen, which attract the capillary layer of the primary septum (Fig. 3-11A). Thus, the secondary septum contains a double capillary layer (see Fig. 3-11B), which matures into a thin definitive septum containing a single capillary layer (Fig. 3-12). Septation, similar to branch-

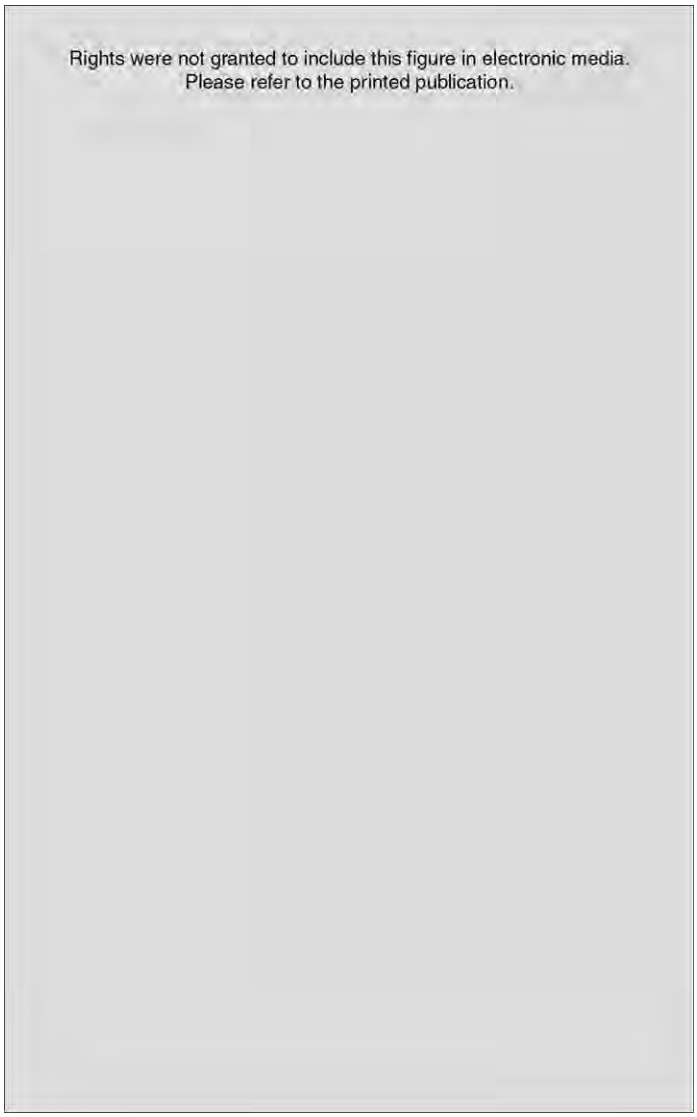

Figure 3-12 Alveolar septal formation and maturation. **A,** Primary septum with double capillary layer. At sites of future secondary septal formation, PDGF-A–positive myofibroblast precursors start to produce ECM proteins elastin and tenascin-C. **B,** Secondary septum is growing into airspace, with elastic fibers as driving force. Further ECM proteins like decorin and chondroitin sulfates are predominantly deposited in septal tips (small rhombs). Expression of matrix metalloproteinases-2/9 *(small dots)* increases after formation of secondary septum. **C,** Mature secondary septum with single layer of capillary and thinned interstitial tissue. (From Roth-Kleiner M, Post M: Similarities and dissimilarities of branching and septation during lung development. Pediatr Pulmonol 40:113-134, 2005.)

ing, is a complex process that is controlled by myriad transcription and growth factors, as well as by numerous interactions involving the mesenchyme and ECM components.[152] Transcription factor GATA-6 overexpression impairs alveolization, probably by altering the differentiation of type I and type II epithelial cells.[153] Similarly, TTF-1 overexpression decreases alveolization and impairs differentiation of type I and type II cells.[154] Retinoic acid (RA) is crucial for the septation process. It is found in alveolar wall fibroblasts, which produce elastin at the sites of outgrowth of secondary septa.[155-156] Alveolization is decreased in RARγ or RAR∝ null mutant mice.[157,158] On the contrary, RARβ signaling inhibits alveolar formation in the early postnatal period. Vitamin A deficiency in premature neonates is considered a risk factor for developing bronchopulmonary dysplasia, which is marked by decreased alveolization.[159] On the other hand, vitamin A supplementation in premature neonates was beneficial in improving lung development and preventing bronchopulmonary dysplasia.[160]

Similar to branching, alveologenesis is influenced by growth factors. FGF signaling via receptors FRFR-3 and FGFR-4 affects alveolization, chiefly via changes in elastin homeostasis.[161] Similarly, PDGF-A and receptor PDGF-R∝ play crucial roles in alveolization via the regulation of tropoelastin.[162] Inhibiting or blocking VEGF signaling reduces both alveolization and pulmonary vascularization.[163,164] Overexpression of TGF∝, whose signaling is mediated through the EGF receptor, impairs secondary septation by affecting metalloproteinase expression and elastin homeostasis.[165,166] Matrix metalloproteinases, particularly MMP-2 and MMP-9, play an important role in septation by contributing to basement membrane thinning and interstitial tissue reduction during this phase of alveolar maturation.[167] Elastin is the key ECM component during septation because it is considered to drive alveogenesis.[155] Its precursor, tropoelastin, is highly expressed by myofibroblasts in the tips of secondary septa,[168] and the tropoelastin production peak coincides with the septation peak in rats.[169] Elastin is essential to alveolar septation and is markedly increased in infants and animals with bronchopulmonary dysplasia.[170]

Lung Vessel Development

Lung vessels develop through at least two concurrent processes: vasculogenesis, or in situ formation of new vessels from angioblasts; and angiogenesis, in which new vessels sprout from existing vessels. Intussusception is another pattern of vessel development, in which an existing capillary divides in two via the formation and growth of transcapillary tissue pillars.[171]

A recent study showed that distinct endothelial cell subpopulations were observed early in the developing lung and possibly arose from distinct genetic lineages.[172] These findings are beginning to suggest explanations for the functional heterogeneity of pulmonary vascular cells in both health and disease.[170,173,174] VEGF is involved in angiogenesis and vasculogenesis and has been found in epithelial cells.[175,176] VEGF receptors are expressed in the endothelium from 38 days of gestation in humans. Recent studies demonstrated reciprocal control between blood vessels and airways: thus, VEGF overexpression disrupted the assembly of the vascular network and stopped the airway branching process.[177] Another tyrosine kinase receptor, Tie-2, is expressed on endothelial cells, binds to angiopoietin, and is involved in vessel assembly and vascular network stabilization.[178,179]

Endothelial nitric oxide synthase is expressed by the lung vessel endothelium throughout development. Nitric oxide stimulates endothelial proliferation, migration, and tube formation and inhibits apoptosis.[180] The control of smooth muscle cell differentiation in vessel walls is regulated in part by angiopoietin and the Tie-2 receptor[181] and in part by TGFβ.[182] Another important regulator of vasculogenesis and angiogenesis during lung development is oxygen

tension.[183] Hypoxia affects many of the genes that regulate molecular vascular development (e.g., VEGF, Flk-1, Tie-2, PDGFb, bFGF, iNOS, and endothelins).[184,185]

Role of Apoptosis in Lung Development

Apoptosis occurs throughout lung development (Table 3-1).[186,187] Apoptosis shifts from the mesenchymal tissue layer during early development to both the epithelial and mesenchymal tissue layers during the canalicular stage of development.[188-189] Increased apoptosis of alveolar epithelial type II cells occurs concomitantly with decreased cell prolifera-tion in late gestation.[190] Throughout lung development, apoptosis occurs in the peripheral mesenchyme, at the site of epithelial branching morphogenesis and interstitial tissue remodeling.[191] Apoptosis is mediated by proapoptotic factors (e.g., TGFβ)[192] and antiapoptotic factors (e.g., IGF-1 and nitric oxide).[193,194] During gestation, fetal breathing movements and fluid secretion are essential to induce cell proliferation, which must be regulated by apoptosis.[195] After birth, apoptosis plays a major role in alveolar development and maturation.[196,197] Normal lung development is associated with apoptosis, which counteracts proliferation. In premature neonates, mechanical ventilation (which induces mechanical stress) may impair the balance between proliferation and apoptosis.

Developmental Physiology

The mechanical properties of the passive respiratory system (i.e., the chest wall and lung plus the extra- and intrathoracic airways) and the action of respiratory muscles determine the resting volume of the lung, the breathing pattern, and ventilation. Intrathoracic and extrathoracic receptors, bronchomotor tone, vagal reflexes, and modifications in respiratory muscle activity can dramatically alter baseline breathing activity.[198] In the newborn, a high ratio between chest and lung compliance (C_W/C_L ratio) decreases resting volume (VR) and transpulmonary pressure, facilitating alveolar collapse and promoting a decline in C_L. During active breathing, vagal receptors sense changes in lung volume and can elicit reflexes that dynamically modify respiratory mechanics by altering the breathing pattern, bronchomotor tone, and respiratory muscle tone.[198,199] Mechanisms that serve to avoid lung collapse in the newborn include an increased rate of vagally mediated augmented breaths and a dynamic increase of the functional residual capacity (FRC) via prolongation of the expiratory time constant of the respiratory system (t_{RS}). The t_{RS} increase results from postinspiratory activity of the inspiratory muscles, which stiffens the chest wall, or from an increase in laryngeal resistance. With increasing age, there is a transition from active to passive maintenance of FRC via stiffening of the chest wall, which becomes more able to resist the inward recoil of the lung.[199]

FUNCTIONAL RESIDUAL CAPACITY

During breathing in the resting state, the volume of gas in the lungs at FRC represents the lung oxygen stores. The FRC is determined by the static passive balance of forces between the lung and the chest wall. In infants, the outward recoil of the chest wall is very small and the inward recoil of the lung is slightly less than in adults.[58] Consequently, the static passive balance of forces dictates a very low ratio of FRC over total lung capacity (TLC) in infants, which would be inadequate for gas exchange. Measured FRC and estimated TLC values in infants[200] indicate that the dynamic FRC/TLC ratio is about 40%, a value similar to that in supine adults. Thus, the dynamic end-expiratory volume is very likely to be substantially greater than the passively determined FRC in newborns and infants with little outward recoil of the chest wall.[201]

Infants, in contrast to adults, terminate expiration at substantial flow rates (Fig. 3-13).[202] This suggests active interruption of relaxed expiration. To slow expiration and to maintain FRC, the newborn can use two active mechanisms, namely, postinspiratory activity of the diaphragm[203,204] and laryngeal narrowing during expiration,[205] the extreme form of which is the grunting observed in newborns with respiratory distress syndrome. Laryngeal braking of expiration has

Table 3-1
Summarized Role of Apoptosis During Lung Development

Stage	Major Events	Role of Apoptosis
Embryonic	Lung anlage appears, branching morphogenesis starts, with extensive proliferation of epithelial and mesenchymal cells	Apoptosis in mesenchyme around branch points and regions of new lung bud formation
	Few pulmonary vascular connections	No epithelial apoptosis
Pseudoglandular	Bronchial airway tree establishment by dichotomous branching	Apoptosis of interstitial tissue contributes to mesenchymal involution
	Airways are lined with thick epithelium while epithelial cells differentiate	No epithelial cell apoptosis
Canalicular	Respiratory bronchioli appear, decrease of interstitial tissue, airway widening	Apoptosis of interstitial tissue contributes to mesenchymal involution and thinning of the alveolar septa
	Differentiation of type II into type I cells	Increase in apoptosis of epithelial cells as cell proliferation decreases
	Rapid increase of vascular network	
Saccular	Terminal airways widen to form saccules	Increase in epithelial cell apoptosis
	Thinning of interstitium between airspaces	
	Vascular network expands	
Alveolar	Extensive alveolar septation	Transient increase in apoptosis at birth
Microvascular	Double capillary layer in alveolar septa is reduced to a single layer	Final increase in apoptosis to remove excess cells

Data from Del Riccio V, van Tuyl M, Post M: Apoptosis in lung development and neonatal lung injury. Pediatr Res 55:183-189, 2004.

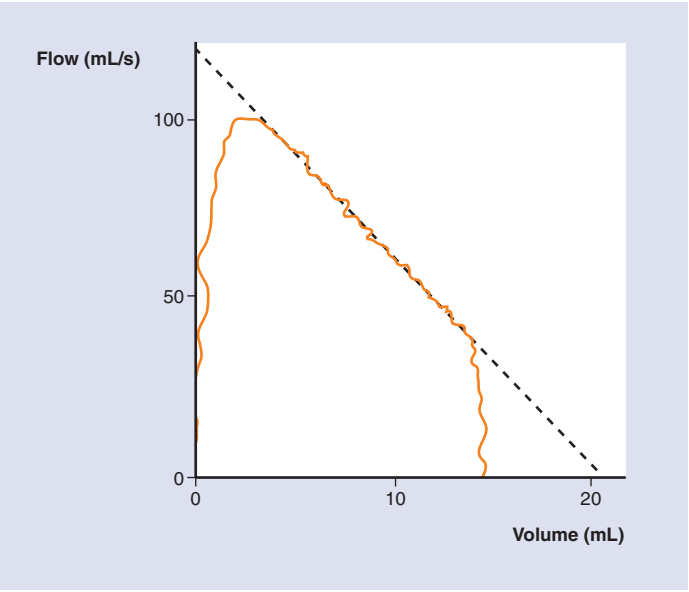

Figure 3-13 Passive flow-volume curve in an infant, showing abrupt inspiration substantially above passive FRC. (From Le Souëf PN, England SJ, Bryan AC: Passive respiratory mechanics in newborns and children. Am Rev Respir Dis 129:552-556, 1984.)

an effect similar to that of autopositive end-expiratory pressure, which increases FRC. FRC would be expected to fall during REM sleep. It has been firmly established that expiratory airflow braking mechanisms are disabled during REM sleep in preterm infants. Postinspiratory diaphragmatic activity is reduced during REM sleep, and animal studies have demonstrated that expiratory laryngeal adduction is substantially diminished during REM sleep.[205] Furthermore, flow studies in human preterm newborns show clear evidence of expiratory braking during non-REM sleep but suggest passive airflow without expiratory braking during REM sleep.[206] The transition from dynamically maintained to passively determined end-expiratory lung volume is believed to occur between 6 and 12 months of age.[207]

MECHANICAL PROPERTIES OF THE LUNG

Elastic Properties

Changes in pressure-volume relationships have been related to changes in the amount, distribution, and structure of elastin and collagen in the growing rat lung.[208] In humans, little is known about the development of the elastic properties of the lung. One study showed that the true elastin content of the lung increased up to a plateau during the first 6 months of life.[209] The pressure-volume relationship has been measured in excised lungs of infants and a few children[210-212] and in vivo in older children using esophageal balloons to measure transpulmonary pressure. In excised preparations, lung pressures of up to 30 cm H_2O were found; in vivo, the TLC is taken to represent full inflation. In excised lungs, when lung volume is expressed as a fraction of the lung volume at 30 cm H_2O, there is a marked change in the overall shape of the pressure-volume curve within the age range examined.[213] The younger lung holds a greater fraction of this volume at low pressure than the older lung. The in vivo quasistatic pressure-volume curves during deflation show that lung recoil increases with age in children older than 6 years.[214]

Studies in animals and in humans have shown that antenatal and postnatal environmental factors modify the elastic properties of the lungs. Protein malnutrition impairs elastin deposition in the lungs and is associated with an upward and leftward shift in the pressure-volume curves.[215] Total respiratory system compliance is higher in neonates born to mothers who live at high altitudes than in those born to mothers who live at sea level.[216]

Compliance, Resistance, and Time Constant of the Total Respiratory System

Compliance of the respiratory system increases during the first year of life, by an estimated 152%.[217] The rate of increase in lung compliance exceeds that of chest wall compliance and accounts in large part for the increase in compliance of the respiratory system during the first year of life. During the same period, the total resistance of the respiratory system decreases by 42%. The considerably smaller decrease in resistance compared to compliance is in line with anatomic findings showing that substantial alveolar formation occurs during the first year of life, whereas the full contingent of conducting airways is present at birth. In human infants, the expiratory time constant of the total respiratory system increases during the first year of life, up to a plateau.[218-220] This change may reflect the increase in compliance caused by rapid alveolar growth. After 1 year of age, the relative stability of this constant suggests that changes in compliance and resistance are balanced after infancy.

Flow-Resistive Properties

During postnatal life, airway growth leads not only to increases in the radius and length of the airways, but also to changes in the mechanical properties of the airway walls. Airway compliance is greater in infants and young children than in adults. In excised preparations, the newborn trachea is twice as compliant as the adult trachea.[222] Radiographic studies in normal infants have shown variations of 20% to 50% in the anteroposterior diameter of the intrathoracic trachea during exertion.[223] This may be related to the smaller amount of cartilage.[111]

Airway, pulmonary, and respiratory resistances have been measured in newborns, infants, and children 5 years of age and older.[215] Airway resistance falls 10-fold on average from full term to adolescence. The inverse of airway resistance, airway conductance, corrected for differences in upper airway resistance and divided by the lung volume at the time of measurement (specific airway conductance) decreases during the first years of life, then remains constant after 5 years of age.[224,225] This profile of change in specific airway conductance strongly suggests that the airways may be well formed and relatively large in newborns but that lung volume may increase disproportionately with airway size during early postnatal life.

The total resistance of the respiratory system is generated by the airways, lung tissue, and chest wall. Little is known about changes in the lung and chest wall components of total resistance. A recent study investigated growth-related changes in the viscoelastic properties of the total respiratory system

by measuring pressure variations after airway occlusion in paralyzed patients aged 3 weeks to 15 years.[226] This measure decreased during the first 2 years of life and increased after age 5, suggesting greater influence of the lung tissue during early postnatal life and greater influence of chest wall viscoelastic properties at older ages. More recently, airway and respiratory tissue mechanics were assessed in normal infants aged 7 weeks to 2 years.[227] Both the forced oscillation technique and the raised volume rapid thoracic compression technique were used to investigate the tissue and airway components of respiratory resistance. Both of these components exhibited a decreasing quadratic relation with increasing length. The maximum volume expired at 0.5 second (FEV0.5) showed an increasing cubic relation with length.

The distribution of resistance along the central and peripheral airways has been studied in excised lungs from infants, children, and adults.[228] These data suggest that the peripheral airways may be disproportionately narrow in children younger than 5 years of age. Disproportionately low peripheral airway conductance values in infants compared to older children should be accompanied by low maximum expiratory flows at low lung volumes. However, relatively high flows at low lung volumes were found in healthy anesthetized infants and children.[229] Furthermore, the maximum expiratory flow at FRC measured from partial expiratory flow-volume curves was higher in neonates and similar in infants to those reported in children and adults.[230,231] Thus, physiologic data do not support the hypothesis suggested by pathologic findings that peripheral airways are disproportionately smaller in infants than in adults.

Abnormal growth of conducting airways (e.g., in lung hypoplasia) is associated with low airway resistance values during infancy.[232] Conceivably, dysregulation during the processes involved in morphogenesis (see Fetal Period in the Developmental Anatomy section) may be responsible for the substantial interindividual variability in postnatal indexes of pulmonary flow-resistive properties.

Postmortem evaluations of airway size in preterm infants show that airway size is normally related to postconceptional age.[111] However, data obtained during childhood suggest that premature birth is associated with impaired airway growth.[233]

The maturation of respiratory mechanics differs between boys and girls. Mixed gender effects were reported in a longitudinal study of 541 infants.[234] Females had significantly lower initial resistance of the respiratory system values (Rrs) than males, but the Rrs decline with increasing length was slower in females. In contrast, although females had lower initial compliance of the respiratory system (Crs) values and a slower Crs decline than males, these differences were not statistically significant. Normal values of respiratory resistance obtained by the interrupter technique (Rint) in preschool children, were reported recently (Fig. 3-14).[235]

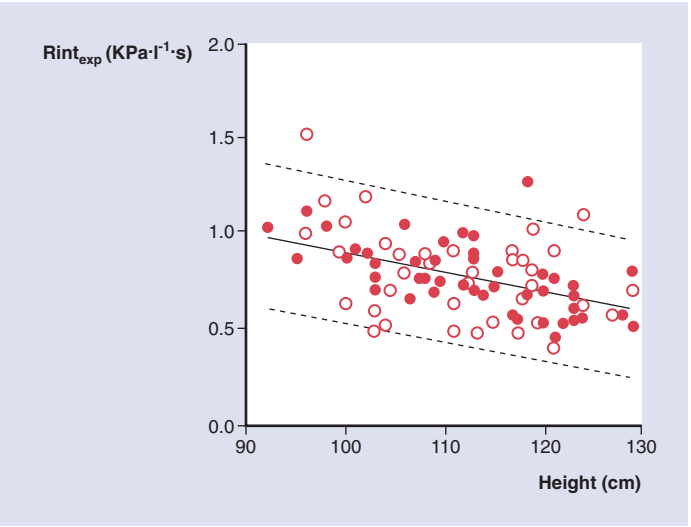

Figure 3-14 Relation between respiratory resistance obtained by the interrupter technique (Rint exp) and length in preschool normal children. (From Beydon N, Amsallem F, Bellet M, et al: Pre/postbronchodilator resistance values in healthy young children. Am J Respir Crit Care Med 165:1388-1394, 2002.)

Gas Exchange

In the newborn, the partial pressure of oxygen in arterial blood (PaO_2) is approximately 70 mm Hg.[236] The PaO_2 in arterialized blood samples rises rapidly until 2 years of age, then slowly until 8 years of age.[237,238] Thereafter, PaO_2 values remain stable and similar to those seen in adults.[239]

The lung volume at which some of the intrapulmonary airways are closed (closing volume, an index of susceptibility to hypoxemia) decreases with age.[240,241] In infants and young children, the closing capacity (closing volume plus residual volume) is sometimes greater than the FRC, and some areas of the lung may be closed throughout part or all of the tidal volume, resulting in impaired gas exchange.

Mechanisms that improve pulmonary gas exchange during growth have been investigated more extensively in piglets than in humans. A study that used the multiple inert gas technique in awake growing piglets showed that low PaO_2 values resulted from both ventilation-perfusion mismatch and limited oxygen diffusion.[242] Oxygen diffusion impairment in piglets was related to an imbalance between oxygen diffusion and oxygen perfusion.[243] This suggests that the capillary transit time in newborns may be too short to achieve the alveolar-capillary diffusion equilibrium and, therefore, that newborns may have little pulmonary vascular reserve for gas exchange. In newborns, the ratio of pulmonary diffusing capacity to FRC is close to that in 11- to 13-year-old boys during submaximal exercise.[244]

The fairly low PaO_2 values in infants and young children are close to the steep part of the oxygen-hemoglobin dissociation curve. Any further decrease in PaO_2 can induce severe oxygen desaturation, for instance during sleep apneas (see Respiratory Control section). Using new techniques for noninvasive measurements of oxygen saturation, data have been obtained in healthy full-term infants and children during sleep.[245-247]

RESPIRATORY CONTROL

Developmental Aspects

Breathing in mammals relies on a neuronal respiratory network located within the brain stem,[248-249] which receives influences from suprapontine structures involved in sleep-wake, thermoregulation, and arousal processing.[250] Evolving concepts

regarding respiratory control development have stemmed from new knowledge—most notably in the areas of plasticity and genetics.[251] Environmental insults may alter the developmental programming of the neuronal respiratory network, leading to abnormalities that may persist in infancy and perhaps adulthood. Recent studies in newborn mice with targeted gene deletions showed links between the expression of specific genes and the development of individual components of respiratory control.[252] Mechanisms underlying respiratory control immaturity in newborns remain incompletely understood. Immaturity affects all facets of respiratory control including breathing rhythmicity and its modulation by suprapontine influences and by afferents from central and peripheral chemoreceptors and other sources. Because of this immaturity, infants, particularly those born prematurely, are vulnerable to homeostasis disruption by apneas. Respiratory control immaturity may contribute to the mechanisms that lead to SIDS,[253] especially in preterm infants.[254]

The brain stem neural network includes three groups of neurons[248]: (1) the dorsal respiratory group containing the tractus solitarius, the first central relay of the arterial chemoreflex; (2) the ventral respiratory group with the pre-Bötzinger complex (preBötzC), which contains part of the rhythm-generating neurons; and (3) the pontine respiratory group. During early embryonic development, shortly after neural tube closure, the hindbrain is temporarily partitioned into rhombomeres along an anterior-posterior axis. This process takes place during the second half of the first month of pregnancy in humans. At the end of the segmentation period, a primordial regular rhythm can be recorded in isolated hindbrain preparations from mice.[255] Loss of genes responsible for hindbrain segmentation during early embryonic development, such as *Krox20,* leads to severe breathing instability at birth that usually results in death.[255-256] *Krox20* deletion leads to rostral medulla hypoplasia and loss of neurons of the reticular formation closed to the noradrenergic groups of neurons A5 (Fig. 3-15).[256,257]

Later during development, each of the neuronal populations exhibiting specialized functions in the brain stem respiratory network exhibits specific developmental programming and gene expression profiles, which appear to be controlled by a set of transcription factors that are specific of particular types of neurons participating in the generation and modulation of respiratory rhythm at birth (see Fig. 3-15).[257] It has been shown that the transcription factor *MafB* is a marker for a subpopulation of preBötzC neurons in null mutant *MafB* newborn mice that die from central apneas at birth.[258] Development of the noradrenergic nuclei is governed by a cascade of transcription factors that includes *Phox2b, Phox2a,* and *Mash-1* in the locus coeruleus (A6). *Phox2b* is also expressed

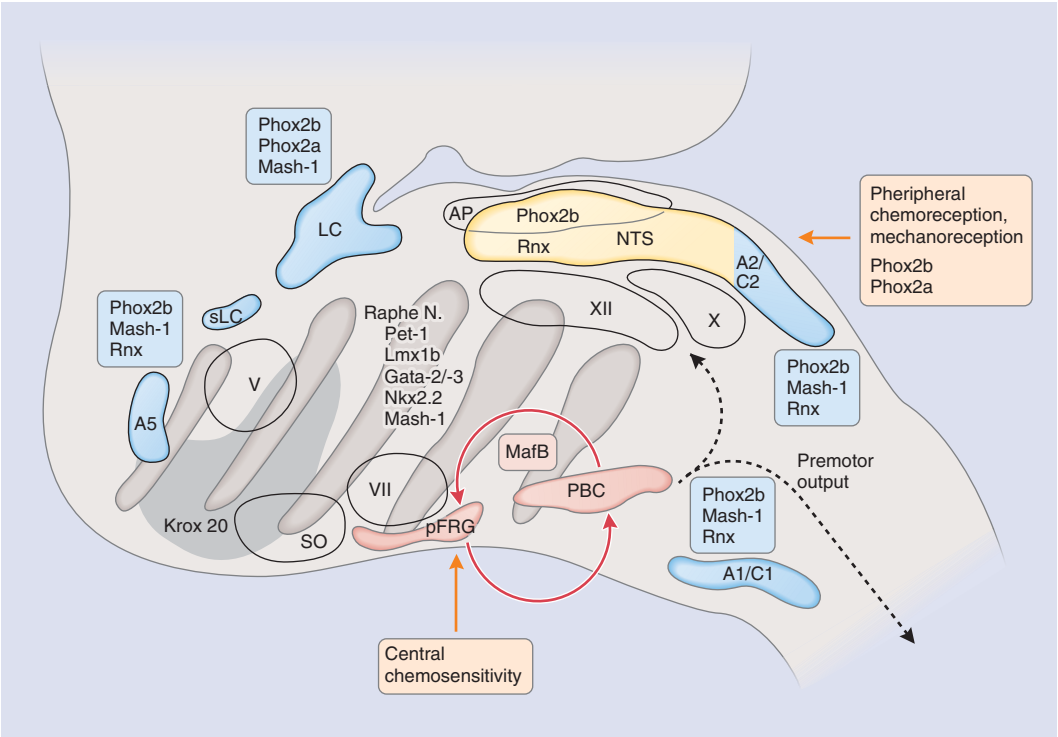

Figure 3-15 Transcription factor requirement in the development of respiratory hindbrain neurons. Schematic representation of respiratory groups of neurons in the sagittal view of the brain stem (forebrain, *left;* spinal cord, *right*). Rhythmogenic group of neurons in red (PBC, preBötzinger complex; pFRG, parafacial respiratory group). (Nor)adrenergic group of neurons in *blue* (A1/C1; A2/C2; A5; A6, locus coeruleus; sLC, sub-locus coeruleus). Nucleus tractus solitarius (NTS), in *light orange;* Raphe nuclei (Raphe N.) in *brown hatching.* (AP, area postrema; SO, superior olive; V, VII, X, XII, motor nuclei). Central and peripheral chemoreception represented by *orange arrows*. Transcription factors required for correct development of each group of neurons are indicated next to the affected groups. *Krox20* deletion leads to rostral medulla hypoplasia and the loss of neurons of the reticular formation close to the A5. (From Blanchi B, Sieweke MH: Mutations of brainstem transcription factors and central respiratory disorders. Trends Mol Med 11:23-30, 2005.)

in the NTS. Differentiation of the serotoninergic neurons of the brain stem is controlled by transcription factors such as *Mash-1*. Studies of the respiratory phenotype of mutant newborn mice have helped to understand how disruption of genes such as *Phoxa*, *Phox2b*, or *Mash-1* can alter one or more components of respiratory control.[259-261] Furthermore, transcription factor mutations were identified recently in human developmental central respiratory disorders. *PHOX2B* is the disease-causing gene of congenital central alveolar hypoventilation.[262] Mutations or polymorphisms of genes involved in the development of modulatory neurons have been described in victims of SIDS.[263] The development and plasticity of the brain stem respiratory network also depends on neurotrophic factors, such as brain-derived neurotrophic factor (BDNF).[264-265]

Neurotransmitters that mediate synaptic communication exhibit dramatic changes during fetal and postnatal life.[266] Perinatal surges occur for some of them, including the excitatory amino acid glutamate.[266] Postnatal developmental changes in brain stem neurotransmitters were described recently in rats.[267] A dramatic shift occurs on postnatal day 12, with drops in glutamate and its *N*-methyl-D-aspartate (NMDA) receptors and sharp rises in receptors for the inhibitory neurotransmitter GABA. The transient predominance of inhibitory over excitatory neurotransmission during this period may increase the risk of respiratory-control failure in response to stress. Such neurochemical changes may contribute to the underlying mechanisms of SIDS during a critical period of vulnerability. Furthermore, prenatal and postnatal stress may alter the programming of neurotransmitter expression, thereby leading to further respiratory control vulnerability.

Pattern of Breathing, Apneas, and Gasping

Fetal breathing has been chiefly investigated in sheep. During early fetal life, the sheep fetus shows regular continuous breathing.[268] With differentiation of the electrocortigram at about 120 days of gestation (term being 147 days), the fetus exhibits an irregular breathing pattern with apneas. Breathing movements occur during a behavioral state akin to REM sleep in the newborn[269] and are governed by the behavioral respiratory control system rather than by the metabolic respiratory control system.[270] During high-voltage electrocortical activity, fetal breathing movements are inhibited and near-total apnea occurs.[271] Prenatal maturation of respiratory control allows generation of rhythm-driving ventilation that can adjust to homeostatic demands after birth.[272] At birth, respiratory control switches from discontinuous to continuous. Figure 3-16 shows changes in the relative importance of various respiratory drive mechanisms at birth, in newborns, and in infants.[273]

Over the last decades, many studies have shown that periodic breathing and apnea are common respiratory patterns that resemble fetal breathing in premature infants. These respiratory patterns are inversely related to gestational age, with the youngest infants having the most significant apneic events. With advancing postconceptional age, apneas decrease in frequency.[274-276] However, apneas of prematurity can persist beyond full term in very preterm infants.[277] Central, mixed, or obstructive apneas occur in preterm

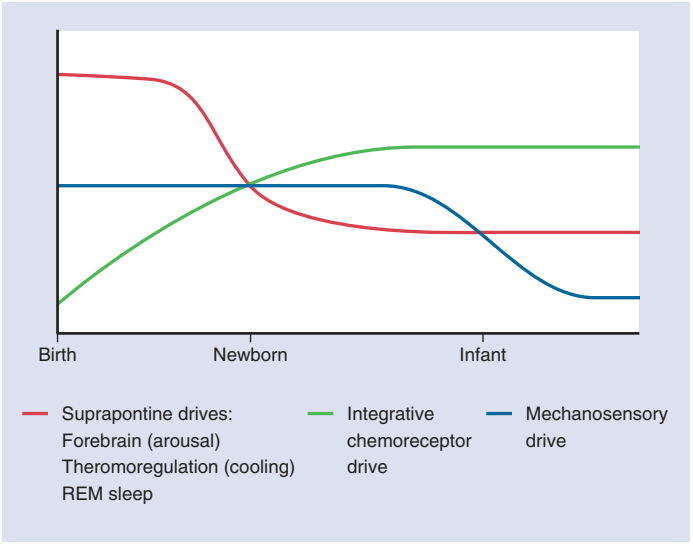

Figure 3-16 Relative importance of different respiratory drive mechanisms after birth. (From Lagercrantz H, et al. In Crystal RG, West J [eds]: The Lung: Scientific Foundations. New York, Raven, 1991, pp 1711-1722.)

infants. Studies in preterm lambs have shown that upper airway closure is an important feature not only of mixed or obstructive apneas, but also of central apneas, and involves both passive pharyngeal collapse and active glottal closure.[278] A beneficial consequence of glottal closure during central apneas is maintenance of a high lung volume, which increases alveolar O_2 stores and limits arterial O_2 desaturation. Bedside experience shows that the severity of hypoxemia after apnea is not closely related to apnea duration: thus, even brief apneas can cause profound hypoxemia in some infants. Periodic breathing has often been considered benign in premature infants. However, data are now available showing that periodic breathing frequently precedes apneas[279] and may be associated with upper airway obstruction[280] and with significant desaturation in some preterm infants. Repeated hypoxemia due to severe apneas can induce major neurologic disabilities including neurocognitive impairments.[281]

Reflexes originating in the laryngeal chemoreceptors, including laryngeal chemoreflexes (see upper airway section) and non-nutritive swallowing, contribute to the occurrence of apnea, bradycardia, and hypoxemia in early life. Immaturity of the preterm newborn impairs the coordination between swallowing and breathing. This may lead to apnea, especially in preterm infants. Non-nutritive swallowing has been reported with central, obstructive, or mixed apneas in human newborn.[282] In preterm lambs, apneas associated with non-nutritive swallowing occur chiefly during non-REM sleep.[283]

In full term infants, apneas are chiefly central and of short duration. The frequency of apneas decreases with postnatal age. Mixed and obstructive apneas are rare in term infants. Table 3-2 shows indices of mixed and/or obstructive apneas during the first 6 months of life in term infants.[284-287] One study conducted in more than 1000 infants between 2 and 28 weeks of postnatal age showed that obstructive and mixed apneas were significantly more common between 2 and 7 postnatal weeks than in any other age group and that obstruc-

Table 3-2
Indices of Mixed and/or Obstructive Apneas in Healthy Infants During the First 6 Months of Life

Reference	Type of Apneas	Duration of Apnea	Mean Index (age in parentheses)		
285	M and OA	≤10 sec	1.04 (6 wk)	0.40 (12 wk)	0.20 (24 wk)
		>10 sec	0.07 (6 wk)	0.02 (12 wk)	0,00 (24 wk)
286	OA	>6 sec	0.05 ± 1 (2-5 wk)	0.00 (6-13 wk)	—
287	M and OA	≤10 sec	0.63 (4 wk)	0.57 (12 wk)	0.22 (24 wk)
288	M and OA	≤10 sec	0.05 (0.1-0.7) (4-8 wk)	0.5 (0.1-2) (9-19 wk)	—

Index, number of apneas per hour of sleep; MA, mixed apnea, OA, obstructive apnea; sec, second; wk, week.

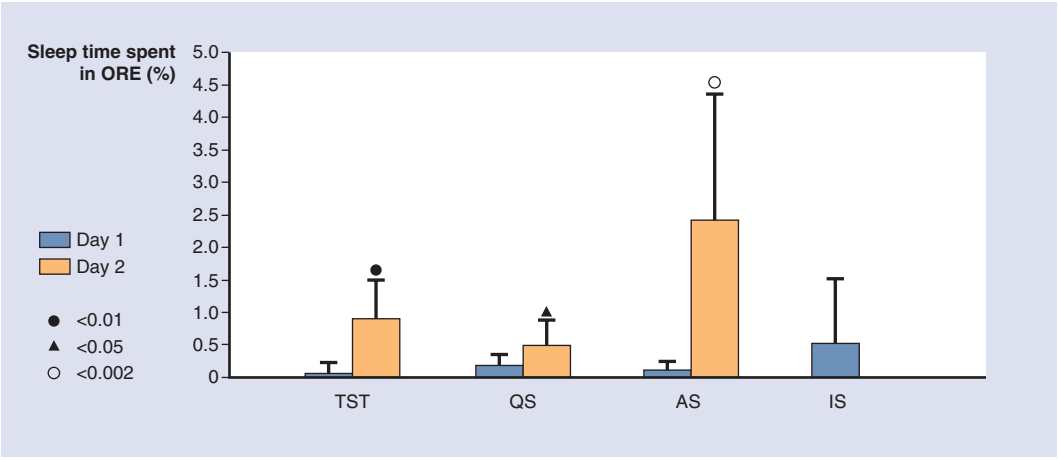

Figure 3-17 Sleep spent in an obstructive respiratory event (ORE) during total sleep time (TST), quiet (non-REM) sleep (QS), active (REM) sleep (AS), and indeterminate sleep (IS). The values are expressed as percentages. Day 1 is the baseline; day 2 figures were taken after a sleep deprivation recovery nap. *Bars* indicate the standard deviation. Percentage of time spent in an obstructive respiratory event significantly increased after sleep deprivation during total sleep time (full circle, $P < 0.01$), quiet sleep *(triangle, $P < 0.05$)*, and active sleep *(open circle, $P < 0.002$)*. (Redrawn from Canet E, Gaultier CL, D'Allest AM, Dehan M: Effect of sleep deprivation on respiratory events during sleep in healthy infants. J Appl Physiol 66:1158-1163, 1989.)

tive apneas were significantly more frequent in boys than in girls.[287]

The frequency of apneas during early life is influenced by sleep state. Apneas are more common in REM sleep than in non-REM sleep in both preterm and term infants.[276] The greater instability of REM sleep compared to non-REM sleep during early life may result from overall immaturity of brain stem respiratory network, as well as from phasic inhibitory mechanisms inherent to REM sleep. Frequent apneas during REM sleep may reflect exaggeration of normal phasic inhibitory-excitatory central mechanisms that occur during this sleep state. Irregular phasic respiratory patterns of REM sleep occur in synchrony with other brain stem phasic activities, such as rapid eye movements.[288]

A number of factors can suddenly increase the number and duration of apneas, thereby compromising infant's homeostasis. Medications such as phenothiazine increase the number of apneas, especially of the obstructive type.[289] The prone position is associated with a higher frequency of central and obstructive apneas.[290] An increase in body temperature exacerbates breathing instability, inducing higher rates of periodic breathing episodes and central apneas in REM sleep but not in non-REM sleep.[291,292] Brief sleep deprivation increases the number of short obstructive respiratory events (apneas and hypopnea) in REM sleep (Fig. 3-17).[293] In infants whose homeostasis is disturbed, the risk of increased respiratory instability appears greater in REM than in non-REM sleep.[289,291,293]

Prenatal insults such as maternal smoking lead to increased postnatal breathing instability. Increases in both the frequency and duration of obstructive apneas have been reported in babies born to mothers who smoked during pregnancy.[294] Infants who subsequently died of SIDS experienced higher rates of obstructive and mixed apneas than did healthy infants[295] and frequent obstructive apneas may predispose infants to SIDS.[253] A study of apnea monitor recordings from infants who died at home indicated that complete airway obstruction occurred immediately before death.[253]

Recovery from apnea depends on arousal from sleep (see arousal section). Failure to terminate apnea results in auto-resuscitation, the last-resort mechanism used by mammals to ensure survival during exposure to severe hypoxia. Studies in newborn rats and mice identified factors that influence hypoxic gasping patterns, such as postnatal age,[296] core temperature,[297] prenatal nicotine exposure,[298] and intermittent hypoxia.[299] Failed auto-resuscitation from hypoxic apnea by gasping has been documented in SIDS victims.[300,301] In children, apneas are rare and predominantly central. Recent studies provided normative values for apneas in healthy children.[246,247]

Reflexes Originating from the Lung and Chest Wall

Reflexes originating from the tracheobronchial tree and within the lung parenchyma have significant effects in newborns, who differ in this respect from adults. Vagal innervation is of crucial importance in maintaining postnatal breathing and alveolar ventilation.[302,303] The Hering-Breuer inflation reflex is an important mechanism for regulating the rate and depth of respiration in newborn mammals. In human infants, the activity of this reflex can be expressed as the relative change in expiratory time after end-expiratory occlusion compared to the resting expiratory time during spontaneous breathing. This parameter has been measured during non-REM sleep in infants younger than 1 year of age. The results showed that the reflex persisted beyond the neonatal period and exhibited no variation in activity during the first 2 months of age.[304] Later, activity of the reflex correlated negatively with age.[304] The postnatal period characterized by high reflex activity is longer in preterm infants, suggesting delayed maturation.[305] The reflex is stronger during REM sleep than during non-REM sleep in newborn infants.[306] The Hering-Breuer deflation reflex occurs in newborn infants, including those born prematurely.[307] It may play an important role in protecting FRC in the newborn infant. Irritation of the tracheobronchial tree induces apneas in human preterm infants.[308] Activation of bronchopulmonary C-fiber afferents induces bronchoconstriction in newborn dogs.[309] Activation of C-fiber afferents may play a role in inflammatory lung diseases in infants.

Various reflexes that arise in the rib cage influence the intercostal and phrenic motoneurons. These reflexes are of potential importance in newborns, whose rib cage is compliant and therefore prone to distortion during REM sleep. Rib cage distortion is associated with breathing pattern changes, including decreases in inspiratory time and tidal breathing, prolongation of expiratory time, irregular breathing, and even apnea.[310,311]

Chemoreception

PERIPHERAL CHEMORECEPTORS

Peripheral chemoreceptors are activated by changes in the partial pressure of oxygen and trigger respiratory drive changes aimed at maintaining normal partial pressure levels. Studies in fetal lambs have demonstrated that peripheral chemoreceptors are functionally active and can be stimulated by further decreasing the already low fetal PaO_2.[312] The initiation of breathing at birth immediately results in a very substantial PaO_2 increase. After birth, developmental changes affect carotid body histology with increases in the numbers of type I-cells and nerve fibers,[313] changes in biological properties of O_2-sensitive K^+ and O_2-sensitive Ca^{2+} channels in the type I-cell membranes[314] and in levels of neurotransmitters and/or their receptors.[315] All these changes may play a role in the maturation of peripheral chemoreceptor responses to hypoxia. Furthermore, growth factors such as BDNF and GDNF (glial cell line-derived neurotrophic factor) are synthesized in the developing carotid body and mediate trophic support for chemoafferent survival.[264]

The mechanisms underlying postnatal carotid body resetting of O_2 sensitivity remain unelucidated. Resetting of peripheral chemoreceptors is essentially complete about 24 to 48 hours after birth in healthy human full-term infants tested during non-REM sleep using either the hyperoxic test[316] or alternations in inspired oxygen.[317] Studies of peripheral chemoreceptor function must take into account environmental temperature and behavioral states. The ventilatory response to hyperoxia is greater in REM than in non-REM sleep, in both warm and cool environments.[318] Importantly, the ventilatory response to the hyperoxic test varies widely in infants,[319] perhaps at least partly as a result of genetic factors affecting chemoreceptor function.[320] Delayed resetting of peripheral chemoreceptors has been reported in newborn mammals subjected to hypoxia during the perinatal period.[321,322] Perinatal hypoxia increases the amount of dopamine, the most abundant inhibitory neurotransmitter, in the carotid body.[322] A similar delay has been reported in infants with chronic hypoxia resulting from bronchopulmonary dysplasia.[323-324] Because peripheral chemoreceptors play a key role in initiating the ventilatory, cardiovascular, and arousal responses to hypoxia and asphyxia, this delay may be among the factors that place infants with bronchopulmonary dysplasia at greater risk for SIDS.[323] The relation between apnea occurrence and peripheral chemoreceptor function requires further investigations. Impaired function, as well as exacerbated function, of peripheral chemoreceptors has been reported in preterm infants with frequent apneas.[325,326]

In newborns, steady-state hypoxia produces a biphasic response with a transient increase in ventilation (hyperpneic phase) followed by a decrease to or below the baseline level (hypoxic ventilatory decline) (Fig. 3-18).[327] The hypoxic ventilatory decline has been ascribed to various mechanisms such as immaturity of the peripheral chemoreceptors, decreased oxygen consumption,[328] and central inhibitory transmission.[329-331] The biological significance of the hypoxic ventilatory decline is debated. The hypoxic ventilatory decline may be an adaptive respiratory response of the developing mammal that conserves oxygen while decreasing the meta-

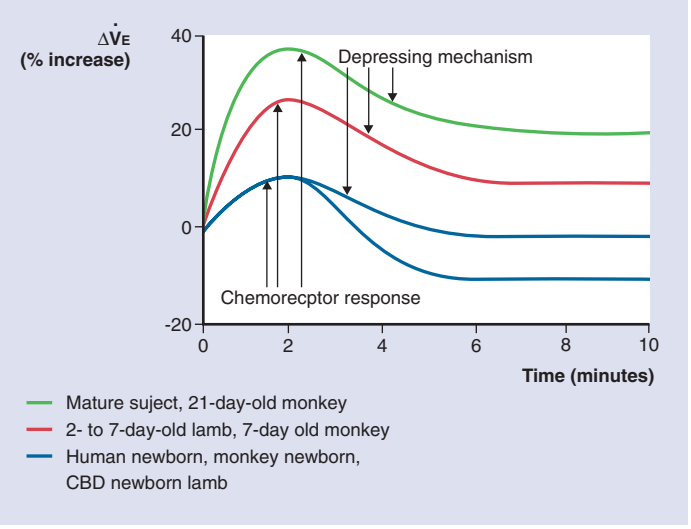

Figure 3-18 Ventilatory response to steady-state hypoxia in the newborn. The newborn has a biphasic response to hypoxia. $\Delta\dot{V}_E$, change in expiratory gas flow. (Redrawn from Davis GM, Bureau MA: Pulmonary and chest wall mechanics in the control of respiration in the newborn. Clin Perinatol 14:551-579, 1987.)

bolic rate, a combination that protects the brain from hypoxic damage.[328] Alternatively, the hypoxic ventilatory decline may be a potentially harmful consequence of immaturity of the O_2-sensing pathways. Prenatal insults, such as hypoxia[332] or exposure to nicotine,[333,334] and postnatal insults, such as hypoxia or hyperoxia,[335-337] compromise the defense mechanisms against hypoxia during early life. Perinatal O_2 plays a role in the development of the hypoxic ventilatory response. Perinatal hypoxia elicits plasticity in developing O_2 sensitivity that has consequences in adulthood.[335] Intermittent hypoxia during the early period of life induces an excitatory form of plasticity with increased hypoxic ventilatory response in neonatal rats.[336,337] Neonatal separation from the mother has been shown to affect early programming of the hypoxic ventilatory response.[338] Finally, the ventilatory response to hyperoxia was increased in preterm infants treated with caffeine for apneas.[339]

CENTRAL CHEMORECEPTORS

Central chemoreception is believed to occur at widely distributed sites.[340] However, there is little agreement on when and how each of the sites is involved in respiratory control.[341] Hypercapnia is a major stimulus for increasing ventilation in neonates, as shown by many studies of the ventilatory response to hypercapnia in newborn mammals.[342] Hypercapnia seems to elicit no metabolic response, in contrast to hypoxia.[343] The ventilatory response to hypercapnia is influenced by gestational and postnatal age. In preterm infants, hypercapnia induces a sustained increase in tidal volume; however, respiratory rate drops as a result of an increase in expiratory time that may originate in central inhibitory mechanisms.[344] Postnatal changes in hypercapnic ventilatory responses appear to vary across species. Early studies in humans found that ventilatory responses increased with postnatal age.[345] However, a decline of the ventilatory response to hypercapnia at the end of the first week followed by an increase was found in rats, suggesting a critical postnatal biphasic ventilatory response period with low CO_2 sensitivity.[346,347] This critical period may be associated with increased vulnerability, which may contribute to the mechanisms underlying SIDS.[348] Studies in children showed stronger hypercapnic ventilatory responses compared to adults.[349]

The roles for central and peripheral chemoreceptors in ventilatory responses to hypercapnia during development have not been fully separated.[350] Ventilatory responses to hypercapnia are weaker during REM sleep than during non-REM sleep (Fig. 3-19),[351] in both preterm and full term infants.[70,351-353] Mechanisms that contribute to the decreased responses during REM sleep may include a smaller contribution of the rib cage to ventilation,[352] a weaker central output to the diaphragm,[353] and inhibition of abdominal muscle recruitment.[70]

The influence of genetic factors on the considerable interindividual variability of hypercapnic ventilatory responses in human infants is an important issue for future research. A weak hypercapnic ventilatory response may predispose to apnea in infants.[354] Attenuation of the hypercapnic ventilatory response has been reported in disorders such as myelomeningocele or Prader-Willi syndrome.[354] Congenital central hypoventilation syndrome, the autosomal genetic disorder related to a heterozygous *PHOX2B* gene mutation,[262] is characterized by absent or markedly reduced hypercapnic ventilatory responses.[354]

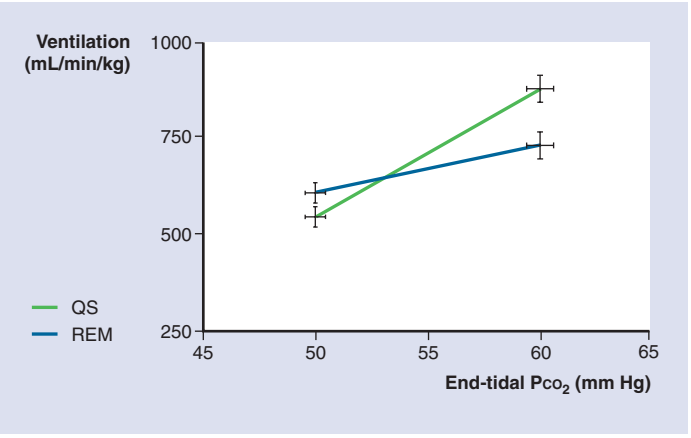

Figure 3-19 Partial end-expiratory pressure of carbon dioxide versus minute ventilation for REM sleep and quiet (non-REM) sleep (QS). Data are means ± 95% confidence intervals for position. Data are from 46 tests in five full-term babies. (Redrawn from Cohen G, Xu C, Henderson-Smart D: Ventilatory response of the sleeping newborn to CO_2, during normoxic rebreathing. J Appl Physiol 71:168-174, 1991.)

Perinatal hypercapnia in the first 2 weeks of life causes a transient decrease in hypercapnic ventilatory responses in both male and female rats.[355] Thus, perinatal hypercapnia elicits only transient plasticity, contrasting with the long-lasting plasticity induced by perinatal hypoxia.[335]

Thermoregulation

Hypothalamic mechanisms that increase ventilation are active before birth.[356] Cooling of the skin provides a potent drive to breathing in the neonatal period (see Fig. 3-16). Ambient temperature is closely linked to metabolic rate, especially in early postnatal life, when the basal metabolic rate is high and provides an abundant tonic sensory input that influences the breathing pattern. Metabolic rate is the lowest when environmental temperatures are within the neutral range.[357,358] In a hypoxic environment, the body temperature of the newborn decreases, which contributes to decreased oxygen consumption and to improved hemoglobin oxygen saturation.[330]

In adults, thermoregulatory mechanisms are impaired during REM sleep. In contrast, in newborns, REM sleep seems associated with maintenance of homeothermia in both cool and warm environments.[357] Greater activity of the metabolic response during REM than non-REM sleep favors instability of breathing. Thus, a small increase in body temperature is associated with a significant increase in the time spent with periodic breathing during REM sleep, but not non-REM sleep, in preterm infants[291] and with an increase in the number of central apneas in infants.[292] In preterm infants, thermal challenges within the physiologic range increase peripheral chemoreceptor gain during REM sleep but not during non-REM sleep.[319] High body temperature was associated with decreases in the threshold and latency for reflex contraction of the laryngeal adductor in newborn dogs,[359] suggesting that hyperthermia may permit reflex laryngeal closure in newborns. Finally, the vagally mediated reflex response to lung inflation is stronger during hypoxic hyperthermia than during normoxia.[360] Interactions between

developmental changes in thermoregulation, respiratory control, and metabolic demands may play a role in the risk of SIDS.[361]

Arousal Responses

Arousal from sleep is the most important protective response to danger-signaling stimuli during sleep. Decreased arousability may be a risk factor for SIDS.[362] Spontaneous arousals, arousal patterns after apneas, and arousal responses to various stimuli (such as hypercapnia, hypoxia, and auditory stimuli) have been studied in infants. Many studies included infants within the peak age range of SIDS occurrence (i.e., 2 to 4 months). Criteria for scoring arousals varied across studies. The infant arousal response typically starts by subcortical arousal with an augmented breath followed by a startle then by cortical arousal.[363-365] Different types of arousal have been considered: awakening (behavioral arousal), electroencephalographic (EEG) arousal (cortical arousal) longer than 1 or 3 seconds,[366] movement arousal,[367] and subcortical arousal.[363-365] Finally, subcortical activation was scored when there was no EEG modification longer than 3 seconds despite at least two of the following: gross body movement, heart rate change, or breathing pattern change.[368]

Spontaneous arousal activity occurred more frequently during REM sleep than non-REM sleep in infants.[365] Spontaneous subcortical arousals were more frequent than cortical arousals in infants.[365] Spontaneous cortical arousals were less common in the prone sleeping position compared to the supine position during REM compared to non-REM sleep in infants.[366] The mean number of spontaneous cortical arousals (EEG arousals longer than 3 seconds) was 9 per hour of sleep in children.[246,247]

The occurrence of arousals at the end of apneas was studied in infants and children. Behavioral arousal occurred in fewer than 10% of apneas in preterm infants.[370] Arousal was more common in long versus short, mixed versus central, and severe versus mild apneas.[370] EEG arousal longer than 1 second was uncommon at the end of obstructive apneas in infants and children with obstructive sleep apnea (OSA),[371] whereas movement arousal occurred at the end of most respiratory events in children with OSA.[369]

Hypercapnia is a potent stimulus causing arousal from sleep. Behavioral arousal has been studied in infants and young children during non-REM sleep.[372-374] All tested infants and children exhibited behavioral arousals when the end-tidal partial pressure of carbon dioxide ($PETCO_2$) was around 50 mm Hg. In children with OSA, arousal occurred at higher $PETCO_2$ values than in control children.[375]

Hypoxia is less effective than hypercapnia in causing arousal from sleep. Few infants exhibited behavioral arousal in response to hypoxic stimuli during non-REM sleep.[372,373,376,377] Studies in lambs showed that arousal in response to severe hypoxia was delayed during REM sleep compared to non-REM sleep.[378] However, in a recent study human infants invariably showed arousal in response to mild hypoxia during REM sleep but often failed to arouse in non-REM sleep.[379]

Other stimuli can lead to arousal from sleep in infants. In near-term infants, the esophageal acid infusion test increased the rate and duration of EEG arousals during REM sleep.[380] The auditory arousal threshold decreased with maturation between 44 and 52 weeks of post-conceptional age and remained unchanged thereafter.[381]

Several factors impair arousal from sleep. Arousal to auditory stimuli was less frequent in the prone than in the supine sleeping position,[382] after short-term sleep deprivation,[383] in warm thermal conditions,[384] when bedclothes covered the face of the infant,[385] and in infants born to mothers who smoked during pregnancy.[386] In contrast, swaddling was associated with increased arousal responsiveness to auditory stimulation during sleep.[387] Incomplete arousal was suggested in SIDS victims, who had fewer cortical arousal responses than control infants.[368]

Arousal response habituation occurs with repeated exposure to stimuli such as intermittent hypoxia in newborn mice[388] or intermittent hypercapnic hypoxia in piglets.[389] Repetitive tactile stimulation induced habituation of the arousal response in human infants.[390] The cortical response is eliminated first, then the startle response, and finally the augmented breath. Elimination of each of these responses occurred more rapidly in REM than in non-REM sleep. Rapid habituation to innocuous stimuli is probably beneficial in avoiding sleep disruption. However, in situations requiring protective arousal, habituation may have deleterious effects. Furthermore, REM sleep, during which habituation develops more rapidly, is the predominant sleep state in young infants.

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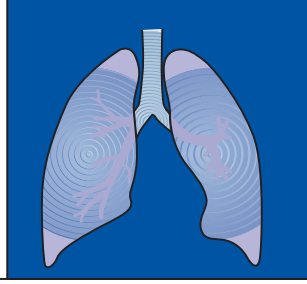

CHAPTER 4

Lung Cell Biology

John W. Upham, Stephen M. Stick, and Yuben Moodley

TEACHING POINTS

- The various cells within the lung serve to facilitate gas exchange, maintain the anatomic structure of the airways and alveoli, provide protection against infection, and maintain immunologic tolerance against innocuous foreign proteins.
- While cell types are often classified as having predominantly structural or immunologic functions, this distinction is artificial. Many structural cells play a key role in lung inflammation, whereas the various migratory immune cells affect the phenotype and function of structural cells.
- Recent decades have seen a rapid increase in knowledge of cell lung biology in both health and disease, providing an important foundation for the development of new approaches to the treatment of lung disease.

The lung consists of a variety of cell types that function together to supply the body with oxygen and eliminate the carbon dioxide produced by cellular metabolism. These cells include both structural elements that maintain the anatomic structure of the airways and alveoli, and a variety of migratory cells (generally of hemopoietic origin) that provide protection against infection and the maintenance of immunologic tolerance. This chapter describes the biology of the key cells within the lung, and while for convenience the discussion is divided into *structural* cells and *immunologic* cells, such a distinction is artificial. For example, although epithelial cells do exert an important barrier function within the lung, they also secrete a variety of biological molecules that regulate immune processes. Similarly, although the immunologic functions of T cells are well recognized, they may also influence the behavior of structural cells such as airway smooth muscle cells.

EPITHELIAL CELLS

Epithelial tissue is found throughout the body and performs a variety of functions, many of which are organ specific. In the lung, the epithelium forms a protective lining in the airways and alveoli. The lung epithelium is not, however, a simple passive barrier because it plays an active role in lung homeostasis and immunity—both innate and adaptive. The epithelium also produces the airway surface liquid layer that contributes to the mechanical properties of the lung and is an essential component of the lung's defense against infective, irritant, and toxic exposures.

Epithelial Structure

The airway epithelium is composed of at least 12 different cell types, which vary in abundance throughout the lung. In the proximal airways (the trachea and main bronchi), the epithelial cell layer is thicker, and composed of tall, ciliated cells, basal cells, and secretory cells known as *goblet cells*. As the airways branch out and become smaller, the epithelial layer becomes thinner, until at the level of the bronchioles, it is composed of a single layer of short cuboidal cells (Fig. 4-1).

Junctional complexes bind epithelial cells, permit intercellular communication, and form a barrier that regulates the passage of water and solutes from the lumen across the epithelium. The junctional complexes consist of tight junctions, adherens junctions, and desmosomes (Fig. 4-2). In addition to these junctions, the gap junction forms an intercellular channel that allows the exchange of ions and small molecules between adjacent cells. Epithelial cells are not only attached to each other, but are also anchored by hemidesmosomes to the basement membrane—a thin sheet of collagen, laminin, and fibronectin.

Epithelial tissues can be classified on the basis of their structure. In the proximal airways, the epithelium is pseudostratified. Although there appears to be a layer of ciliated columnar cells overlying basal cells, each cell is, in fact, anchored to the basement membrane.

The diversity of cell types, each with distinct physiologic functions, that makes up the epithelium serves to optimize mucociliary clearance, regulation of fluid homeostasis, and the synthesis and secretion of a large number of host defense proteins. The various cell types are influenced by infection and other inflammatory stimuli and can themselves influence host defense function and epithelial repair. In the healthy lung, the normal spatial arrangement and activation state of epithelial cells are tightly regulated, and epithelial cells interact with professional phagocytes and lymphoid cells of the acquired immune system. Furthermore, an extensive system of tracheal-bronchial glands is lined by distinct epithelial cell types that produce mucus, fluid, and other host defense proteins critical for mucociliary clearance. Type II epithelial cells found predominantly in the alveoli are important for surfactant secretion, an essential factor for maintenance of normal mechanical function of the lung. A deficiency of

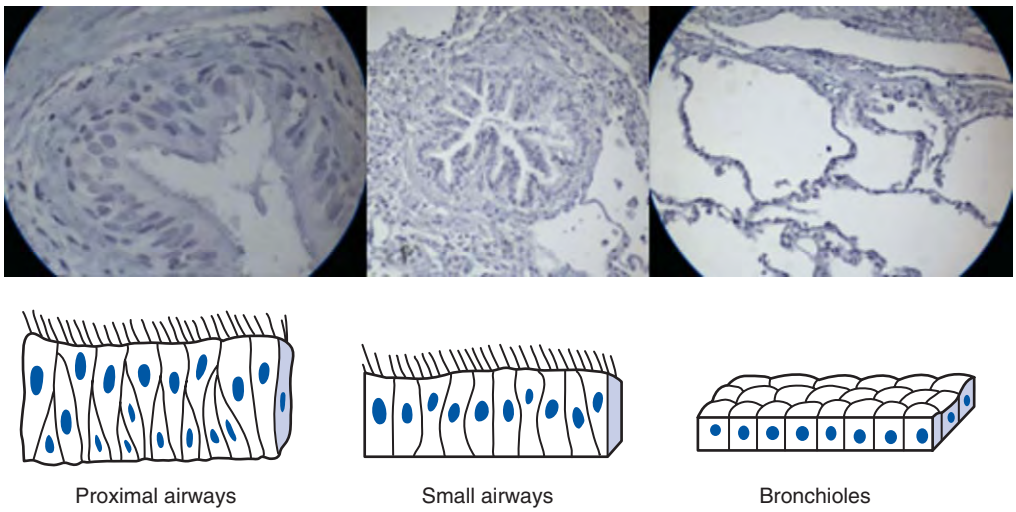

Figure 4-1 Structure of the epithelium throughout the airways. The proximal airways are lined with pseudostratified columnar epithelium. As the airways decrease in diameter the height of the epithelium also decreases, until, in the alveoli and bronchioles, it is composed of short nonciliated cuboidal cells.

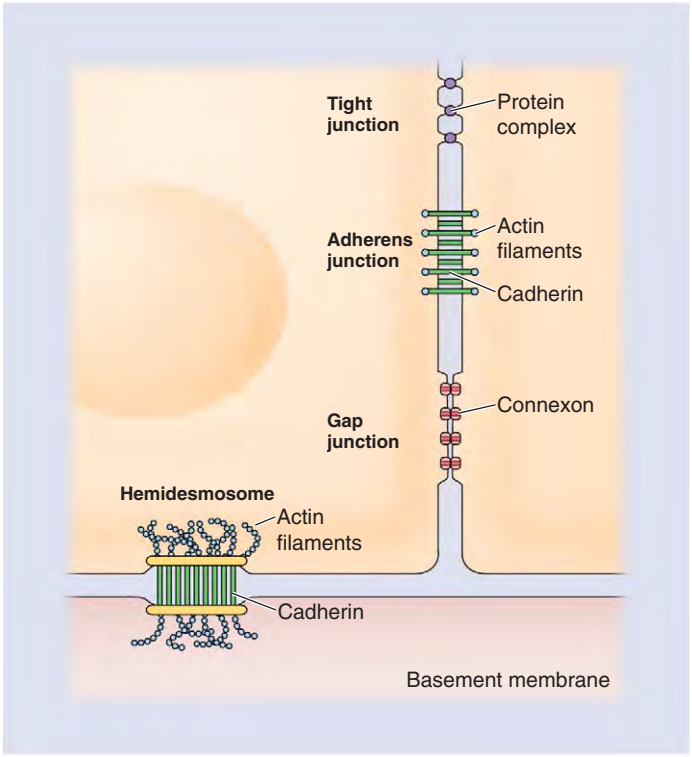

Figure 4-2 Epithelial cells are connected by junctional complexes. Junctional complexes consist of tight junctions, adherens junctions, and desmosomes. Gap junctions allow the exchange of ions and small molecules. Epithelial cells are anchored by hemidesmosomes to the basement membrane.

normal surfactant such as is found in preterm infants and genetically determined deficiency syndromes can result in respiratory distress.

Epithelial function

BARRIER FUNCTION

The epithelium in the lungs is constantly exposed to particulates, viruses, bacteria, pollen, allergens, oxidants, and other potentially toxic substances. The epithelium acts as a barrier, protecting the highly sensitive underlying smooth muscle and sensory nerves from stimulation and damage by these agents. There are two mechanisms hypothesized to explain the effective barrier function of the respiratory epithelium. In the *mechanical model,* epithelial cells control the volume of the airway surface liquid (ASL) that overlies the epithelium that is critical for effective mucociliary clearance. Epithelial cilia propel this mucus layer upward (the mucociliary escalator) toward the throat, where it is expectorated or swallowed. The *chemical shield model* predicts that the epithelium absorbs salt but not water from the ASL to form a low salt environment that facilitates the antimicrobial activities of defensins. The mucus layer also contains antioxidants in sufficient quantities to protect the lung from inhaled oxidants, growth factors, cytokines, and chemokines that are required for airway homeostasis and repair. In addition to the defense provided by the combined action of the cilia and production of ASL, epithelial tight junctions that play a major role in maintaining epithelial integrity are able to restrict the movement of molecules across the epithelium. Desmosomes and gap junctions also contribute to the structural integrity of the epithelium (see Fig. 4-2). Epithelial cells are capable of internalizing particles to clear them from the lung.[1]

BEYOND BARRIER FUNCTION

Although traditionally thought of as a simple barrier, the epithelium plays a central role in maintaining airway homeostasis and responds to inadvertently inhaled agents such as pollutants, allergens, and microorganisms, as well as intentionally inhaled agents such as aerosol therapy.

The airway epithelium plays an important role in airway homeostasis. For example, epithelial cells can directly influence underlying smooth muscle tone by releasing an array of bronchoconstrictors such as endothelin[2] and leukotrienes,[3] and bronchodilators such as prostaglandin E_2 (PGE_2),[4] and nitric oxide (NO).[5] The epithelium also produces enzymes such as neutral endopeptidase,[6] that are responsible for the breakdown of potent bronchoconstrictors such as tachykinins, bradykinin, endothelin, and angiotensin I and II from inflammatory cells.

Airway epithelial cells can be activated by inhaled allergens and particulates to produce proinflammatory mediators. This process can be either direct, where the inhaled sub-

stance interacts directly with the epithelium, or indirect, via activation of other constituent airway cells (e.g., macrophages). House dust mite allergens such as Der p 1 and Der p 9 induce epithelial cells to release granulocyte-macrophage colony-stimulating factor (GM-CSF), interleukin (IL)-6, and IL-8,[7] via the activation of protease activated receptors on epithelial cells.[8] Diesel exhaust particles,[1] bacterial endotoxins,[9] and pollutants such as NO_2,[10] also activate epithelial cells and cause increased release of proinflammatory mediators. Alternatively, epithelial cells can be indirectly activated when macrophages or granulocytes release cytokines such as tumor necrosis factor (TNF)-α, IL-1β, and IL-6 in response to stimulation by allergens and viruses.[11]

The epithelium recruits inflammatory cells to the airway by releasing inflammatory cytokines and chemokines. For example, lipopolysaccharide induces release of LTB_4, a potent neutrophil chemoattractant.[3] Indirect activation of epithelial cells by TNF or IL-1 causes them to release RANTES, a cytokine with potent chemotactic activity for monocytes[12] and eosinophils.[13] Epithelial cells also release IL-8, which can attract $CD4^+$ lymphocytes.[14]

Epithelial cells can also enhance the inflammatory response by preventing inflammatory cell apoptosis, thereby delaying the clearance of inflammatory cells from the lung. Intercellular adhesion molecule (ICAM)-1, expressed on epithelial cells, is a ligand for integrins expressed on the surface of neutrophils, and leads to their retention in the airway.[15] Granulocyte colony-stimulating factor (G-CSF) and granulocyte-macrophage colony-stimulating factor (GM-CSF), released from epithelial cells, promote neutrophil survival.[16]

In addition to nonspecific responses to environmental exposures, the epithelium also expresses specific receptors that recognize viral and bacterial components. The responses triggered by these receptors are crucial elements of the innate immune system. The best characterized are the Toll-like receptor (TLR) family. TLRs sense infection through recognition of PAMPs (pathogen-associated molecular patterns), leading to dendritic cell maturation and antigen presentation, and the activation of pathogen-specific T cells.[17] Although TLR expression is classically associated with bone marrow-derived immune cells, human airway epithelial cells can also express functional TLR2, TLR3, and TLR4,[18-20] and possibly a range of other TLRs. In doing so, epithelial cells are able to convert the recognition of pathogen-associated molecules into signals for antimicrobial peptide expression, barrier fortification, proliferation of epithelial cells and modulation of the host immune response.[21] Bacterial lipopeptides induce epithelial cells to produce the antimicrobial peptide beta defensin-2 in a TLR2-dependent manner,[20] whereas respiratory viral infections can induce airway epithelial cell expression of TLR3, thereby sensitizing the airway epithelium to subsequent microbial pathogens.[18]

FIBROBLASTS

Fibroblasts are important structural cells and are especially prominent within the interstitium of the normal lung. A prominent endoplasmic reticulum and Golgi apparatus characterize their ultrastructure. The cytoplasm contains numerous vesicles, mitochondria, vacuoles, and intermediate filaments. In vivo, they display a few microfilaments and intermediate filaments, and in culture they establish gap junctions. In addition, cultured fibroblasts are more flattened, polarized, and possess numerous stress fibers and a smooth nuclear outline.[22] In a resting state, the cytoplasm is reduced and spindle-shaped with long cytoplasmic extensions. When activated, however, such as in healing wounds, fibroblasts display a rounded nucleus with a prominent nucleolus. The cytoplasm is extensive with a prominent granular appearance of the rough endoplasmic reticulum indicative of active protein synthesis.[22]

Until recently, the fibroblast was thought to be a homogeneous cell with limited roles and functions related to tissue structure. However, it is now well established that the fibroblast is central to wound healing.[23] During resting physiologic conditions, fibroblasts provide scaffolding for the extracellular matrix (ECM) proteins. In addition, they are responsible for the synthesis and turnover of ECM proteins such as type 1 collagen and proteoglycans.[24] However, more recent studies have demonstrated an expanding role for fibroblasts in tissue homeostasis. To this end, fibroblasts have a role in angiogenesis,[25] physiologic aging,[26] remodeling of tissue,[27] cell differentiation, and the release of mediators that may be instrumental in fertility and parturition.[28]

In addition to the aforementioned functions, fibroblasts also serve as sentinel cells, expressing a number of surface molecules that are more traditionally associated with immune cells. As such, they express CD40, originally described on B lymphocytes and dendritic cells,[29] which induces the expression of the intercellular adhesion molecule (ICAM-1), vascular cell adhesion molecule (VCAM-1), the cytokines interleukin-6 (IL-6), IL-8, IL-1, and prostaglandins.[29] Under resting conditions, only low-level surface expression of CD40 occurs, but this increases dramatically during inflammation, constituting a significant pathway by which fibroblasts mobilize inflammatory cascades during tissue injury and wound repair.[29]

There is increasing evidence from both cell cultures and tissue biopsy specimens demonstrating that the fibroblast phenotype is heterogeneous. Fibroblasts for example, expressing the thymocyte antigen 1 (Thy 1(+) fibroblasts) show profibrogenic characteristics by expressing higher levels of collagen.[30] In contrast, Thy 1-negative fibroblasts have a greater proliferative responsive to cytokines such as IL-6, TGF-β, and PDGF.[30,31] As such, different types of fibroblasts may play distinct roles during inflammation and repair. Differences between fibroblasts may also occur as a result of their site of origin in the body[32] or in terms of the receptors that they express, such as major histocompatibility (MHC) class II antigens, complement C1q, IL-1 receptor, and integrins.[30,33]

However, during wound healing and under the influence of mediators released from neighboring cells, fibroblasts assume a more dynamic role and become important effector cells.[24] They acquire a migratory phenotype and enter the wound where they deposit ECM[34] and induce wound contraction.[35] Fibroblasts are implicated in the active immune response of the tissue and release numerous cytokines, growth factors, chemokines, and other inflammatory mediators.[36] The growth factors involved in fibroblast activation include TGF-β, connective tissue factor (CTGF), insulin-like growth

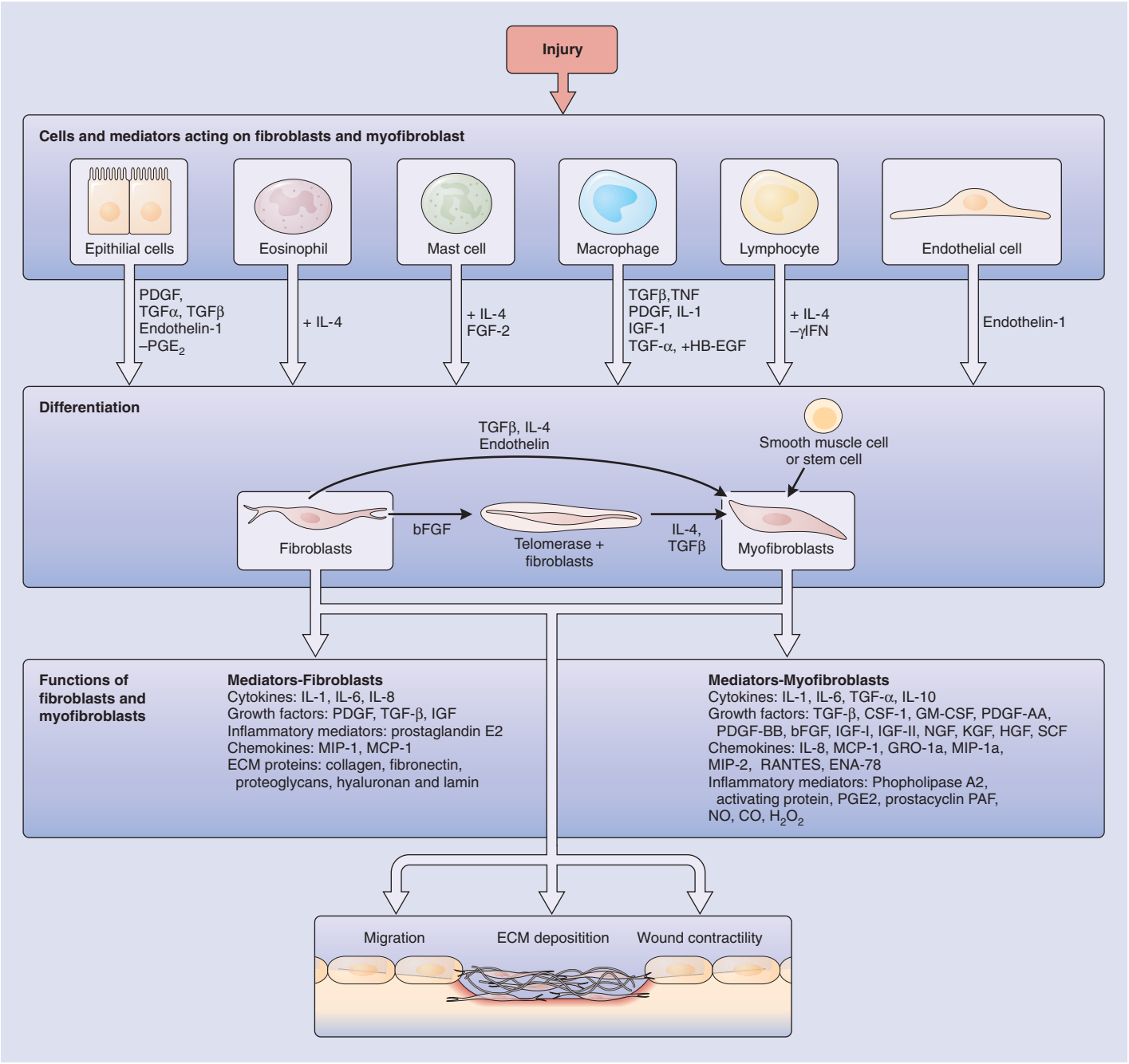

Figure 4-3 The role of fibroblasts and myofibroblasts in fibrosis. An initial injury results in the release of proinflammatory and profibrotic mediators from cells within the lung. These mediators result in the differentiation of fibroblasts to myofibroblasts. In addition, they influence fibroblast and myofibroblast migration, ECM deposition, and wound contractility. In turn, fibroblasts and myofibroblasts release mediators that perpetuate inflammation and fibrosis.

factor (IGF), platelet-derived growth factor (PDGF) and fibroblast growth factor (FGF). Cytokines such as IFNγ, IL-10, and IL-12 can inhibit fibroblast proliferation, whereas IL-1, IL-13, TNF-α, and endothelin-1 are fibroblast mitogens. Of note, IL-6 can act both as an inhibitor or promoter of fibroblast proliferation.[37] Figure 4-3 outlines the role of fibroblasts in pulmonary fibrosis.

An important, but largely unexplained role for fibroblasts in wound healing is their apparent ability to differentiate into myofibroblasts. Myofibroblasts resemble a smooth muscle cell in many respects and are central to wound repair. The transdifferentiation of adventitial fibroblasts to myofibroblasts is induced by TGF-β, IL-4, and endothelin-1.[38] Recently a fibroblast representing a telomerase-expressing phenotype has also been shown to differentiate into a myofibroblast.[39]

MYOFIBROBLASTS

The myofibroblast is characteristically found during wound healing and morphologically displays an indented nucleus, a feature associated with cellular contraction, a large endoplasmic reticulum, and numerous mitochondria.[40] Notably, the myofibroblast is best defined by its cytoskeletal protein

content which may comprise either vimentin (V-type), vimentin and desmin (VD-type), vimentin and α-smooth muscle actin (VA-type), or vimentin, desmin and α-smooth muscle actin (VAD-type).[40-42] The contractile protein most abundant in myofibroblasts is α-smooth muscle actin (α-SMA), although desmin and smooth muscle myosin may also be present. The myofibroblasts found in the lung septa are usually desmin positive.[41,42] Specialized structures of myofibroblasts such as microfilament bundles or stress fibers that are usually found below the cell membrane and parallel to the main axis of the cell usually force wound contraction, whereas a well-developed rough endoplasmic reticulum signifies a prominent synthetic function.[43] There are qualitative differences in the synthesis of collagen I, III, and IV between the various types of myofibroblasts. Myofibroblasts arising from various phases of wound healing, such as those obtained from granulation tissue, display structural differences such as an abundance of cytoplasmic microfilaments, dense bodies, and basal lamina-like material.[43]

Myofibroblasts play a role in normal physiological processes such as organogenesis, tissue morphogenesis, mesenchymal-epithelial interactions, and cell differentiation.[32] In addition, the unique characteristics of the myofibroblast, namely the expression of contractile proteins, makes this cell well adapted for its role in wound repair. However, the source of myofibroblasts involved in wound repair is unknown. Possible precursors include progenitor stem cells, the neural crest, or as a result of the transdifferentiation from peribronchial tissue, perivascular fibroblasts, and epithelial cells.[41,44] Myofibroblasts are a key source of collagen production and ECM proteins. An additional property is their capacity for wound contractility as a result of the rearrangement of the abundant intracellular microfilaments.[45] Myofibroblasts are also inflammatory cells and generate a variety of cytokines, chemokines, inflammatory mediators, and growth factors that may perpetuate the inflammatory response and fibrosis.[41] Activated myofibroblasts also express cell adhesion molecules that recruit inflammatory cells to the sites of injury.

Fibroblasts and Myofibroblasts During Wound Repair

Following an injury, fibroblasts and myofibroblasts infiltrate the wound where they perform a variety of roles. Several lines of evidence have demonstrated that these cells undergo apoptosis (programmed cell death) and this is a crucial phase for normal wound repair.[46-48] Apoptosis is highly regulated by pro-and anti-apoptotic molecules. The cell membrane is characteristically intact during apoptotic cell death as compared with cell necrosis. The intact cell membrane prevents the extrusion of proinflammatory cell contents into surrounding tissue, thereby promoting wound repair. Much of our knowledge of apoptosis of fibroblasts and myofibroblasts has been gleaned from cutaneous models of wound healing. Following wound healing of the skin, fibroblast and myofibroblast apoptosis begins on day 12, peaks at day 20, and is resolved by day 60 of wound repair. The postulated mechanism of apoptosis in fibroblasts is via the IL-1β-dependent production of nitric oxide (NO) that reduces the expression of the anti-apoptotic molecule Bcl-2.[49,50] In contrast, TGF-β inhibits fibroblast and myofibroblast apoptosis by not only inhibiting the expression of NO but also by inducing the anti-apoptotic Bcl-2 molecule without affecting the expression of the pro-apoptotic Bax protein.[49] The fall in TGF-β levels during wound repair is a further mechanism implicated in fibroblast apoptosis. Apoptotic fibroblasts are then phagocytosed by macrophages.[51]

SMOOTH MUSCLE CELLS

The smooth muscle cell is flat with a large nucleus, no nucleolus, and occupies the walls of both airways and blood vessels. This brief review will limit discussion to airway smooth muscle. Smooth muscle in the airway surrounds the lamina propria and the concentration of smooth muscle differs between the proximal, cartilaginous, and distal noncartilaginous airways. Matsuba and Thurlbeck demonstrated that the percentage of the airway occupied by smooth muscle in children is 2.8 in proximal and 10 in distal airways.[52] The orientation of airway smooth muscle is transverse in the trachea and helical or geodesic around the central and peripheral airways, with this arrangement functioning to control airflow to the alveoli.

There is heterogeneity in smooth muscle cells in the airway with at least three different types of smooth muscle cells identified in the airway. These include a contractile, synthetic, and "hypercontractile" subtype.[53] The nonproliferative contractile phenotype is characterized by a high concentration of contractile proteins and reduced synthetic intracellular organelles.[54] In contrast, the synthetic smooth muscle, which may differentiate into a contractile phenotype, possesses numerous synthetic organelles and a low density of contractile proteins. The hypercontractile cell shortens at high velocity in cell culture because of elevated concentrations of smooth muscle light chain kinase.[55] The role of these subtypes in vivo needs to be further investigated.

The smooth muscle consists of thick (predominantly myosin), thin (predominantly actin) and intermediate (predominantly desmin) filaments. Actin is arranged in hexagonal bundles that run along the long axis of the cell and are surrounded by myosin filaments. The intermediate filament forms connections with the cell membrane and is thought to maintain the myofilament system and structure of the smooth muscle cell.[56] The thin and intermediate filaments breach the inner membrane of the cell and form electron-dense areas called *dense plaques*. These plaques are coupled to each other in adjacent cells and mediate the transmission of tension between the contractile machinery and the ECM. The myosin fibers have a globular end—the myosin head—at the amino terminus that contains the functional motor domains comprising the actin-binding regions and the nucleotide adenosine triphosphate (ATP).[57] Neural stimulation results in an increase in intracellular calcium, leading to the enzymatic hydrolysis of ATP and conformational change in the myosin head. Myosin generates a force by repeatedly attaching to the actin, undergoing a conformational change and detaching.[58] This "lever arm hypothesis" suggests that the force is generated in repeated mechanical cycles. Contraction of smooth muscle is regulated by external factors such as the ECM. The smooth muscle cells are sensitive to external mechanical

Table 4-1
Inflammatory Mediators Released by Smooth Muscle

Adhesion molecules	Growth factors	Chemokines	Cytokines	Other mediators
ICAM	PDGF	MCP-1,2,3	IL-8	PGE_2
VCAM	GM-CSF	RANTES	IL-6	sPLA-2
			IL-11	NOS
			IL-5	
			IL-2	
			IL-12	

Table 4-2
Factors Promoting and Inhibiting Smooth Muscle Hyperplasia

Promoters of smooth muscle hyperplasia		
Growth factors	Peptides	Inflammatory mediators
PDGF	Thrombin	Leukotriene D4
EGF	Serotonin	IL-1
FGF-2	Endothelin	TNF-α
Inhibitors of smooth muscle hyperplasia		
	β2 agonists	
	Glucocorticoids	

stimuli by the binding of their transmembrane integrin receptors to ECM ligands. Mechanical forces result in the activation of the integrin receptors and their related transducer proteins vinculin, talin, and paxillin. The transducer proteins result in the phosphorylation of focal adhesion kinase (FAK) that in turn allows an increase in intracellular calcium and activation of the contractile proteins.[59]

In addition to the role of contraction, smooth muscle also plays a central part in immune regulation in the airway, as summarized in Table 4-1. The smooth muscle cell expresses the adhesion molecules ICAM and VCAM following stimulation by TNF-α, IL-1, interferon (IFN), and lipopolysaccharide.[60] These adhesion molecules augment the interaction of smooth muscle cells with inflammatory cells, thereby further perpetuating the release of inflammatory cytokines and chemokines as well as the proliferation of smooth muscle cells. The cytokines secreted by smooth muscle following stimulation by IL-1, TNF-α, and IFN include macrophage chemotactic factor (MCP)-1, 2, and 3, RANTES, eotaxin, GM-CSF, IL-8, IL-6, IL-11, IL-5, IL-2, and IL-12.[61-63] Growth factors secreted include PDGF-BB, stem cell factors, and lipid mediators such as PGE_2, s-PLA2, and NOS.[64] As such, smooth muscle plays an intrinsic role in the augmentation of the inflammatory cascade.

The signaling pathways that drive smooth muscle growth are divided into the polypeptide growth factors that activate receptor tyrosine kinase and receptors linked to the guanosine triphosphate-binding proteins (G proteins).[65] These mitogens associated with tyrosine kinase include PDGF, EGF, FGF-2, and IGF.[66] The G proteins binding molecules are thrombin, serotonin, endothelin and leukotriene D4. A third group of mitogens constitute the proinflammatory cytokines such as IL-1 and TNF.[67] These cytokines act via the receptors acting through Src kinase, mitogen-activated protein kinase, Janus kinase, and signal transducer and activation of transcription (STAT) pathways.[68] The PI-3 kinase plays a prominent role in both smooth muscle hyperplasia and migration to sites of injury.[69] Beta 2 agonists and glucocorticoids attenuate the proliferative response of smooth muscle cells.[70] These antiproliferative effects are limited by IL-1β and collagen I, however.[71] The factors regulating smooth muscle proliferation are outlined in Table 4-2.

There are several secondary messenger systems that mediate smooth muscle constriction or relaxation. The seven domain transmembrane G-coupled receptor plays a vital role in smooth muscle cells. This receptor comprises stimulatory (Gs) and inhibitory (Gi) subunits.[72] The major agents causing constriction are histamine (H1 receptor), acetylcholine (M3), leukotriene (D4) and bradykinin (B3).[73,74] Ligation of these receptors stimulates the Gi protein of the G-coupled receptor and the activation of phospholipase C, resulting in an increase in intracellular calcium and muscle constriction. Beta 2 agonists cause smooth muscle relaxation by receptor activation of the Gs subunit of the G coupled receptor. This subunit results in the activation of adenyl cyclase and protein kinase leading to membrane hyperpolarization, inhibition of myosin light chain activation, and increased reuptake of calcium.[75]

Several studies have demonstrated that there is both hyperplasia and hypertrophy of smooth muscle cells in the asthmatic airway. The mechanisms are as yet undefined but molecules implicated in this process include cytokines, endothelin, leukotriene D4 and a variety of growth factors.[76] Smooth muscle cells in the lung are heterogeneous. Ebina and colleagues demonstrated that there are two patterns of thickening in lungs of patients with fatal asthma.[77] In the type I group, there was thickening in the large airways in contrast to the diffuse thickening throughout the lung in the type II subgroup. The significance and pathogenesis of these changes need further verification. The role of fibroblasts, myofibroblasts, and smooth muscle cells in pathologic states will be further highlighted in subsequent chapters.

IMMUNE RESPONSES TO INHALED ANTIGENS

The mucosal surfaces lining the airways and alveoli are exposed to an array of inhaled environmental antigens and particulate matter, and the lung has remarkably little inflammation under normal circumstances, given the volume of air inspired each day and the large surface area of the respiratory epithelium. A key task for the immune system is, therefore, to discriminate between innocuous antigens and potential pathogens, minimizing the risk of tissue damage and at the same time defending against the risk of serious infection. Under normal circumstances, and in the absence of tissue damage, inhaled soluble proteins do not induce strong immune reactions, but instead lead to a state of immunologic hyporesponsiveness known as *inhalation tolerance*. In contrast, immune mechanisms within the lung become highly activated when exposed to replicating pathogenic microbes that are able to activate the innate immune system via TLRs and other pattern-recognition receptors.

The lungs have specific defense mechanisms to protect them from microbial pathogens. The nose and upper airway filter and condition inspired air, and the cough reflex and mucociliary blanket remove many inhaled particulates. The innate immune system relies on a relatively restricted range

of receptors that are able to respond in a rapid but stereotyped way to pathogens. Collectins (surfactant proteins), defensins, lactoferrins, mannose-binding lectin, complement, and lysozyme are secreted into the airway and alveolar lumen to provide nonspecific protection against infection, whereas alveolar macrophages and neutrophils express pattern recognition receptors and are the principal innate immune cells in the normal lung. In contrast, the adaptive immune system relies on dendritic cells, T cells, and B cells to generate an enormously diverse and exquisitely specific response to foreign antigens. Although the response to initial antigen exposure is relatively slow, the adaptive immune system generates long-lasting immune memory and provides a measure of protection against subsequent antigen exposure. Further description of the mechanisms of host defense against infection are provided in Section VII, Chapters 31 through 43. Mast cells and eosinophils are discussed elsewhere in relation to asthma.

Inhaled antigens are generally deposited on the epithelium by impaction or sedimentation. The mucociliary layer and tight junctions between epithelial cells limit access of antigen to immunocompetent cells. Those antigens that are able to penetrate the epithelial barrier are taken up by antigen-presenting cells (APCs). If the host has not previously been exposed to a particular antigen, activation of naïve T cells takes place in regional lymph nodes following presentation by migrating dendritic cells. In contrast, recall or memory responses to previously encountered antigens can occur within the airway submucosa or lung interstitium. The mechanisms by which inhalation tolerance develops and is maintained involve APCs (alveolar macrophages and lung dendritic cells) and T cell deletion, T cell anergy, and suppression by specific regulatory T cells.

DENDRITIC CELLS

Dendritic cells (DCs) are highly migratory cells that were first described over 30 years ago as a novel population of cells in mouse lymphoid organs, and were subsequently shown to be highly potent accessory cells.[78,79] Their major role within mucosal tissues is to sample environmental antigens, and then to migrate to regional lymph nodes where they present processed antigenic peptide to T cells. As such they are fundamental to the generation of appropriate immune responses to inhaled foreign antigens.

DCs are a heterogeneous class of antigen-presenting cells, and several DC subpopulations have been identified in humans and mice.[80,81] These include both myeloid, or *conventional* DCs, and the plasmacytoid DCs that have a unique ability to produce large amounts of type I interferons, and are thus critical for host defense against virus infection. Various DC populations with differing functions have been described in the mouse lung[82] although complete characterization of human lung DC subsets is very much in its infancy.

In the airway, DCs form a tightly-meshed network above and below the basement membrane of the respiratory epithelium,[83] such that they are ideally situated to monitor the external environment, sample inhaled antigens, and function as *sentinels* of the immune system. Studies in experimental animals have suggested that postnatal maturation of DCs in the respiratory tract is delayed relative to other tissues,[84] and the limited available data suggest that a similar situation exists in humans.[85] The paucity of functioning lung DCs in early life may play a role in the increased susceptibility of neonates to allergic and infectious respiratory diseases.

DCs in the gut epithelium are able to extend their processes through tight junctions in order to sample antigens from the gut lumen,[86] and lung DCs are likely to utilize a similar approach to take up inhaled antigens. While mucosal DCs in healthy tissues are adept at antigen uptake, they have a poor capacity to present antigen to T cells. Pathogens, tissue damage, and inflammation induce DCs to undergo a process of *maturation* or activation, leading to enhanced costimulatory molecule expression and an increased capacity to activate antigen-specific T cells. In contrast, when DCs take up innocuous antigens in the absence of inflammatory stimuli, DC activation does not occur. This leads to immune tolerance via a variety of mechanisms, including the induction of regulatory T cell populations.

Following antigen uptake, lung DCs rapidly transport antigen to the T cell zones of regional lymph nodes,[87] although a significant proportion of antigen-loaded DCs can also remain within the lung where they are able to activate T cells locally long after antigen exposure.[88-90] Although migration of DC to regional lymph nodes has traditionally been thought to be inextricably linked to DC activation, this now appears to be an oversimplification because some DCs clearly migrate to regional lymph nodes under steady-state conditions without undergoing maturation and are thus able to induce tolerance.

Not only are DCs major players in the initiation and amplification of immune responses, they also regulate the qualitative nature of these events, significantly influencing Th1/Th2 polarization,[91-93] through their expression of costimulatory molecules (e.g., CD80, CD86, CD40, OX40 ligand, and inducible costimulatory ligand) and via their secretion of soluble mediators such as IL-6, IL-10, IL-12, and prostaglandin E_2. A variety of microbial stimuli have the ability to program DCs to induce Th2 responses, including components of fungi, nematodes and cholera toxin.[94-96] Inhaled lipopolysaccharide (LPS), signaling through TLR4, can promote either a Th1 or a Th2 response in the airways depending on the dose of LPS, suggesting that the strength of microbial signaling may play a role in Th1/Th2 polarization.[97]

DCs are particularly responsive to signals received from the tissue microenvironment. Exposure of DCs to epithelial cell-derived thymic stromal lymphopoietin or PGE_2 and mast cell-derived histamine polarize the maturation of myeloid DCs into Th2 promoting DCs.[98-100] In contrast, other cytokines such as transforming growth factor β (TGF-β) and vascular endothelial growth factor promote *tolerogenic* DCs.[101,102] TLRs on DCs react not only to microbial components but also to endogenous ligands such as fibronectin, heparan sulfate, and heat shock proteins that are released in response to tissue injury,[103-105] and this is likely to be a mechanism by which DCs monitor tissue well-being.

For most healthy individuals, lung DCs induce tolerance to inhaled innocuous antigens, whereas in those who develop allergic asthma, tolerance induction is thought to be defective such that otherwise harmless allergens induce airway inflam-

mation. In contrast, lung DCs become activated and highly immunogenic when exposed to pathogenic microbes.

ALVEOLAR MACROPHAGES

Macrophages are specialized for the phagocytosis of particulate matter and the recognition of microbial pathogens, and are the most common immune cell in normal bronchoalveolar lavage fluid. Under normal conditions, they closely adhere to alveolar epithelial cells, and are generally kept in a quiescent state, producing minimal amounts of proinflammatory cytokines in order to minimize the risk of damage to the delicate gas-exchanging structures of the lung. In steady state, lung macrophages release inhibitory molecules such as TGF-β, IL-10, PGE_2, IL-1 receptor antagonist, and nitric oxide through which they inhibit the function of nearby DCs and T cells—thereby suppressing the induction of adaptive immunity.[106,107] Although normal alveolar macrophages have a high capacity for phagocytosis and antigen uptake and express major histocompatibility molecules, they are poor at presenting antigen to T cells, and do not generally migrate to regional lymph nodes where immune responses are initiated. Accordingly, macrophages may not play a major role in antigen presentation in the normal lung, although they may transfer antigen fragments to DCs that then migrate to lymph nodes and activate T cells.

Macrophage function changes abruptly in response to microbial pathogens. Engagement of TLRs and other pattern-recognition receptors leads to macrophage activation with the release of cytokines such as IL-1, IL-6, and TNF and activation of phagocytosis and cytotoxicity. Inflammatory monocyte precursors are recruited by chemokines from the circulation to the lung. These newly recruited monocytes are permissive for DC activation and T cell priming such that the usual macrophage "brake" on the adaptive immune system is temporarily released, and a window of opportunity opens up to allow immune responses to be initiated. Once the microbial load has been contained, the newly recruited monocytes will revert to the typical suppressive phenotype of resident alveolar macrophages.

Whereas phagocytosis of microbes leads to proinflammatory cytokine release, when macrophages ingest apoptotic cells, they do so in a way that does not induce inflammation,[108] but rather they release inhibitory molecules such as TGF-β and PGE_2.[109] The ability of macrophages to clear apoptotic cells is thought to be crucial to the resolution of inflammation and development of fibrosis, and there is some evidence that this function is defective in human disease.[110,111]

T CELLS

Most T cells within the lung express a T cell receptor (TCR) made up of α and β chains that recognize short peptides complexed to major histocompatibility (MHC) antigens. CD8 cells recognize antigenic peptide in the context of class I MHC and initiate cytotoxicity, typically directed against virally infected host cells. In contrast, CD4 cells respond to antigenic peptide in the context of class II MHC and provide help for B cells and antibody production. A second lineage of cells display a TCR made up of γ and δ chains. These γδ T cells are preferentially localized to the epithelium and recognize a more limited range of antigens than αβ T cells.

Within the circulation both naïve and memory (antigen-experienced) T cells are found in similar numbers. Naïve T cells traffic from the peripheral blood to lymph nodes and spleen, have a higher threshold for antigen activation, and can only respond to antigen-bearing dendritic cells. In contrast, memory T cells have a lower threshold for antigen activation, and can respond to a variety of APCs, in addition to dendritic cells. Memory T cells can traffic to a wider range of anatomical locations compared with their naïve counterparts because of a differing pattern of adhesion molecule and chemokine receptor expression, allowing them to accumulate in both lymphoid tissues and epithelial organs such as the lung. Most of the T cells in the normal lung display the phenotype of effector memory cells, with few detectable naïve or central memory cells.[112]

Functionally distinct subsets of T cells have been defined, based on differing patterns of cytokines that they produce (Table 4-3). This was initially defined in relation to CD4 T cells, where polarized T helper 1 (Th1) cells express the transcription factor T-bet and produce the cytokines interferon-γ and lymphotoxin, whereas T helper 2 (Th2) cells express the transcription factor GATA-3 and secrete the cytokines IL-4, IL-5, IL-9, and IL-13. CD8 cells (Tc1 and Tc2 subsets), natural killer (NK) cells, and eosinophils can also produce similar cytokine profiles. The definition of these T cell subsets has been extremely useful in understanding the pathogenesis of inflammatory lung diseases such as allergic asthma, sarcoidosis, tuberculosis, and a variety of other respiratory infections.

However, the Th1/Th2 paradigm is less useful in understanding immune responses to noninfectious antigens in the healthy lung. The recent recognition of a third class of T cells, the various regulatory T cells (Tregs), has shed light on the processes that mediate immune tolerance in the lung. Tregs were initially identified as a population of CD25+ CD4 cells that were able to inhibit both type 1 and type 2 immune responses. Some Tregs develop in the thymus, while others develop in the periphery. Further research has shown that the transcription factor Foxp3 is critical to the development of functional Tregs.[113,114] TGF-β is a critical factor regulating the development of Tregs, whereas TLR engagement of dendritic cells can inhibit Treg function.[115] Tregs can regulate allergic airway inflammation in animal models,[116] although this can be inhibited via IL-6 signaling.[117] CD4+ CD25+ Foxp3+ cells mediate their regulatory effects via contact-

Table 4-3
Characteristic Features of Th1, Th2, and T Regulatory Subsets

	Th1	Th2	T regulatory
Differentiation induced by:	IL-12	IL-4	TGF-β
Transcription factors	T-bet, STAT-4	GATA-3, STAT-6	Foxp3
Secreted cytokines	IFN-γ	IL-4, IL-5, IL-9, IL-13	IL-10, TGF-β
Role	Cell-mediated immunity	Humoral immunity	Immunoregulation

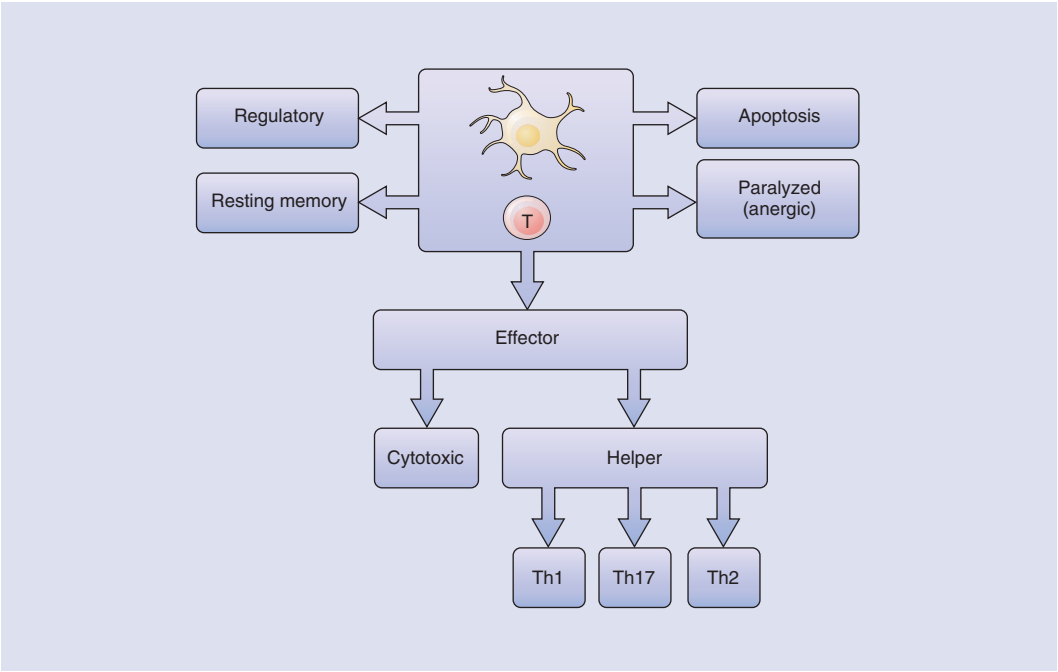

Figure 4-4 T cell responses can take many directions. Following an encounter with an antigen-presenting cell, naïve T cells can respond in a variety of ways, including apoptosis (programmed cell death), the induction of effector T cells, regulatory T cells, and a form of immunologic paralysis known as anergy. After initial T cell expansion, a small number of cells will survive as long-lasting memory cells, ready to respond rapidly in the event of later exposure to the same antigen.

dependent mechanisms, whereas there are other populations of suppressive T cells that mediate their effects directly through secreted IL-10 and TGF-β.

A distinct subset of helper T cells has recently been defined by their capacity to make the IL-17 family of cytokines. This cytokine provides defense against extracellular bacteria but may contribute to tissue inflammation in autoimmune disease,[118] and appears to be involved in neutrophil recruitment to the lung.[119] Thus, when T cells first encounter antigenic fragments presented by dendritic cells, their survival and differentiation can proceed in several different directions, as shown in Figure 4-4.

NATURAL KILLER CELLS AND NATURAL KILLER T CELLS

NK cells and NK T cells are characterized by natural cytotoxicity, the ability to rapidly lyse targets, especially virally infected cells. Although NK cells are devoid of TCR, NK T cells express a restricted repertoire of T cell receptors and are able to recognize a limited range of glycolipid antigens presented in the context of the MHC-like protein CD1d. Aside from their well-known role in host defense against infections, NK cells and NK T cells possess important immunoregulatory roles, releasing cytokines that are important in the early phase of Th1/Th2 polarization. Large numbers of NK T cells can be found in the lungs of people with asthma, and may play a role in disease pathogenesis.[120]

B CELLS

Relatively few isolated B cells are present in the airway mucosa and alveolar walls, and are instead congregated in regional lymph nodes, or in loosely organized lymphoid aggregates. These lymphoid aggregates are thought to be capable of T- and B-cell responses to inhaled antigens, and appear to be most prominent in young children, or in the context of lung inflammation.[121-123]

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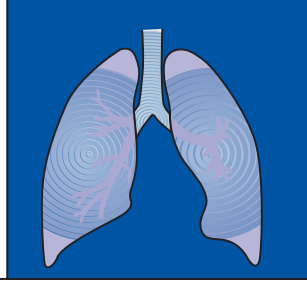

CHAPTER 5

Host Defense Systems of the Lung

J. Brian Kang and Gary L. Larsen

TEACHING POINTS

- Host defense of the lung is mediated by several complex but complementary processes, which include mechanical, nonimmunologic, and immunologic responses.
- The different components of the host defense mechanism undergo developmental changes. Young children are more susceptible to pulmonary infections because of these normal maturational processes.
- The mechanisms that protect the lung can also have the potential to produce harmful effects (e.g., inflammation).

From the first breath at the time of birth, the lungs must be protected from numerous insults from the environment. This defense takes many forms and has evolved to include mechanical as well as biochemical processes that work in an integrated fashion to safeguard the respiratory tract. This chapter reviews the host defense systems found in humans that protect this organ from injury. Because of this book's focus on pediatric respiratory medicine, information on the developmental aspects of the various components of lung defense is presented.

GENERAL CONCEPTS OF LUNG DEFENSE

Protection of the respiratory tract is provided by several complex but complementary processes.[1,2] The host defense systems normally prevent entry into or rapidly remove foreign material from the lungs. These systems include filtration of potential environmental pathogens from inspired air, cough to clear material from air passages, and mucociliary clearance to eliminate substances not cleared by the first two mechanisms. Both nonimmunologic and immunologic responses of the lung to potentially injurious agents commonly lead to inflammation.

FILTRATION AND DEPOSITION OF ENVIRONMENTAL PATHOGENS

The upper airway and the branching airways within the lung constitute the first line of defense against airborne particles. As ambient air containing suspended solid and liquid particles is drawn toward the gas-exchanging areas of the lung during inspiration, three major mechanisms of deposition come into play: inertial impaction, gravitational settlement, and diffusion.[3] In general, many larger particles (>10 μm) are trapped in the nose and upper airways (above the cricoid ring) as a result of inertial impaction. This mechanism of deposition is based on the principle that the inertia of a particle causes it to maintain its original direction for a distance depending on the density of the particle and the square of its diameter. Thus, when the stream of air changes direction or velocity, such as happens in the nasopharynx and at the divisions of larger airways within the lung, the larger and more dense particles are likely to hit the walls in these areas and be trapped. This is the primary means of deposition for the majority of larger particles within the respiratory tract. Indeed, because of this mechanism, the lung is spared the task of dealing with many large particles because they are filtered from inspired air before they penetrate the lung. Smaller particles are deposited primarily by gravitational settlement in the deeper recesses of the lung, with the speed of this process again related to the density of a particle and the square of its diameter. Diffusion takes place because airborne particles are displaced by the random bombardment of gas molecules, leading to collision with the airway walls. Compared to the first two processes, diffusion is responsible for a smaller percentage of total lung deposition.

Factors Influencing Particle Deposition

Regional deposition within the upper and lower respiratory tract as a function of particle size has been estimated by several investigators.[4] Figure 5-1 summarizes the results for uncharged, unit-density spheres orally inhaled at the mean breathing pattern of an adult male at 5-second respiratory cycle period and 300 cm^3/second flow rate. The total deposition of particles was partitioned into four regions of the respiratory tract: extrathoracic, upper bronchial, lower bronchial, and alveolar regions. The alterations that might be expected in a smaller subject are discussed later.

Several factors other than particle size also influence deposition. Primary among them are flow rates during inspiration. The greater the flow rate (as seen with exertion), the greater the impaction of particles. Conversely, the probability of a particle being deposited in an airway as a consequence of gravity or diffusion increases as airflow at the mouth decreases or breath-holding occurs. Other factors that may be important include changes in the size of a particle such as occurs with either evaporation or hygroscopic growth. Electrostatic changes may also have significant effects. A change from nose to mouth breathing also alters patterns of

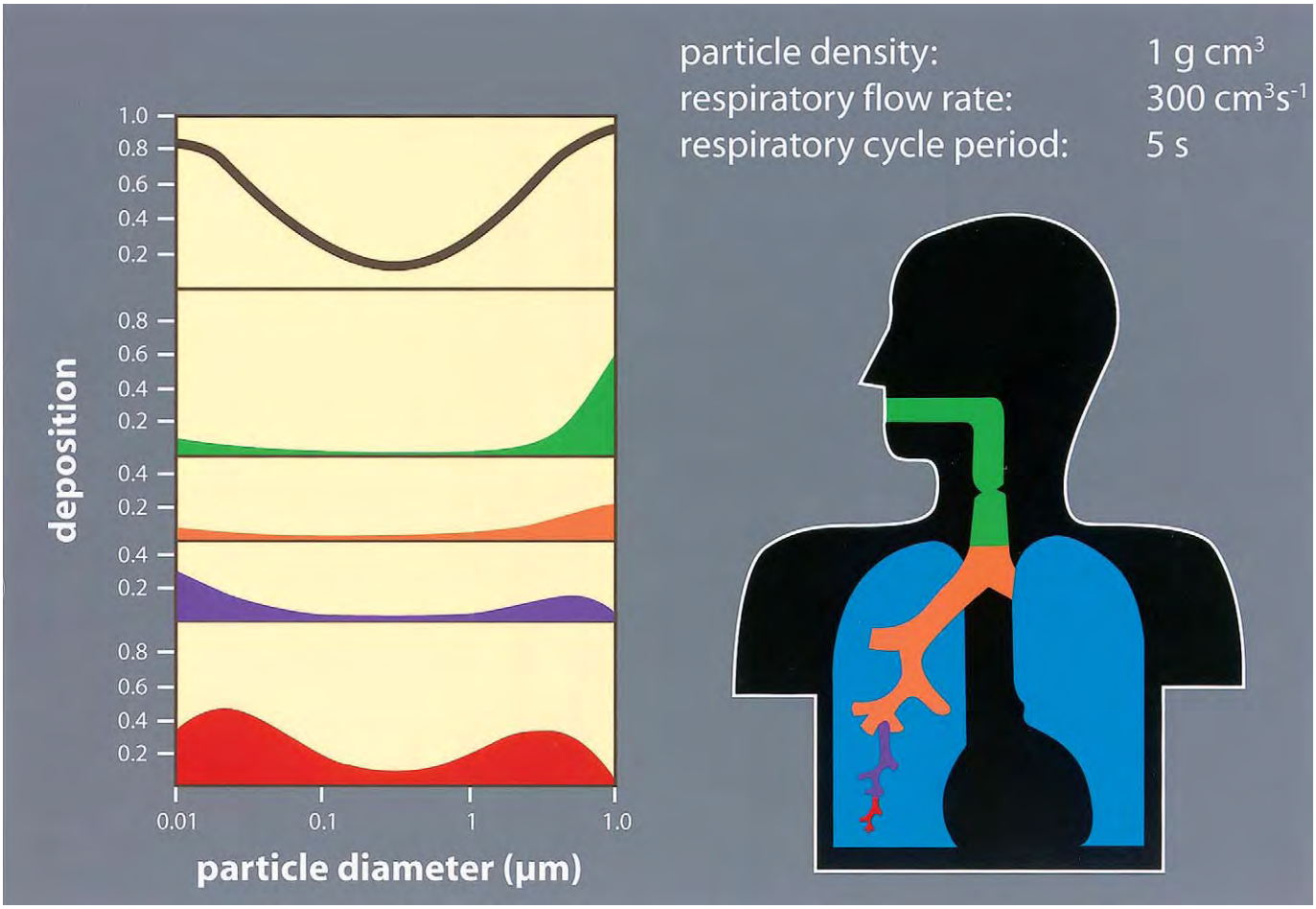

Figure 5-1 Total and regional deposition of orally inhaled unit-density spheres in the human respiratory tract as predicted by the International Commission on Radiological Protection deposition model. See text for discussion. (From Heyder J: Deposition of inhaled respiratory particles in the human respiratory tract and consequences for regional targeting in respiratory drug delivery. Proc Am Thorac Soc 1:315-320, 2004.)

deposition. These and other factors, including the influence of diseases of the airways on particle deposition, have been reviewed.[3]

A child's airway may be subjected to many types of insults (Fig. 5-2).[5] In this figure, the aerodynamic diameter of the particles is plotted against the deposition fractions taken from the calculations of Yu and colleagues.[6] The sizes and sites of deposition are of pathogenic importance in terms of the pulmonary symptoms produced by these insults. For example, the size of pollens leads to their deposition in the larger central airways before they reach the "pulmonary" compartment. As discussed in Chapter 57, allergic asthma in children is felt to be associated with inflammation within the central airways, with less pathology found within the gas-exchanging areas of the lung.

Changes in Particle Deposition with Growth

Studies of particle deposition have been performed primarily on adults; thus relatively little is known about particle deposition in infants and children. However, studies to date suggest that some important differences exist. For example, it has been estimated that the young child receives a potentially larger nasal dose of an aerosol than an adult because of aerosol deposition.[7] In addition, calculations based on casts of airways from infants to adults indicated that smaller (younger) subjects usually have greater tracheobronchial deposition efficiencies than larger (older) individuals.[8] For example, it has been estimated that the tracheobronchial dose per kilogram of body mass for particles with diameters of 5 μm may be six times higher in the resting newborn than in the resting adult if equivalent deposition efficiencies are operative above the larynx.[8] Additional predictions of tracheobronchial deposition have been made for infants, children, and adolescents.[9] Thus, for most particle diameters between 0.01 and 10.0 μm and for most states of physical activity, smaller individuals probably exhibit greater tracheobronchial deposition efficiencies than larger individuals. Considering the greater ventilation capacity per kilogram of body mass for smaller subjects, this suggests that the initial deposited tracheobronchial dose for young children may be well above that for the adult.

COUGH AS A MECHANISM TO PROTECT THE AIRWAYS

Several neurally mediated reflexes help protect the airways. These reflexes, which may occur separately or together, include sneezing, coughing, and bronchoconstriction. This discussion focuses on cough because of its important role in

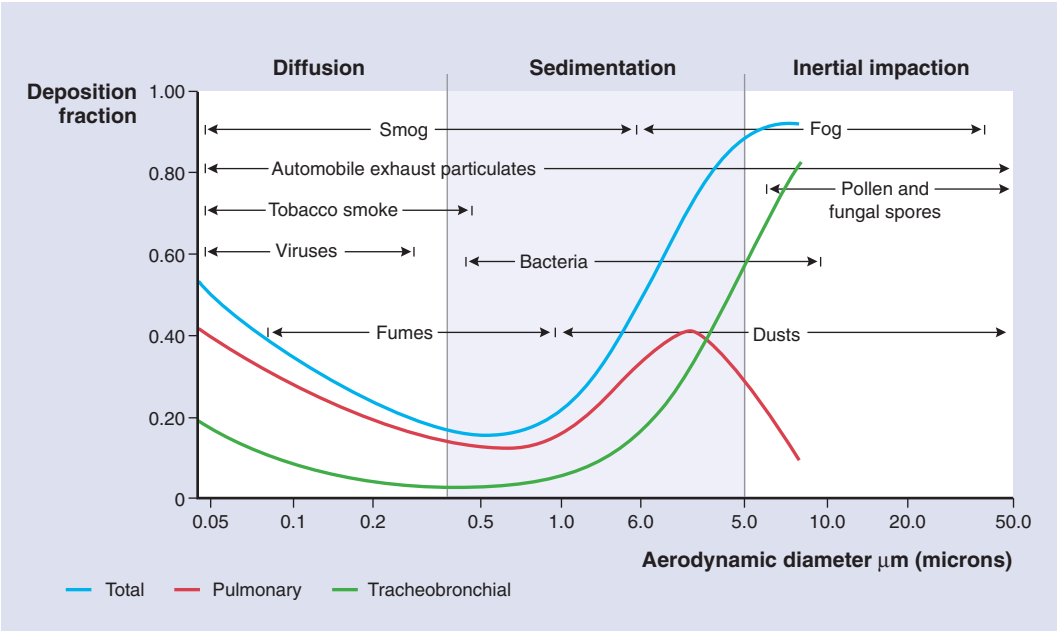

Figure 5-2 The size-deposition relation is shown for several stable particles of varying aerodynamic diameter for the tracheobronchial and pulmonary compartments of the lung. The total curve represents the sum from the two compartments. The deposition fractions are from the calculations of Yu and colleagues[6] and are for mouth breathing at less than 0.25 L/sec. The particle diameters over which diffusion, sedimentation, and inertial impaction are most important are displayed as are the approximate sizes of some common environmental insults. (From Dolovich MB, Newhouse MT: Aerosols: Generation, methods of administration, and therapeutic applications in asthma. In Middleton E, Reed CE, Ellis EF, et al. [eds]: Allergy: Principles and Practice, 4th ed. St Louis, Mosby, 1993, pp 712-739.)

limiting exposure to and deposition of potentially pathogenic material within the airways.

Cough must be considered an integral part of the mechanisms of airway defense against inhaled particles (e.g., dust) as well as noxious substances (e.g., cigarette smoke, ammonia fumes). Thus, the cough that occurs in otherwise normal individuals within a smoke-filled environment should be considered a protective reflex that helps limit the insult to the lower respiratory tract. In addition, cough should be considered an adjunct to the normal mechanisms of mucociliary clearance (see later section), becoming especially important when usual methods of mucus clearance are impaired or overwhelmed. This section emphasizes cough as a protective defense in otherwise normal individuals. The differential diagnosis of cough is dealt with in Chapter 10, whereas specific disease states in which cough is a prominent feature are discussed in the chapters on those disorders.

Although much is known about the stimuli and disease processes that elicit cough, knowledge concerning cough receptors in humans is incomplete and based on findings from animal models.[10] However, several general comments can be made. First, it is clear that cough-sensitive nerves extend from the larynx to the division of the segmental bronchi. Based primarily on studies performed in animals, it appears that several nerve fibers are involved in the production of cough. Adaptations of the cough reflex seen in humans in response to different types of airway stimulation suggest that there are different receptor populations with separate afferent neuronal pathways within the airways.[11] Sensory fibers and their specific stimuli have been delineated in the cough reflex of several animal models. Most authorities agree that more than one fiber type makes up the afferent neural fibers leading to cough and these fibers can differ from those that reflexively narrow the airways.[12]

Vagal afferent receptors that may be involved in cough and the regulation of airway tone have been reviewed.[10] Within the airways, the larynx and points of proximal airway branching appear to be especially important as sites where receptors initiate the cough reflex. Within the larynx, "irritant" receptors with myelinated afferents mediate cough and bronchoconstriction; less is known about laryngeal nonmyelinated afferents and their receptors. Thus, when cough and bronchoconstriction have been evoked from the larynx, myelinated afferents are usually implicated, but participation of laryngeal C-fiber receptors cannot be excluded. It is helpful to divide the afferent nerve endings of the lower airways (tracheobronchial tree) into four types: slowly adapting pulmonary stretch receptors (SARs); rapidly adapting stretch or irritant receptors (RARs); pulmonary C-fiber receptors or J receptors; and bronchial C-fiber receptors.[10] Although all four types have been implicated in regulating bronchomotor tone and in mediating cough, the myelinated irritant receptors (RARs) have received the most attention as initiators of cough reflexes. Various stimuli to C-fiber receptors and RARs are outlined in Table 5-1. Although the receptors respond to many of the same stimuli, the sensitivities vary greatly. C-fibers are activated by many of the same chemical and irritant stimuli that excite RARs; however when compared with RARs they are less sensitive to mechanical stimuli.[13] There is lack of clear evidence that C-fiber receptors are primary sensory input to the cough reflex. It appears that in response to stimuli, C-fiber receptors may release neuropep-

Table 5-1
Stimuli to C-Fiber Receptors and RARs

	C-Fiber Receptors		
	Pulmonary	**Bronchial**	**RARs**
Mechanical	Inflation	Inflation Foreign bodies	Inflation Deflation Dust Mucus Foreign bodies
Chemical	Irritant gases Cigarette smoke Capsaicin Volatile anesthetics	Irritant gases Capsaicin	Irritant gases Cigarette smoke Capsaicin Volatile anesthetics
Mediator	Acetylcholine Histamine Serotonin Prostaglandins Bradykinin Substance P	Histamine Serotonin Prostaglandins Bradykinin	Acetylcholine Histamine Serotonin Prostaglandins Bradykinin Substance P
Disease	Microembolism Pulmonary edema Pneumonia	Bronchial congestion	Anaphylaxis Microembolism Atelectasis Bronchoconstriction Pulmonary edema

RARs, rapidly adapting stretch receptors.
From Widdicombe JG: Sensory neurophysiology of the cough reflex. J Allergy Clin Immunol 96:S84-S90, 1996.

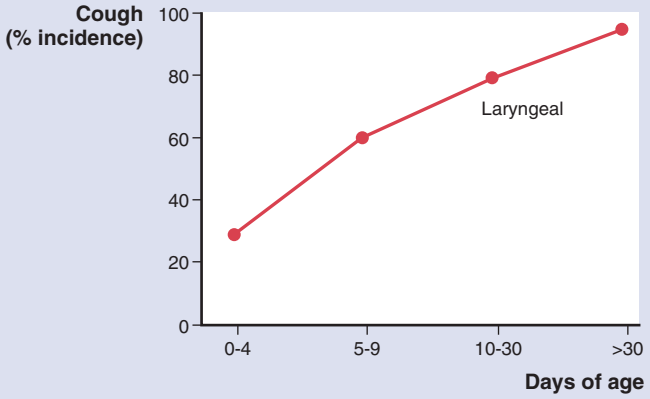

Figure 5-3 The percent incidence of cough in full-term infants as a function of age. Stimulation of the pharynx and vocal cords was obtained by direct laryngoscopy followed by the squirting of saline onto the vocal cords. Any cough resulting from either the introduction of the scope or exposure to saline was considered a positive result. The cough reflex was present in only 27% of 63 infants within the first 4 days of life but occurred in 90% (19 of 21 infants) when the postnatal age was 2 to 11 months (greater than 30 days in the illustration). (Data from Miller HC, Proud GO, Behrle FC: Variations in the gag, cough, and swallow reflexes and tone of the vocal cords as determined by direct laryngoscopy in newborn infants. Yale J Biol Med 24:284-291, 1952; and from Karlsson J-A, Sant'Ambrogia G, Widdicombe J: Afferent neural pathways in cough and reflex bronchoconstriction. J Appl Physiol 65:1007-1023, 1988.)

tides, such as substance P, which in turn stimulates RARs to cause cough and neurogenic inflammation.[12]

Most of what is currently known about the central nervous system relay for cough reflexes is in animal models.[14,15] The afferent system described earlier is transmitted to the first synaptic target in the nucleus tractus solitarius (NTS). The neurons in the NTS interact with a complex network of synapses within the brain stem network to elicit an efferent response via medullary motoneurons. The neuronal interactions within the brain stem network still need to be clarified.

The physiologic consequences of the efferent pathway are better understood and characterized in terms of the four phases of cough. First, inspiration may occur, leading to more efficient use of the expiratory muscles. This is followed by compression, which occurs when the rib cage and abdominal muscles contract while the glottis is closed. Compression leads to increased intrathoracic pressures, which help achieve the high airflows that occur when the glottis opens during expression, the third phase of cough. The final phase, relaxation, is characterized by expiratory muscle relaxation, leading to a fall in intrathoracic pressures. In addition to the clearance of particles by high velocity in the larger airways, there is progressive upward dynamic compression of the smaller airways, thus squeezing materials upward during a series of coughs throughout expiration.

Developmental Aspects of Cough

The development of cough has been reviewed.[16] Based on the observation that less than one half of both term and premature infants cough when stimulated by direct laryngoscopy and spraying of the vocal cords with saline (Fig. 5-3),[17] there has been speculation that the peripheral receptors and central neural mechanisms mediating cough reflexes are ineffective early in life. This, combined with a musculoskeletal system that is undergoing development (e.g., compliant rib cage and airways, mechanically disadvantaged diaphragm), has led to the concern that cough is not only less common but also less effective in the neonatal period.[16] Studies in newborn animals have led to speculation that sparse RAR activity as well as lower activity of SARs in newborns contributes to the weaker response to tussigenic stimuli in the early stages of development.[18] In terms of changes with age, a cough reflex was present in 90% of infants older than 1 month (see Fig. 5-3),[17] suggesting that this potential impairment in lung defense is not long lasting in these otherwise normal subjects. This same investigation found that less than one half of premature infants had cough reflexes at comparable postnatal ages.

MUCUS SECRETION AND CLEARANCE

A critical mechanism for removing particles from the entire system of conducting airways (nasopharynx and tracheobronchial tree) is mucociliary clearance. The contributions of the nose to lung defense have been reviewed[19] and are not addressed except to emphasize that many larger particles are removed from inspired air in the nasopharynx before they enter the lungs. Particles that escape this first line of defense encounter a film of mucus that covers most of the surface of the tracheobronchial epithelium. Deposition on this film leads to eventual removal from the airways as the mucus is propelled to the oropharynx, where it, along with unwanted particles, is swallowed or expectorated.

Secretory cells and their products are important for maintaining a healthy environment within the lower respiratory tract.[20] Respiratory secretions consist of a double layer on the surface of the airway epithelium. The inner layer of periciliary fluid (sol phase) is the environment in which cilia beat and is probably supplied by transepithelial ion and water transport. The outer mucus layer (gel phase) is viscous in nature. Because it is nonabsorbent to water, it may prevent dehydration of the sol phase. Respiratory mucus in the tracheobronchial tree is produced by both submucosal glands and goblet cells. The former are confined to cartilaginous airways, whereas the latter extend farther into the periphery of the conducting airways. Although goblet cells are present in the epithelia of all ciliated regions of human airways, they become progressively fewer in number in the more distal bronchioles. The submucosal glands are primarily under parasympathetic neural control, and goblet cells secrete products when directly irritated. The thickness of the mucus layer is fairly constant, at least throughout the larger airways (5 to 10 μm). It appears possible that mucus is normally secreted in response to stimulation of the airway surface and that the small plaques generated in this fashion become the vehicles for removing trapped particles, including bacteria.[21] Mucus may appear to be a continuous sheet within the trachea because the impact of particles is greater in this larger airway and because mucus generated in all lower airways converges for clearance within the trachea. The importance of mucus in the defense of the lung was suggested by the observation that particle transport failed in the absence of mucus but was restored by the placement of autologous or heterologous mucus on the ciliated epithelium.[22]

Tracheobronchial mucus consists of a mixture of secretions from the surface epithelium and submucosal glands as well as tissue fluid transudate.[23] It is composed primarily of water (95%), glycoproteins (2% to 3%), proteoglycans (0.1% to 0.5%), and lipids (0.3% to 0.5%). The major glycoproteins are mucins which are found in two forms: the secreted gel-forming mucins which give the mucus its characteristic elasticity and the membrane-bound mucins present on the epithelial surface, which may act as cell surface receptors.[20] By forming oligomers, the mucin proteins form a gel that possesses fairly low viscosity and elasticity, allowing it to be easily cleared by the cilia. Although currently there are 19 identified mucin genes (MUC), the principal secreted mucins for the airway mucus gel are MUC5AC and MUC5B. MUC5AC mucins are produced predominantly by goblet cells in the surface epithelium, whereas the MUC5B mucins are secreted from the submucosal glands. The gel-forming mucins can be changed in amount, type, and size in certain inflammatory airways disease (e.g., asthma, cystic fibrosis) thereby impairing mucociliary clearance.[24]

Ciliated cells within the tracheobronchial tree of humans have approximately 200 cilia per cell.[25] Cilia are complex structures, with their axonemes enclosed in extensions of the epithelial cell membrane (Fig. 5-4).[26] Congenital ciliary defects that cause respiratory disease and infertility, as well as acquired abnormalities found in cilia, are dealt with in Chapter 67.

Cilia beat in one plane with a fast, effective stroke (power stroke) followed by a recovery stroke that is two to three times slower. The normal beat frequency in several species, including humans, ranges between 12 and 22 Hz.[27] Throughout most of the beat cycle, cilia move through the periciliary fluid beneath the layer of mucus, with their tips penetrating the mucus only during the effective stroke. Cilia work not alone but as members of a metachronous wave. Although there is evidence in mammalian respiratory epithelia for nervous and hormonal control of mucus secretions, there is no convincing evidence of direct nervous or hormonal control of ciliary beat frequency. Rather, it may be that an increase in the mucus load stimulates ciliary activity.[21]

Mucociliary Clearance as a Function of Age

Cells needed for the production and clearance of mucus are present within the developing airway from a very early period of prenatal development.[28] Ciliated cells are differentiated in the proximal airways by week 13 of gestation, with differentiation proceeding centrifugally during fetal development. Ciliary activity that is coordinated begins during the saccular phase. Submucosal or bronchial glands are present in the trachea by week 10 of gestation, whereas goblet cells appear by week 13. The rate at which mucociliary clearance occurs at various postnatal ages has not been well characterized because of the difficulty of performing such studies in infants and small children. However, it is known that mucociliary clearance does decrease in older subjects. By analyzing the decrease in the bronchial radioactivity of an aerosol of resin particles labeled with technetium 99m, researchers noted that clearance was significantly lower in subjects older than 54 years of age compared with subjects 21 to 37 years of age. In addition, a significant negative correlation was obtained between the ages of the healthy subjects and their rate of mucociliary clearance.[29]

PULMONARY INFLAMMATION

Nonspecific and antigen-specific (immune) mechanisms of lung defense commonly lead to an inflammatory response that is responsible for protecting this organ. Inflammation also has the potential to injure the lung,[30] but discussion of the deleterious aspects of inflammation is reserved for Chapters 6, 57, and 61.

Definition and General Features of Inflammation

Inflammation is broadly defined as a nonspecific protective reaction of vascularized tissues to injury.[31] The classic clinical features of this phenomenon are related to an increase in blood flow in vessels (calor and rubor), an increase in vascular permeability and cellular infiltration (tumor), and the release of materials at the site of inflammation that leads to pain (dolor). In general, this process is self-limited and leads to the return of the tissue or organ to a normal state both structurally and functionally.

The hemodynamic changes associated with inflammation are often the first to be manifested. Vasodilation, increased blood flow, and enhanced permeability are the fundamental elements of inflammation. These alterations apparently allow the body maximal opportunity to recruit inflammatory cells and bring plasma proteins to the site of injury. This has practical importance in terms of both effectively mounting an

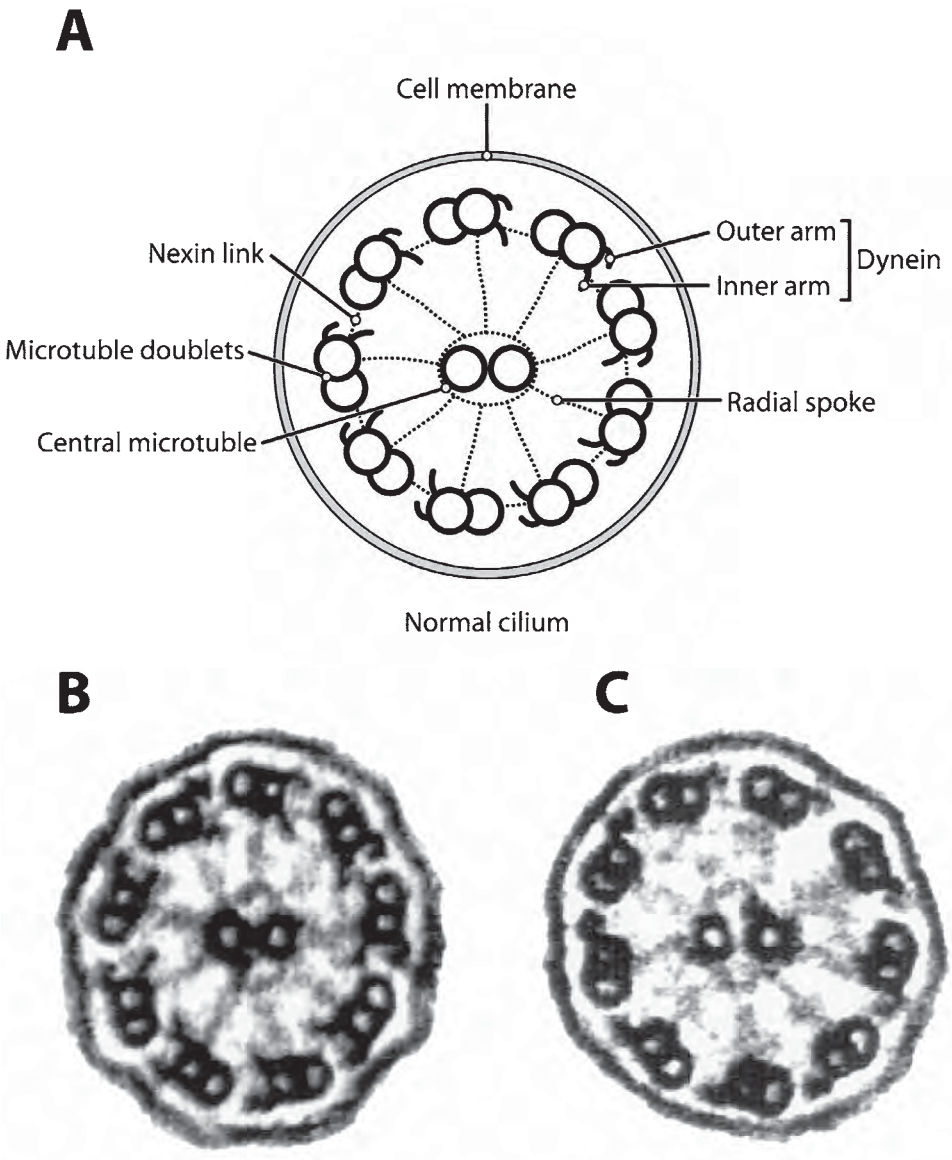

Figure 5-4 **A,** Diagram of the ultrastructure of a normal cilium showing a single pair of central microtubles surrounded by nine microtubule doublets. Each doublet is connected to the next pair by nexin links. From each doublet, inner and outer dynein arms project to the adjacent doublet. Radial spokes connect the central pair to the peripheral microtubule doublets. **B,** Transmission electron micrograph of the normal ciliary cross section. **C,** Transmission electron micrograph of a cilium with absent inner dynein arms. (Modified with permission from Chilvers MA, O'Callaghan C: Local mucociliary defence mechanisms. Paediatr Respir Rev 1:27-34, 2000.)

appropriate response and limiting the process when it is no longer needed. For example, the plasma proteins may lead to resolution of the process by bringing plasma proteinase inhibitors to sites of inflammation (see later section).

The histologic picture seen in an acute inflammatory reaction within the lung is shown in Figure 5-5. The response was produced by the instillation of C5a des Arg into the peripheral airways of normal rabbits.[32] This proinflammatory (phlogistic) fragment is generated from the fifth component of complement (C5) during complement activation through either the classic or alternative pathway and induces neutrophil chemotaxis (directed migration of neutrophils), oxygen radical generation, and neutrophil granule exocytosis.[33] The same type of inflammatory response may be seen in other vascularized tissues of the body after exposure to C5a des Arg or in the lung after exposure to other stimuli, such as immune complexes and bacteria. Thus, this example is meant to display the typical histologic picture of inflammation within one region of the lung (alveoli). The sequence of permeability, neutrophil accumulation, and later mononuclear phagocyte infiltration occurs before resolution of the process. Over several days, the alveoli clear, and the alveolar walls assume their normal thickness and cellularity. A similar histologic evolution in terms of progression and resolution of the process is seen in both the large and small airways.[34]

One of the fundamental features of inflammation is the redundant nature of the process. Interactions of the kinin, clotting, fibrinolytic, and complement pathways are, in part, responsible for this redundancy in that they each permit generation of inflammatory mediators while also allowing for amplification of the response by recruiting mediators from the other systems. In addition, a mediator or mediators with similar actions may be produced by many different cells within the lung. Therefore, the inflammatory response is complex, with the possibility for generating multiple phlogistic mediators by several types of cells. This built-in redundancy amplifies the response in a normal individual and preserves the response if one system is deficient.

Ontogeny of the Inflammatory Response

Knowledge about the ontogeny of inflammatory responses within the lung is limited. Most studies of ontogeny have been performed in animals, leaving researchers to speculate

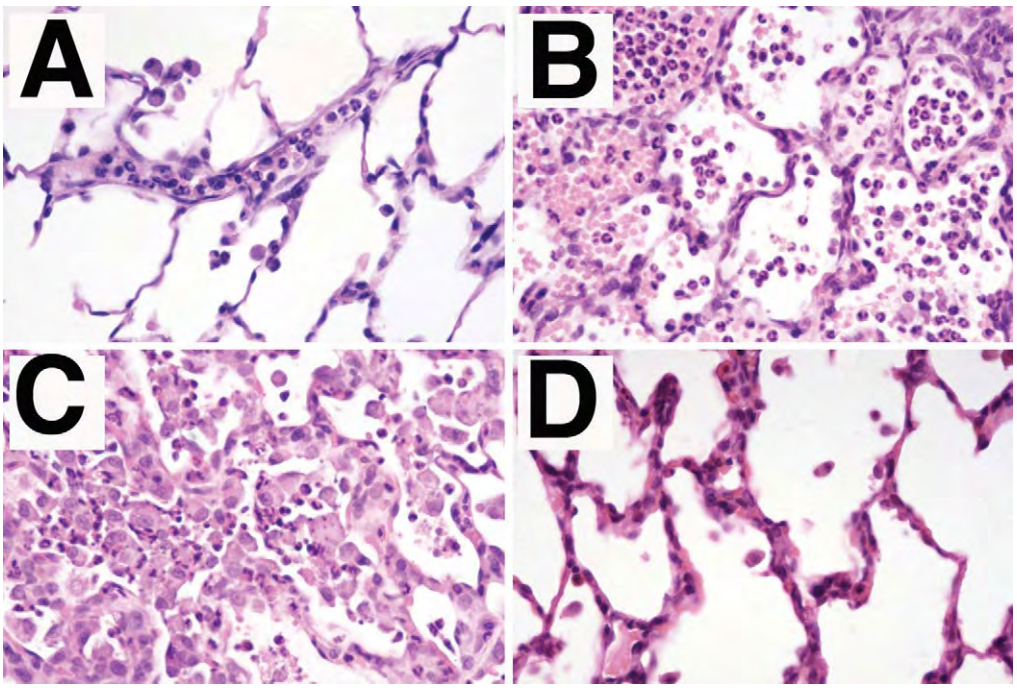

Figure 5-5 Inflammatory response produced by instillation of C5a des Arg into the airways of rabbits. **A,** In the normal lung, resident alveolar macrophages are present in some alveoli, but neutrophils are not seen. **B,** After 6 hours of administration of this C5 fragment, granulocytes (primarily neutrophils) and a protein-rich fluid are apparent in the alveoli. **C,** By 24 to 48 hours the neutrophils are replaced by mononuclear cells. **D,** Over several days, the alveoli clear, and there is almost complete return of the alveolar wall to its normal thickness and cellularity. (Courtesy Gary L. Larsen and Cori Fratelli: National Jewish Center for Immunology and Respiratory Medicine, Denver.)

about the relevance of the findings in humans. However, a few observations should be cited to stress that the inflammatory response has age-dependent features.

Macrophages have not been identified within the lung during the pseudoglandular and canalicular phases of fetal development.[35] In the rabbit, the influx of pulmonary macrophages into the alveoli precedes birth by several hours and occurs when phosphatidylcholine is released into the extracellular space by type II cells.[36] Animal studies have also shown that neonatal pulmonary macrophages have reduced opsonic receptor function, defects in ingestion or killing of bacteria, diminished free radical production, and impaired chemotaxis.[37] In terms of other inflammatory cells, some studies suggest that cellular functions (i.e., intracellular killing of organisms, oxidative metabolism, migration) of circulating human neutrophils are also immature in the neonate.[38] In addition, newborn and perinatal animals are hyporesponsive to several vasoactive mediators as well as mediators that produce directed migration (chemotaxis) of inflammatory cells.[39] This immaturity or defect in the pulmonary inflammatory response may help explain the observation that bacterial infections of the respiratory tract are frequently encountered and can be quite severe in the young infant (see Chapter 34).[37]

Chemical Mediators of Inflammation

An *inflammatory mediator* may be defined as a chemical messenger that acts on blood vessels and cells to contribute to an inflammatory response.[31]

VASODILATION

Of the features associated with the inflammatory process, vasodilation has been the least studied. Despite this limitation, this feature is generally considered to be critically important for the full expression of an acute inflammatory reaction. In this respect, local blood flow is an important determinant of the amount of exudate produced. A number of mediators, including histamine and various eicosanoids (products of arachidonic acid metabolism), are involved in the regulation of local blood flow. For example, prostaglandins (PGs) may exert their effects in part by modulating blood flow. In addition, it is now apparent that PGs can have marked proinflammatory effects as potentiators of the effects of other mediators. PGE_2 and PGI_2 injections induce vasodilation, presumably by acting on cells of the blood vessel wall.[31] In addition, vasodilator PGs have been detected in inflammatory exudates. At physiologic concentrations PGE_2 and PGI_2 have been shown to synergize with other mediators, such as histamine and bradykinin, to cause increased vascular permeability and edema.[40] Although prostaglandins have little or no effect on leukocyte migration in vivo,[40] a potentiating effect of vasodilator PGs has been noted with chemotactic factors,[41] suggesting that local vasodilation enhances the migration of neutrophils into tissue.

Other products of the cyclooxygenase pathway of arachidonic acid metabolism, such as thromboxane A_2, have vasoconstricting properties.[31] Thus, the eicosanoids generated during an inflammatory process may have contrasting actions. In addition, a vasodilating PG may have effects that may be either proinflammatory or antiinflammatory. For example, PGs may inhibit leukocyte and mast cell secretion,[31,40] thus limiting the inflammatory response. Therefore, the concentration and mix of mediators generated at a site within the lung may define the overall effect on the tissue.[42]

ALTERED PERMEABILITY

In many types of tissue injury, increased permeability occurs in at least two phases: an early, transient increase occurring almost immediately after an insult to the tissue and a late or second phase beginning after a variable latent period but persisting for hours or days. Evidence indicates that the early,

transient permeability seen with certain types of challenges is due to the release of histamine. Mediation of the delayed phase of exudation is more complex and has been attributed to various factors, including kinins, PGs, neutrophils, and lipoxygenase products of arachidonic acid metabolism.[31]

Histamine is the mediator most often associated with an early increase in permeability after various insults to the lung. Although histamine is widely distributed, the histamine contained in mast cells within the lungs provides the primary source for acute pulmonary inflammatory reactions. Mast cells are commonly located around blood vessels and may be stimulated to release their products by several stimuli, including various drugs, allergen immunoglobulin E (IgE) interactions, and complement fragments (C3a and C5a) produced through activation of either the alternative or the classic pathway. The concept that histamine increases vascular permeability by causing contraction of the endothelial cells of the postcapillary venule, thus creating inter-endothelial junctions for the passage of fluid and proteins, has been reviewed.[43]

Bradykinin can also increase vascular permeability. The generation of this mediator is complex and involves several steps and pathways.[44] First, Hageman factor (factor XII of the clotting system) is activated by contact with a negatively charged surface or by contact with a variety of biological materials. This enzyme then activates (and is activated by) plasma kallikrein. The kinin is cleaved from kininogen by this kallikrein or kallikrein from tissues, as well as possibly by other proteases such as plasmin. Once generated, kinins are rapidly broken down in plasma and tissues by kininases and within the circulation undergo almost complete inactivation during one passage through the pulmonary circulation.[45]

Platelet-activating factor, or acetylglyceryl ether phosphorylcholine, is another mediator that can cause increases in vascular permeability as well as other proinflammatory events.[46] When inhaled into the human lung, platelet activating factor is thought to generate secondarily eicosanoids,[47] making it possible that these secondary products are responsible for some of the acute effects of this mediator. Because of its ability to aggregate rabbit platelets, this lipid was initially referred to as *platelet-activating factor*. However, it has subsequently been shown to also be a potent chemotactic factor for polymorphonuclear leukocytes. In addition, the molecule causes these cells to degranulate and stimulates an increase in oxidative metabolism. Appropriately stimulated neutrophils, eosinophils, monocytes, alveolar macrophages, and endothelial cells synthesize and release this biologically active lipid.

Several other molecules generated within the lung can increase permeability.[31] These include fibrinopeptides, fibrin degradation products, various lymphokines, and anaphylatoxins (C3a, C5a).

CELLULAR INFILTRATION

As displayed in Figure 5-5, one of the most noticeable histologic features of an inflammatory response is accumulation of cells within the pulmonary tissue. Early in the reaction, the infiltrate is predominantly composed of neutrophils, whereas at a later time the picture is dominated by mononuclear phagocytes. The molecular mechanisms by which leukocytes migrate out of blood vessels are now being defined.[48] Central to the whole process is the concept that chemotactic factors are generated at an extravascular site and pass through the vessel wall to initiate the first step in the emigration of the cells from the vasculature: the adhesion of leukocytes to the endothelium. A number of inducible cell adhesion molecules, including vascular cell adhesion molecule-1 and intercellular adhesion molecule-1, have been identified as being critical to this process.[48]

Research in the area of inflammation has emphasized the identification of molecules that produce directed motion of inflammatory cells along a concentration gradient (chemotaxis). Some of the most potent neutrophil chemotaxins are C5 fragments.[32] These fragments are low-molecular-weight factors produced through the cleavage of C5 by a variety of endopeptidases. C5 convertases derived from the classic or alternative complement pathways cleave the 74-amino acid terminal fragment termed *C5a*. Other proteases, including plasmin, trypsin, kallikrein, and bacterial proteases, may cleave the C5 molecule at the same or a different site, generating fragments with similar biological activities.

Within the lung, the chemotactic factors produced by alveolar macrophages after various challenges probably act with the complement system to mount a full inflammatory response. Alveolar macrophages have been recognized for some time to synthesize and secrete low-molecular-weight protein chemoattractants as well as low-molecular-weight lipids with chemoattractant activity.[49,50] One characterized mediator that is a potent chemoattractant for neutrophils in vitro and that is expressed after immune stimulation of many cell types, including macrophages, is interleukin-8 (IL-8).[51] The observation that this cytokine may also be expressed in human bronchial epithelial cells[52] again underscores the potential for redundancy of the inflammatory process.

Other specific chemoattractants for inflammatory cells include lymphokines such as IL-1 produced by monocytes and macrophages,[53] factors produced by mast cells, and lipid mediators. One potent lipid chemotactic for neutrophils is the arachidonic acid metabolite, 5,12-dihydroxyeicosatetraenoic acid, or leukotriene B_4 (LTB_4). Arachidonic acid is converted to LTB_4 and related compounds in human neutrophils, monocytes, eosinophils, and macrophages. In some leukocytes, such as the human alveolar macrophage, LTB_4 may be the major product formed from arachidonic acid.[49,54] LTB_4 stimulates neutrophil chemotaxis, enhances neutrophil-endothelial interactions, and stimulates neutrophil activation, leading to degranulation and the release of mediators, enzymes, and superoxides.[54]

In much of the systemic microvasculature, the predominant site of neutrophil margination and emigration is the postcapillary venule.[55] In the lung however, much of the neutrophil sequestration and emigration occurs throughout the pulmonary capillaries.[56,57] Studies suggest that inflammatory mediators reduce the deformability of neutrophils in the narrow capillaries, thereby lengthening the capillary transit times, and/or stop neutrophils, increasing the concentration of neutrophils at inflammatory sites.[57]

OXYGEN RADICALS

The neutrophil is armed to use both the reduced form of nicotinamide-adenine dinucleotide phosphate (NADPH) oxidase system and the granule constituents in a cooperative

manner to fight invading organisms. In terms of the former, the plasma membrane of the neutrophil is the location of the enzyme NADPH oxidase that underlies this cell's ability to generate a family of reactive oxidizing chemicals, including superoxide anion, hydrogen peroxide, and the hydroxyl radical.[58] The bulk of superoxide generated by the cell dismutates to hydrogen peroxide, which is rapidly catabolized. Myeloperoxidase, an enzyme that is localized to the azurophilic granules of neutrophils and that is released in substantial amounts into the extracellular fluid when this cell is triggered, catalyzes peroxidative reactions.[59] In combination with hydrogen peroxide, myeloperoxidase can oxidize halides to their corresponding hypohalous acids. In most instances, this reaction involves chloride with the formation of hypochlorous acid (HOCl). Studies have now revealed that under a variety of conditions, human neutrophils can be triggered to generate HOCl as a major product of oxidative metabolism.[58] HOCl is a powerful oxidant that rapidly attacks biologically relevant molecules, creating a derivative group of oxidants known as *chloramines*. Although chloramines are less powerful oxidants than HOCl, they are able to chlorinate or oxidize a wide range of target molecules.[58,60] As long as hydrogen peroxide is supplied, myeloperoxidase uses plasma chloride to generate HOCl until the pool of oxidizable targets is consumed. Only then does HOCl generation come to a halt as the oxidant attacks and oxidatively autoinactivates myeloperoxidase itself.[60] Using in vitro systems, Klebanoff[59] and Test and Weiss[60] have shown that neutrophils can use the large quantities of reactive chlorinated oxidants to mediate extracellular cytotoxicity. However, it has been more difficult to implicate these oxidants in vivo. This is probably because most in vitro systems use simple, plasma-free buffers to maximize the interactions of HOCl and the target population of cells, whereas in more physiologic surroundings, HOCl attacks both cellular targets and plasma constituents. Thus, the oxidant's extracellular cytolytic potential is dissipated.

Another mechanism through which products of the respiratory burst might participate in lung defense is through the production of mediators of inflammation that potentiate an inflammatory response. A link may exist between the occurrence of aggressive oxygen species and the stimulation of eicosanoid biosynthesis.[61] Reactive oxygen species have also been shown to be signal transduction molecules to activate the chemotactic cytokine IL-8 and the cell surface adhesion protein, intercellular adhesion molecule-1, which orchestrate the transendothelial migration of neutrophils to sites of inflammation.[62]

NEUTROPHIL GRANULES

Neutrophils contain many storage granules, which in turn contain microbicidal substances and digestive enzymes.[49] There are four major groups of secretory compartments within neutrophils: primary (azurophilic) granules, secondary (specific) granules, tertiary (gelatinase) granules, and secretory vesicles.[63,64] The granules are distinguished by their protein content and the physiology of their secretory processes. Primary granules are related to lysosomes and contain myeloperoxidase (MPO); a variety of proteolytic enzymes, including elastase, cathepsins, and proteinase-3; and several microbicidal substances, including lysozyme, defensins, and bactericidal permeability increasing protein. Secondary granules contain most of the cell's lysozyme as well as lactoferrin, which may facilitate the formation of the hydroxyl radical,[65] making it a potentially important contributor to the microbicidal activity of neutrophils. Other specific granule contents include procollagenase, plasminogen activator, cytochrome *b*, histaminase, vitamin B_{12} binding protein, and receptors for fMet-Leu-Phe, iC3b, and laminin.[63] Tertiary granules contain gelatinase, a matrix metalloproteinase, and integrins. Secretory vesicles appear to replenish membrane enzymes (alkaline phosphatase and ATPase) on release to the cell surface after cell activation. Activation of neutrophils results in discharge of primary granules into developing phagosomes and the secretion of specific granule contents into these phagosomes as well as into the extracellular milieu. Thus, secondary granules are thought to have more of an external secretory function in cases in which their contents modify the external environment. This modification of the environment may be important for neutrophil infiltration into tissues as well as for tissue remodeling that is part of the reparative process after an insult.

A critical part of the role of the neutrophil in defense of the lung is the cell's adherence to and ingestion of particles and microorganisms by the process of phagocytosis and the subsequent killing of potentially pathogenic organisms.[63] The membrane surface components that mediate the phagocytosis of inert particles (e.g., carbon) are not well characterized. However, receptor-mediated phagocytosis can occur when microorganisms are opsonized by C3b, iC3b, or antibody. When neutrophils come in contact with such particles, there is an accumulation of actin filaments at the site of particle attachment. As the advancing pseudopod comes into contact with the particle, further receptor-opsonin interaction occurs. When the particle to be ingested is completely surrounded, the opposing pseudopods fuse to form a sealed phagosome within the cytoplasmic compartment. The contents of the phagosome fuse with primary granules to form the phagolysosome. Within the phagolysosome, defensins are major antimicrobial agents with activity against a variety of bacteria, fungi, and certain viruses.[66] The actions of these and other highly cationic proteins involve the donation of protons to form bonds with negatively charged substances at the microbial surface. Disruption of cell membrane permeability and transport mechanisms may lead to death of the cell. Other antimicrobial agents work through other mechanisms. For example, lysozyme is bactericidal because of its enzymatic cleavage of the β-1-4 bond between *N*-acetylglucosamine and *N*-acetylmuramic acid residues in bacterial cell walls. In addition to facilitating hydroxyl radical formation, lactoferrin may retard bacterial growth by binding iron so that it is not readily available to the microorganism. Elastase, a neutral protease found within primary granules, degrades proteins of gram-negative rods.[67] These and other microbicidal mechanisms of defense used by neutrophils have been reviewed.[63]

The contents of neutrophil granules also have the potential to injure the lungs and other organs.[58] Although neutrophil granules contain a large family of enzymes, their greatest potential for acting as mediators of tissue destruction probably resides in three particular enzymes: elastase and collagenase found in primary granules and gelatinase found in secondary granules. Normally, tissues are protected against

injury because they are bathed in powerful plasma antiproteinases. For example, the host's primary defense against unchecked elastase-mediated damage is α_1-proteinase inhibitor, a 52-kD glycoprotein that irreversibly inhibits neutrophil elastase by forming an enzyme-inhibitor complex. Additional protection is provided by the fact that metalloproteinases (collagenase, gelatinase) are synthesized in a latent, inactive form.

NONIMMUNOLOGIC RESPONSES OF THE LUNG

Stimuli Leading to Inflammation

Stimuli that produce inflammation may do so through immunologic and nonimmunologic mechanisms, part of the innate host response. For example, the inhalation of endotoxin or noxious gases may lead to inflammation through the direct effects of the agents without participation of antigen-specific cell or humoral mechanisms directed at the stimulus. Gram-negative bacteria to which the host has been previously exposed may produce inflammation through a combination of processes. Thus endotoxin within the cell wall may serve as a stimulus for the migration of polymorphonuclear leukocytes into the site of infection.[53] When bacteria-specific antibodies are also present, an antigen-antibody complex may also initiate an inflammatory reaction. Because both processes are critical in lung defense and may provide effective deterrents only when combined, their separate components should be understood. For this reason, various aspects of nonimmune and antigen-specific defenses are considered separately. As will become apparent, some cells (e.g., macrophages, mast cells) and extracellular factors (e.g., complement) have important roles in both types of defense.

Cells of Importance in Nonimmune Responses

Some resident cells within the respiratory tract can initiate and perpetuate inflammatory reactions by virtue of their location and cellular functions. These include pulmonary macrophages, airway epithelial cells, mast cells, and polymorphonuclear leukocytes.

PULMONARY MACROPHAGES

Macrophages are pulmonary representatives of the mononuclear phagocytic system and are present in alveoli and respiratory bronchioles (alveolar macrophages) as well as more central airways. For simplicity, the term *pulmonary macrophage* as used in this section refers to the entire population of mononuclear phagocytes within the lung, independent of the maturity of the cell, and thus includes recently recruited blood monocytes as well as macrophages that have resided within the lung for several weeks. The interstitial compartment as well as the walls of conducting airways also contain macrophages.[49] These mobile cells represent a critical line of defense against injurious agents that escape clearance by the mechanisms of impaction, cough clearance, and mucociliary clearance. Many of these cells reside within the periphery of the lung, where these protective mechanisms are no longer effective because of the small size and structure of the airways.

Pulmonary macrophages have an important role in maintaining normal lung function through their ability to scavenge particulates, kill microorganisms, recruit and activate other inflammatory cells, and function as accessory cells in normal immune responses. A critical activity of pulmonary defense is the phagocytosis and killing of microbial organisms performed by macrophages. Pulmonary macrophages engulf particulates, including microorganisms and macromolecular debris, nonspecifically as well as via a variety of receptors that include Toll-like receptors (TLRs), complement receptors that recognize C1q and C3b fragments, Fc receptors, and surfactant protein A (SP-A) receptors that recognize SP-A opsonized bacteria.[68] TLRs derive their name from the *Drosophila* protein Toll, with which they share sequence similarity. This family of receptors is recognized as important in host defense and function through recognition of primitive repetitive microbial patterns and subsequently produces a number of responses, including antimicrobial peptide production, cytokine release, and apoptosis.[69] Besides pulmonary macrophages, TLRs are also found on airway epithelial cells, neutrophils, lymphocytes, mast cells, and endothelium.[70]

The highly ruffled plasma membrane and numerous surface folds (lamellae) of a macrophage indicate the active motile and phagocytic potential of this cell. When a particulate is phagocytized in the airway, the macrophage is usually activated to release a variety of mediators both into the phagolysosome that surrounds the ingested particle and also into the local environment of the cell. Within the cell, the respiratory oxidative burst along with lysosomal proteolytic enzymes, phagolysosomal acidification, and microbicidal cationic proteins are used to kill ingested microorganisms.[68,71] In contrast to the mechanisms of killing described for neutrophils, mature macrophages have little myeloperoxidase, so production of the hypohalide radical is not a factor in macrophage defense unless there is a source of myeloperoxidase in the environment (neutrophils). Although macrophages are thought to be capable of protecting the lung against *Staphylococcus aureus*, they may require help from neutrophils to kill *Klebsiella pneumoniae* and *Pseudomonas aeruginosa*.[71] Thus, it is important that macrophages be able to initiate at least a localized inflammatory response with attraction of neutrophils so that certain microorganisms can be effectively eliminated from the respiratory tract.

The secretory products of pulmonary macrophages are diverse (Box 5-1) and include oxidants, bioactive lipids, cytokines, polypeptide growth factors, and proteases as well as antiproteases.[68] These products are important not only for host defense but also for the resolution of inflammation and repair of the lung (see later section). The secretory products also allow the pulmonary macrophages to initiate and perpetuate an inflammatory response by recruiting and activating other inflammatory cells, primarily neutrophils (Fig. 5-6) but also lymphocytes and monocytes. Specific chemotactic factors include LTB_4[54] and IL-8.[51] Chemotaxins produced directly or indirectly by neutrophils (see later section) may further amplify and propagate an inflammatory reaction.

The ultimate source of the majority of pulmonary macrophages appears to be the bone marrow.[72,73] Monocytes released from the bone marrow enter the lung, where they mature into tissue macrophages. The alveolar macrophage population is also replenished by local proliferation,[74] but it

BOX 5-1 Major Secretory Products of Pulmonary Macrophages

Products that Contribute to Pulmonary Defense

Toxic oxygen species
- Superoxide anion (O_2^-)
- Hydrogen peroxide (H_2O_2)
- Hydroxyl radical (OH)
- Hypochlorous acid (HOCl)

Proteases
- Elastase
- Collagenase
- Cathepsins

Complement components
- C1, C2, C3, C4, C5
- Factor B, factor B, properdin

Bioactive lipids
- Cyclooxygenase metabolites (PGE_2)
- Lipoxygenase metabolites (LTB_4, LTC_4, LTD_4)
- Platelet-activating factor (PAF)

Cytokines/Chemokines
- IL-1, IL-6, IL-8, IL-10, IL-12
- Transforming growth factor beta (TGF-ß)
- Tumor necrosis factor (TNF)

Products that Resolve Inflammation and Repair the Lung

Antioxidant
- Glutathione

Antiproteases
- α_1-Proteinase inhibitor
- α_2-Macroglobulin
- Tissue inhibitor of metalloproteinases

Polypeptide growth factors
- Fibronectin
- Platelet-derived growth factor (PDGF)
- Transforming growth factor-α (TGF-α)

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appears that this mechanism is not nearly as important as movement of blood monocytes from the pulmonary capillaries into the lung. In contrast to neutrophils, pulmonary macrophages normally live for longer periods in this environment (weeks to months). The factors that stimulate the influx of monocytes into the respiratory tract during the normal migration of the cell from the bone marrow as well as during inflammatory processes are not as well characterized as those that attract polymorphonuclear leukocytes from the circulation. However, these factors may include complement fragments, fragments of the extracellular connective tissue matrix, and proinflammatory chemokines that are secreted by both resident alveolar macrophages and by airway and alveolar epithelial cells.[68]

AIRWAY EPITHELIAL CELLS

The airway epithelium has a barrier function that in itself is important in defending the lung from environmental pathogens. However, the metabolic activities of cells that line the airways may also be important in responding to potentially injurious agents. In this respect, human airway epithelial cells share with alveolar macrophages the ability to generate the products of arachidonic acid that may initiate or amplify an acute inflammatory reaction.[75] For example, one product of the 15-lipoxygenase pathway, 8,15-dihydroxyeicosatetraenoic acid, is nearly as potent as LTB_4 in its ability to produce chemotaxis of human polymorphonuclear leukocytes. As noted earlier, the potent neutrophil chemoattractant IL-8 may also be expressed in human bronchial epithelial cells.[52] These metabolic properties of airway epithelial cells, coupled with the strategic location of the cells within the respiratory tract, suggest that inhaled materials may stimulate the production of mediators capable of reacting to the challenge by mobilizing neutrophils to the airway. Studies using bronchial epithelial cells from species other than humans also suggest that these cells can produce chemotactic factors for other cells important in host defense and inflammatory responses, including monocytes[76] and lymphocytes.[77]

Airway epithelial cells also play an active role in host defense. Antimicrobial peptides (AMP) are expressed in the respiratory tract and act as endogenous antibiotics.[78,79] AMPs represent a diverse group of peptides with the principal families identified in the respiratory tract being the defensins and the cathelicidins. In vitro studies of animal models and cultured human airway epithelial cells demonstrate that defensins are induced by proinflammatory stimuli, such as cytokines secreted by activated macrophages, and bacterial lipopeptide.[78] Although AMPs are reported to have broad-spectrum activity against gram-positive and gram-negative bacteria, as well as against fungi and enveloped viruses, studies have primarily focused on their antibacterial activity. AMPs are bacteriostatic in nature and appear to mediate their function through disrupting the integrity of the bacterial cell membranes. AMPs also act as chemoattractants for inflammatory cells, including neutrophils, lymphocytes, and macrophages and, therefore, contribute to the inflammatory response.

Alveolar type II epithelial cells produce and secrete surfactant proteins A (SP-A) and D (SP-D) which are members of the collectin (collagen-lectin) family of proteins. SP-A and SP-D have been shown to play a critical role in the host defense of the lung against diverse bacterial, viral, and fungal pathogens.[80] These proteins bind to the surfaces of microorganisms and act as opsonins, thereby enhancing the clearance of these organisms by alveolar macrophages. In addition, SP-A and SP-D interact with various cell surface ligands on inflammatory cells, and activate or inactivate cellular function involving phagocytosis and production of cytokines and reactive oxygen species.[81]

MAST CELLS

Mast cells are frequently found at the interface of the internal and external environment, including the respiratory mucosal surfaces. Pulmonary mast cells are most abundant in the membranous portion of the trachea, beneath the pleura, and in the connective tissue surrounding the small airways and vessels.[82] In humans, mast cells are subdivided by neutral

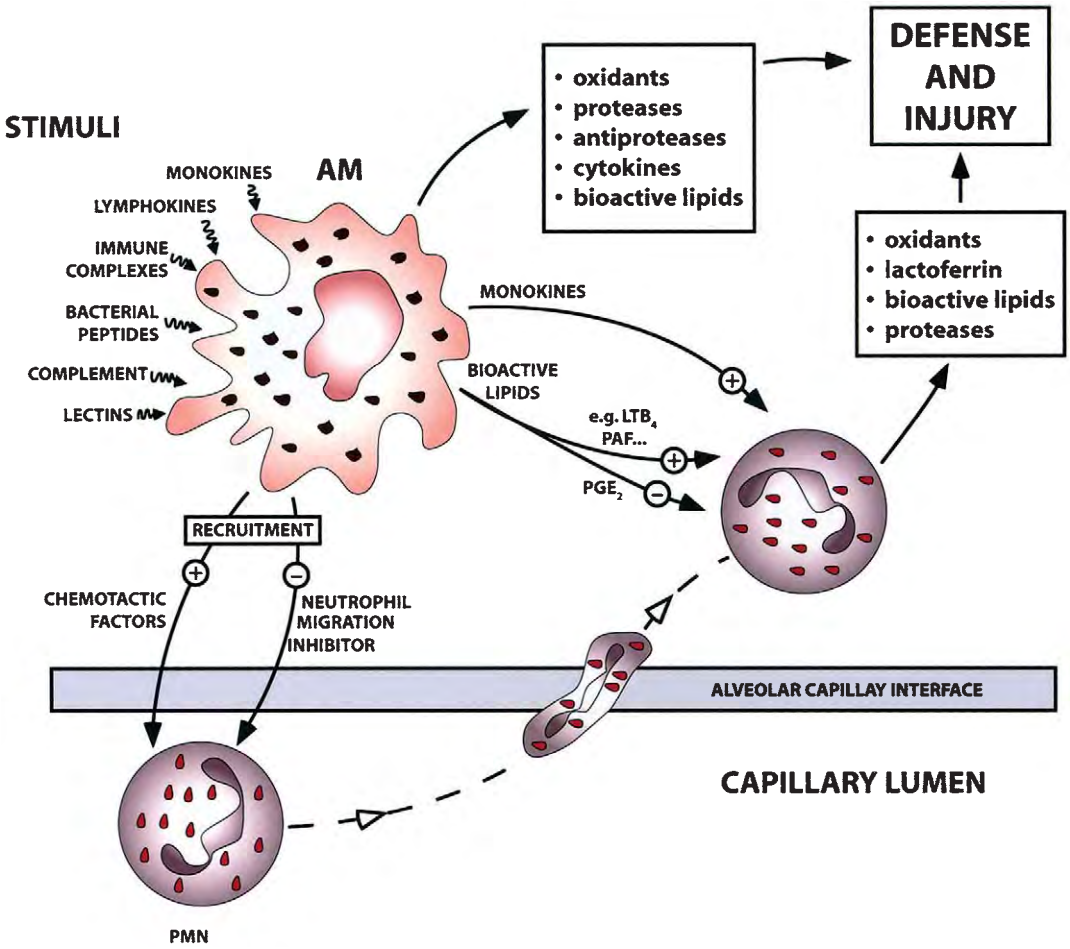

Figure 5-6 Interaction between alveolar macrophages (AM) and polymorphonuclear neutrophils (PMN) in the lung. On stimulation by various stimuli, AM release either chemotactic factors or inhibitory factors for PMN. Chemotactic factors will attract PMN from the capillary lumen to the alveolar space and once in the lumen, the PMN can be activated by various factors released from the AM. Macrophages can also inhibit PMN activity through the release of mediators such as PGE_2, which is important in the resolution of inflammation (see later section). Secretory products released by both AM and PMN are likely to influence defense and injury processes. (From Sibille Y, Reynolds HY: Macrophages and polymorphonuclear neutrophils in lung defense and injury. Am Rev Respir Dis 141:471-501, 1990.)

protease composition.[83] Mast cells with tryptase and not chymase are thought to predominate in the lung (90%), whereas mast cells with both tryptase and chymase make up the other 10% of mast cells identified by the dispersion of mast cells from human lungs. Mast cells are a repository of several mediators with significant inflammatory potential that might limit the entry of unwanted particles into the lung. Two classes of biologically active molecules have long been recognized to be produced by these cells: preformed mediators in secretory granules and membrane-derived lipid mediators, including LTB_4. Mast cells also produce and release other neutrophil chemoattractants including IL-8 and tumor necrosis factor (TNF)-α.[84]

Although mast cells have been most extensively studied in their traditional role as an early effector cell of allergic disease, mast cells have also been demonstrated to play a critical role in defense against bacterial infections, and potentially against viral and fungal pathogens.[85] The role of mast cells is not limited just to recruitment of effector cells via release of chemoattractants. Mast cells also possess a wide variety of membrane receptors that are thought to recognize various microorganims and their constituents, which facilitate its ability to engulf and kill bacteria—including *Escherichia coli* and *K. pneumoniae*.[84] Mast cells also possess a variety of membrane receptors for serum opsonins such as FγR, FcεR, and CR3—which could potentially facilitate mast cell activation by bacteria that are coated with IgG, IgE, and complement molecules, respectively. Mast cells are also known to produce antimicrobial peptides, including cathelicidins and defensins—another important aspect of their function in innate host defense.

POLYMORPHONUCLEAR LEUKOCYTES

Polymorphonuclear leukocytes (neutrophils, eosinophils, basophils) are normally present within the conducting airways and alveolar spaces in very small numbers and are thought to be virtually absent from the interstitial spaces of lung parenchyma.[86] However, a large number of neutrophils, estimated to be up to three times the circulating pool of this cell,[86] are marginated in the pulmonary vascular bed. This pool of cells, as well as the circulating cells, may be attracted to migrate into the lung.

As previously noted, several mechanisms may account for the recruitment of neutrophils into the respiratory tract. First, inhaled substances may directly attract neutrophils.[87] For example, chemotactic factors are present within certain microbial cell walls (formylmethionyl peptides). In addition, complement activation may result in the generation of potent neutrophil chemoattractants.[88,89] Resident alveolar macrophages may also release factors that attract neutrophils.[50] For certain inhaled stimuli, all three mechanisms may be operative and contribute to the pathologic picture.[87]

Neutrophils themselves have the potential to amplify an acute inflammatory reaction in various ways. For example, proteinases such as elastase and cathepsin G that are released from neutrophils during phagocytosis may cleave C5 to yield chemotactically active fragments. This may be especially important in patients with hereditary deficiencies of α-proteinase inhibitor.[90]

Once attracted into the pulmonary tissues, the actions of polymorphonuclear leukocytes include phagocytosis and the removal of particulates from the respiratory tract. The most effective phagocytosis is produced when there is opsonization of particulates with soluble material in the lung. Although the major opsonins are from the IgG class of specific antibodies (especially IgG1 and IgG3), other factors, including the complement fragment C3b, can function in this capacity. Within neutrophils, microbial killing is effected by a variety of systems, including oxygen-dependent and oxygen-independent mechanisms (cationic proteins, proteases, lysozyme).

Extracellular Factors Important in the Defense of the Lung

Although many factors with proinflammatory or antiinflammatory activity are found within the lung,[86,91] one group of proteins stand out in terms of their importance in host defense and participation in an inflammatory response: complement components.

COMPLEMENT

Activation of the complement pathway will lead to one of a series of results: direct lysis of targets, generation of peptides cleaved from complement that aid in the inflammatory process, and opsonization of targets that facilitates phagocytosis. Components of the complement pathways have been found within the lungs of nonhuman primates and humans as defined by examination of bronchoalveolar lavage fluid.[86,91,92] The third component of complement (C3) and the terminal components (C5 to C9) mediate most of the biologically important actions of this series of proteins. Three pathways of complement activation have been defined: (1) classic pathway, (2) alternative pathway, and (3) lectin pathway.[93]

The classic complement pathway is typically activated by antigen-antibody complexes with the involvement of IgM or the IgG1, IgG2, and IgG3 subclasses. Conversely, the alternative complement pathway, in which the early components of the classic pathway are bypassed, can be activated by a wide variety of substances, including complex polysaccharides, lipopolysaccharide, and some immune complexes.[94] The lectin pathway is initiated by the interaction of serum mannose-binding protein (MBP) with microorganisms that bear the appropriate carbohydrates (e.g., mannose, GlcNAc, fucose, and glucose) on their surfaces.[95] On activation, MBP will bind to MBP-associated serine protease (MASP) and activate complement proteins.

The three pathways and the complement components are displayed in Figure 5-7, where it can be seen that activation of the three pathways yields many of the same biologically active products. These products include powerful chemotactic factors derived from C5 that were detailed previously. Activation of the three pathways also leads to the formation of opsonins that facilitate the recognition and killing of microorganisms by phagocytic cells (iC3b). Bactericidal activity is also generated by the activation of the terminal components C5 to C9 and assembly of the membrane attack complex. The site of action of these terminal components appears to be the outer lipid membrane of gram-negative organisms.[96,97] An interesting facet of the complement system is that there exists redundancy in many areas of activity. Although complement deficiencies have been reported, deficiencies of complement protein early in the pathways are typically associated with milder clinical phenotype.[93]

From the standpoint of ontogeny, synthesis of certain components of complement (including C3 and C5) begin in the human fetal liver during the first trimester of gestation.[98] During fetal life, the liver and other tissues continue to produce complement components. Transplacental passage of complement proteins does not occur, and the levels of immunochemically and hemolytically detectable components in normal newborn sera range between 60% and 90% of those found in adult sera. Values found in preterm infants are even lower. The concentrations of these components increase in the first few years of life until they reach normal adult levels. Overall, the activity of alternative pathway components in newborn sera is less than that of the classic pathway proteins.[99]

OTHER FACTORS

Although the complement system is a cornerstone of the noncellular host defense systems, other factors found within the pulmonary environment also contribute to the protection of the lung. The iron-binding protein transferrin is found predominantly in the alveolar spaces,[100] whereas lactoferrin predominates along the airways.[101] Because iron is an essential ingredient for the survival of microorganisms, the ability of these iron-transport proteins to complex free iron in mucosal secretions and alveolar lining fluid may lead to the suppression of bacterial growth. In addition, human lactoferrin has a direct microbicidal effect on several bacteria, including *Streptococcus pneumoniae* and *E. coli*.[102] Two other components of normal bronchoalveolar lavage fluid can be thought of as nonimmune opsonins in that they have the ability to coat certain bacteria and enhance phagocytic uptake of the organism by alveolar macrophages. In this respect, fibronectin has been found to facilitate the uptake of bacteria by macrophages in vitro.[103] Other extracellular bactericidal factors of importance in pulmonary host defense (e.g., lysozymes, degradative enzymes) have been reviewed.[104]

As discussed earlier, various factors within the lung can function as opsonins. For each opsonin, an opsonin-specific membrane receptor on phagocytes is responsible for binding

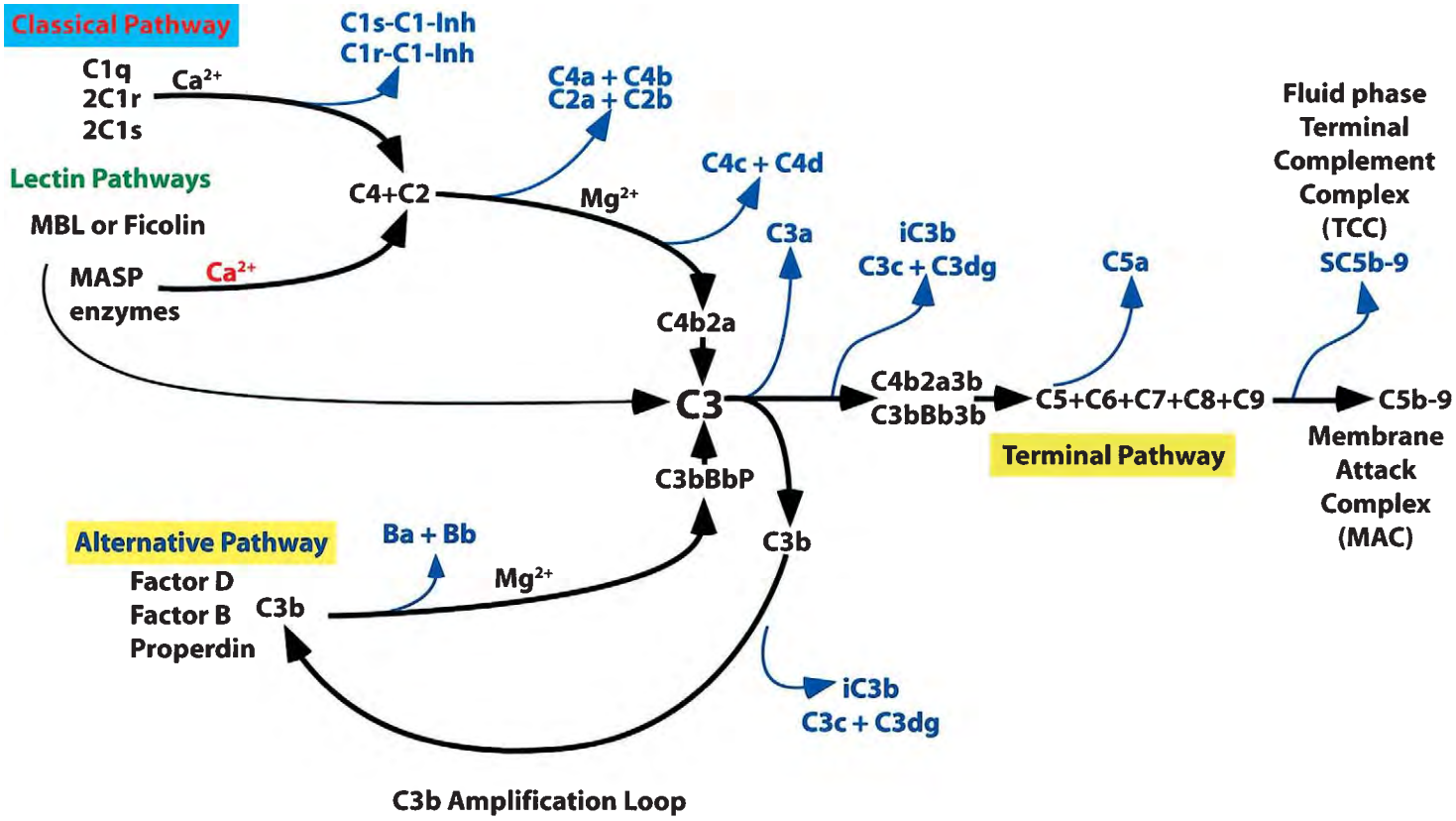

Figure 5-7 Diagram of the classical, lectin, and alternative activation pathways of the human complement system, showing the control steps and where some of the biologically active split products are produced. Products that are important in host defense include chemotactic factors (C5 fragments, including C5a), opsonins (iC3b), and factors with bactericidal activity (membrane attack complex, C5b-9). This system is an important component of the host defense response through its interactions with antibody and through mechanisms that are independent of antibody. (Modified with permission from Giclas P: Introduction. In Rose NR, Hamilton RG, Detrick B, [eds]: Manual of Clinical Laboratory Immunology, 6th ed. Washington, DC, ASM, 2002, pp 109-110.)

particles coated with the opsonin. For example, iC3b is one of the most important non-Ig factors with opsonic activity, with this function mediated via two types of phagocytic receptors: CR1 and CR3. It is beyond the scope of this review to present this information in more detail. Opsonization by various factors and the membrane receptors that help mediate this host defense have been reviewed.[105]

IMMUNOLOGIC RESPONSES OF THE LUNG

Most material with antigenic potential is effectively limited from producing an immunologic response by the mechanisms of defense previously outlined. Thus, for an immunologic response to occur, material must breach defense barriers and reach the responsive lymphoid tissue. When this occurs, a complex series of events transpires that subsequently provides antigen specificity to host defenses within the lung. This specificity is conferred by an elaborate system of receptors on T and B cells and through antibodies. In the context of antigen specificity, a basic function of the immune system is to differentiate "self" from "nonself" at a molecular level, thereby providing additional layers of defense against foreign materials.

It is clear from several lines of investigation that the lung can function as an immune organ. Furthermore, it appears that pulmonary immune reactions are fundamentally similar to those that occur systemically.[106] Although the many studies in which these conclusions were drawn were performed in animal models and not humans, these conclusions appear appropriate, based on current knowledge from many sources. The role of the lung as an immunologic organ has probably evolved in response to the routine exposure of the respiratory tract to microbes and foreign particles that takes place with ventilation.

Overview of Normal Immunologic Responses

Generation of immune responses can be thought of in terms of three functional limbs[107]:

1. The afferent limb includes the processing and presentation of antigen to lymphatic tissue.
2. A central limb involves the interactions of immunocompetent cells that lead to the generation of effector lymphocytes.
3. The efferent limb includes the processes associated with terminal differentiation of effector lymphocytes.

The immune system ultimately exerts its effects through circulating effector cells and molecules that act at locations within the respiratory tract that may be remote from the site of the initial interaction with antigen. In this respect, the immune system consists of two major effector systems: antibody- and cell-mediated immunity. In addition to specificity of antibodies and effector lymphocytes for foreign antigens,

immune responses are generally characterized by clonal expansion of antigen-reactive lymphocytes as well as memory, which leads to accelerated secondary immune responses to antigens.[106] Thus specific antibody and effector T cells may not appear for days after a nonimmune host encounters a foreign antigen that makes its way to lymphatic tissue, but specific antibody as well as sensitized T cells are more readily available in a sensitized host when the invading antigen again finds its way to the respiratory tract.

As noted, the initial phase of an immune response involves the processing, transport, and presentation of antigen to lymphocytes. This is accomplished when antigen deposited within the airways is taken up by an antigen-presenting cell, in which the antigen is processed by partial degradation. To be effective in antigen presentation, the cells must also display relevant antigenic determinants on cell surface membranes, express macromolecular gene products of the major histocompatibility complex (MHC), and secrete cytokines, including IL-1. The cells that can function in this capacity are discussed in a subsequent section.

Lymphocytes are the antigen-reactive cells of the immune system. They are distinguished primarily by certain characteristic cell surface markers called *clusters of differentiation* (CD) and by their receptors for antigen. The nomenclature of the CD markers as well as their expression as a function of T cell maturation has been reviewed in detail.[108] T cells recognize antigens by a membrane structure called the *CD3/T cell antigen receptor complex*, whereas B cells recognize antigens using surface Ig molecules. On T cells, the T cell receptor (TCR) is a disulfide-linked heterodimer composed of either α and β or γ and δ chains. Most mature T cells (more than 90% in both the blood and lungs) have an αβ TCR.[108] The function of T cells expressing the γδ TCR is not clearly understood but could include the downregulation of immune responses in bacterial infections.[109]

In a classic immune response to an exogenous antigen, the antigen-presenting cells interact with helper/inducer T cells (CD4+ cells) on which the TCR recognizes both antigen and class II MHC determinants on the cell presenting the antigen. Interaction of the two cell types, together with secretion of IL-1, leads to activation of the CD4+ cell characterized by elaboration of IL-2 and expression of IL-2 surface membrane receptors. The activated CD4+ cells undergo clonal expansion with differentiation into helper/inducer cells that can activate B cells as well as cytotoxic T cells (CD8+ cells). In addition, activated CD4+ cells can differentiate into effectors of delayed-type hypersensitivity in that this discrete subset of cells elaborate lymphokines such as interferon-γ (IFN-γ), which induce the accumulation and activation of macrophages in the region of the insult.

Pulmonary Cells Important in Immunologic Responses

ANTIGEN-PRESENTING CELLS

Accessory or antigen-presenting cells must be able to engulf and process an antigen by partial degradation. As noted previously, they also display relevant antigenic determinants on cell surface membranes, express both class I and class II macromolecular gene products of the MHC (surface membrane HLA-DR antigens), and secrete cytokines (IL-1 and others). Within the lung, dendritic cells and pulmonary macrophages appear to be the most important in terms of their antigen-presenting capabilities.[110] Dendritic cells have been recognized to be the chief orchestrators of immune responses.[111,112] Even in the absence of active infection, dendritic cells or their precursors are constantly recruited from the blood to the lung. This steady state influx is altered by the presence of inhaled antigens. Various stimuli can induce migration of dendritic cells and include microbial products and inflammatory chemokines, TNF, and IL-1.[113] In rats, inhalation of pathogenic material, such as bacterial or viral particles, induced a very rapid influx of dendritic cells into the airways, and this recruitment was as fast or sometimes ahead of the prototypic neutrophil influx.[111] This observation implies that dendritic cells are an integral aspect of early phases of the innate host response. After antigen capture, dendritic cells will migrate and transport the antigen to the pulmonary lymph nodes. One interesting aspect of this process is that it is rapid and can occur in the absence of any inflammatory stimuli.[111] In the lymph nodes, dendritic cells will interact with T cells to elicit a specific immune response.

LYMPHOCYTES

As with mononuclear phagocytes, lymphocytes are present at or near the airways extending from the nasopharynx to the alveolar spaces. Different levels of lymphatic tissue organization are identifiable in the lung and include lymph nodes (paratracheal and adjacent to major bronchi), lymphoid nodules and aggregates (throughout the submucosa of conducting airways), interstitial lymphoid tissue, and bronchoalveolar cells. The term *bronchus-associated lymphoid tissue* (BALT) has been applied to the organized tissue that is directly subjacent to the bronchial mucosa of the proximal conducting airways.[114] The nodules of lymphoid tissue that make up BALT are separated from the lumen of the airways by lymphoepithelium, a single layer of flattened epithelial cells that lack cilia and are infiltrated with lymphocytes. This structure is thought to facilitate antigen uptake. Although the contribution of BALT to local immune responses is not well defined, it may function as a repository of IgA precursor cells for the synthesis of secretory IgA.

The cellular population found within the more distal airspaces of the lung has become better defined with the use of fiberoptic bronchoscopy, with lavage as a method of sampling the cells and proteins within airways. In this respect, lymphocytes comprise approximately 7% to 10% of the cells obtained by bronchoalveolar lavage from normal humans.[86,91] Of the lymphocytes, the majority are T cells, with the overall number of T and B cells lavaged from airways closely approximating that found in peripheral blood. In addition, it appears that the relative ratio of helper to suppressor T cells in the compartment assessed by lavage is also similar to that in peripheral blood.

The major effector functions of activated T cells include regulation of the various limbs of the immune response, mediation of delayed-type hypersensitivity, and production of cell-mediated cytotoxicity. These biological functions are primarily distributed between CD4+ and CD8+ cells. CD4+ T cells can be divided into two main subsets with distinct cytokine secretion phenotypes, and different functions (Fig. 5-8). T helper 1 (T_H1) cells secrete IL-2, IFN-γ, and TNF-β

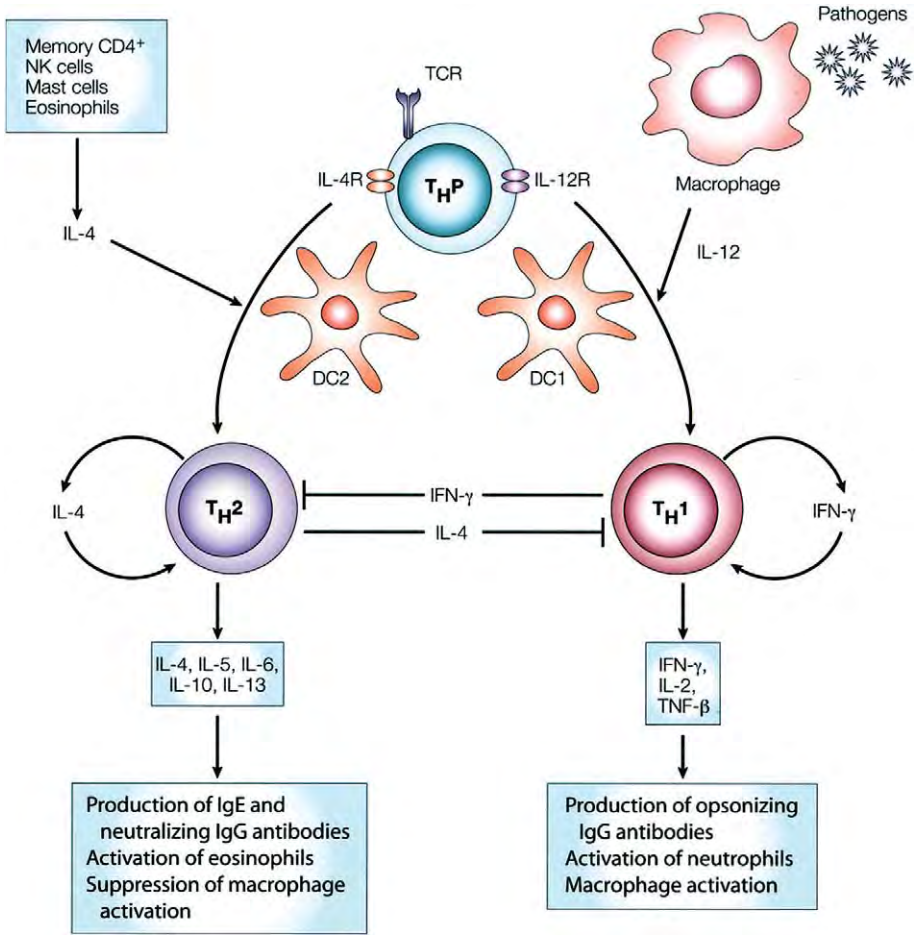

Figure 5-8 Schematic representation of induction and regulation of T_H1 and T_H2 cells. The same T_H-precursor (T_HP) cell can differentiate into T_H1 or T_H2 cells depending primarily on the cytokine microenvironment provided exogenously or from dendritic cells (DC1 or DC2). IL-12 drives T_H1 cells, whereas IL-4 promotes T_H2 cells. IFN-γ and IL-4, produced by T_H1 and T_H2, respectively, can also act as autocrine growth factors as well as inhibitory factors for the opposite subset. T_H1 produces IFN-γ, IL-2, and TNF-ß which mediate production of opsonizing IgG antibodies, activation of neutrophils, and macrophage activation. T_H2 produces IL-4, IL-5, IL-6, IL-10, and IL-13, which mediate production of IgE and neutralizing IgG antibodies, activation of eosinophils, and suppression of macrophage activation. IL-4R, IL-4 receptor; IL-12R, IL-12 receptor. (Modified with permission from Liew FY: T_H1 and T_H2 cells: A historical perspective. Nat Rev Immunol 2:55-60, 2002; Macmillan Magazines Ltd. www.nature.com/reviews.)

which are associated with cell-mediated immunity. The principal role of T_H1 cells is in promoting phagocyte mediated defense against infections. T helper 2 (T_H2) cells secrete IL-4, IL-5, IL-6, IL-10, and IL-13, which can modulate humoral immunity and play a major role in the development of IgE-mediated and mast cell/eosinophil-mediated immune responses.[109] T_H1 cells enhance the microbicidal activity of macrophages, induce IgG antibodies that mediate opsonization and phagocytosis, and support CD8+ antiviral effector T cells.[116] T_H1 cells are central to the development of the delayed-type hypersensitivity reaction. Antigen activation of T_H2 cells leads to the stimulation of IgE class switching in B cells, resulting in the production of antigen-specific IgE, which then mediates the activation of mast cells and eosinophils. The exogenous cytokine microenvironment and dendritic cell interactions strongly determine the nature of the resulting T cell response. IL-12 production drives the development of T_H1 immunity, whereas IL-4 production promotes T_H2 immunity and downregulates production of IL-12. It is thought that IL-12 production is initially triggered through activation of the innate immune response. Macrophages and dendritic cells are the main producers of IL-12; the role of dendritic cell in T_H1/T_H2 polarization has been reviewed.[113,116,117] The cellular sources of the initial burst of IL-4 are still not clearly understood, but could include natural killer (NK) T cells, mast cells, eosinophils, and mature CD4+ T cells.[115] The best understood function of CD8+ T cells is that of cytotoxicity. These cells may also function as suppressors or downregulators of immune response via nonspecific inhibitory cytokines.

Delayed-type hypersensitivity is important in the lung's defense against viruses, fungi, mycobacteria, and other intracellular parasites.[118] As noted previously, this type of response is mediated by T_H1 cells that elaborate lymphokines, inducing the accumulation and activation of additional lymphocytes as well as mononuclear and polymorphonuclear phagocytes. Activation of macrophages in such a fashion is felt to be an important factor in the containment and elimination of intracellular parasites such as *Mycobacterium tuberculosis*. Although the initial stimulus to T_H1 cell activation is antigen specific, the augmented microbicidal activity of macrophages is not restricted to the immunizing organism. In this manner, the T_H1 cells that mediate delayed-type hypersensitivity bring out the important but nonspecific effector cell functions of macrophages.[71] The cellular cytotoxicity mediated by CD8+ cells is important in host defense in that it destroys virally infected host cells. Virally infected host cells display viral antigens on their surface. The CD8+ antigen-reactive cell recognizes the viral antigen as foreign and differentiates into virus-specific cytotoxic T cells.

B cells are the effectors of the humoral arm of the immune response. B cells are present in the lung with the majority existing in BALT or the draining lymph nodes of the lung. B cell development can be divided into two phases: lymphopoiesis, where a multipotent stem cell in the fetal liver and bone marrow undergoes several maturational changes resulting in

mature B cells, and immunopoiesis, which culminates in the generation of a memory B cell or plasma cell.[119] Plasma cells constitutively produce Ig whereas memory B cells produce Ig only in response to reexposure to particular antigens. Mature B cells express both surface IgM and IgG. Crosslinking of these surface Igs with antigen results in B cell activation.

In addition to B and T cells, a third type of lymphocyte is present within the lung: the NK cell.[120] These lymphocytes can bind to and kill both virus-infected and tumor cells by production of cytokines and chemokines (including IFN-γ, TNF-α, IL-8), and by cell-mediated lysis of target cells. NK cells are large, granular lymphocytes that do not express on their surface the CD3 antigen or any of the known TCR chains (α, β, γ, δ) but do express certain characteristic differentiation antigens (CD56 and CD16) and mediate cytotoxic reactions even in the absence of class I or class II MHC expression on the target cells.[121] In children, the most important role of this group of cells may be defense against viral infections, especially members of the herpesvirus family. NK cells kill virus-infected host cells but not normal, uninfected cells. NK cells do not require prior exposure to antigen to respond and thus may provide an initial antiviral defense before antibodies and antigen-specific cytotoxic lymphocytes develop. Although these characteristics of NK cells suggest that they should not be included in a discussion of immunologically specific responses, it is important to note that NK cells also mediate antibody-dependent cellular cytotoxicity through a cell surface receptor located on this effector cell that binds the Fc region of Ig. Thus, antibody dependent cellular cytotoxicity provides a mechanism for NK cells to use the antigen specificity of antibodies to direct their killing activity. The cytotoxic effects of NK cells may also be increased by cytokines, including IL-12, as well as both INF-α and IFN-γ. Because interferons are induced during viral infections, they may play a role in the antiviral immunity mediated by NK cells. Dendritic cells can also influence the proliferation and activation of NK cells through production of IL-12 and through cell-surface interaction. In return, NK cells can provide signals that result in either dendritic cell maturation or apoptosis.[121]

Igs Within the Respiratory Tract

All major Igs (IgG, IgA, IgM, IgE) have been identified in bronchial secretions. Their presence is thought to reflect both local synthesis as well as transudation from serum. Because of relatively low molecular weight of Igs, transudation and exudation into airway secretions may be more important for most subclasses of IgG than for the other classes of Ig (see later section). Conversely, most of the IgA, IgM, and IgE in airway secretions is probably synthesized locally. The two major Igs within the respiratory tract in terms of lung defense are IgA and IgG. In contrast to the relative amounts of Igs found within the bloodstream, the concentration of IgG relative to IgA is low in upper airway secretions but increases in the lower airways so that IgG exceeds IgA in bronchoalveolar lavage fluid.[91]

IgG

An analysis of IgG subclasses was reported on bronchoalveolar lavage fluid analysis in normal adults.[122] In this study, concentrations of IgG1 and IgG2 in lung lavage were similar to those in serum. Local IgG3 concentrations were variable in relation to values in serum, but data pertaining to IgG4 suggested preferential accumulation of this IgG subclass within the lower respiratory tract.

Well-recognized biological activities of IgG are important in the pulmonary immune response of the respiratory tract. The formation of immune complexes either in a fluid phase or on the surface of a cell (including a bacterium and a fungus) leads to the generation of several biologically active products through the activation of complement. In addition, the IgG class of antibody (particularly IgG1 and IgG3) acts as opsonins, facilitating the recognition and killing of microorganisms by phagocytic cells. The frequency with which individuals suffering from agammaglobulinemia or hypogammaglobulinemic states develop significant pulmonary infections illustrates the important role played by this class of proteins in pulmonary defense.

IgA

Secretory IgA is the predominant Ig isotype in the respiratory tract above the larynx. As previously discussed, current evidence suggests that most of the IgA found within the upper and lower respiratory tracts is synthesized locally. IgA has two subclasses, IgA1 and IgA2. Although both subclasses are found in the respiratory tract, it is thought that IgA2 subclass is more important in mucosal immunity. Certain bacterial pathogens produce proteases for IgA1, whereas IgA2 is not susceptible.[119]

The biological activities of IgA relative to pulmonary defense have been reviewed[87] and include activation of the alternative complement pathway with the resultant generation of biologically active products as outlined in the discussion of the complement system. More important, IgA also inhibits viral binding to respiratory epithelial cells and neutralizes toxins. Regulation of antigen entry into the lymphoid tissue of the respiratory tract may also help prevent immune responses to antigens. This antibody isotype may also play a role in antibody-dependent cytotoxicity.

Ontogeny of Immunologic Responses

For the body to mount a fully developed immunologic response, several cells (e.g., macrophages, neutrophils) and mediator systems (e.g., complement pathway, products of macrophages) may be needed. The ontogeny of many of these cells and systems as they relate to lung defense have been summarized in preceding sections. It is beyond the scope of this text to review in detail the ontogeny of lymphocytes starting with fetal development. Therefore, emphasis is placed primarily on the ontogenic events associated with the perinatal period and extending into childhood. Comprehensive reviews that deal with the ontogeny of immunity[123] and the developmental immunology of the lung[98] are available.

All cells of the immune system are derived from pluripotential hematopoietic stem cells, which are first found within the blood islands of the yolk sac.[123] During embryogenesis, these stem cells will migrate to other sites of hematopoiesis: liver, spleen, and bone marrow. Stem cells responsible for generation of T cell and B cell lineage will migrate to the respective sites of development.

The fetal liver by 6 to 8 weeks' gestation contains prothymocytes, which are lymphoid cells that appear to undergo differentiation into T-lineage cells.[124] These prothymocytes colonize the fetal thymus at approximately 8 to 9 weeks' gestation. Shortly after colonization, thymocytes that express proteins characteristic of T-lineage cells are found. In humans, thymocytes from 9-week-old fetuses can express the γδ TCR.[125] By week 10 of fetal development, the αβ TCRs are found, followed by a progressive decrease in the number of thymocytes with γδ TCRs. T cells acquire maturational surface markers by about 16 weeks of gestation. An observed trait of neonatal T cells is their impaired function compared with adult T cells. Diminished functions include T cell-mediated cytotoxicity and T cell help for B cell differentiation. Neonatal T cells also exhibit poor cytokine production in comparison to adults, especially in relation to TH1 cytokines.[126] This particular trait of the neonatal T cell is thought to contribute to impaired responses of other neonatal cell populations that rely on these cytokines for their function. In postnatal life, lymphocytes develop in the primary lymphoid organs, namely the thymus and bone marrow. The development of diversity is felt to occur primarily in these organs, whereas clonal expansion can occur anywhere in the peripheral lymphoid tissue.[108]

The fetal liver is an important site for B cell differentiation during early development. B cells can be detected in human fetal liver at approximately 9 weeks' gestation. Although these cells express IgM on their surface, they lack other Ig classes. By 10 to 12 weeks' gestation, B cells expressing other classes of Ig are detected. B cells become detectable in the peripheral circulation at approximately 12 weeks' gestation and become abundant in the bone marrow at 16 weeks' gestation. Neonatal B cells have increased surface levels of IgM compared to adults and this difference persists for several years.

No information is available on levels of Igs within the respiratory tract of humans as a function of development. However, Ig levels within the blood have been defined as a function of age in healthy individuals.[127] At birth, normal neonates have approximately 10% of the normal adult level of serum IgM, near-adult levels of IgG (the majority from the mother), and little or no IgA. Adult levels of IgM are achieved by 1 to 2 years of age, whereas adult concentrations of IgG are achieved by 4 to 6 years of age. Adult levels of serum IgA are not usually attained until near the time of puberty. Given that IgG is the one antibody isotype found within the lung that relies heavily on transudation from the bloodstream (see previous section), the amounts found within the lung might be expected to reflect these ontogenic differences found within the blood.

The ability to mount an antibody response in the perinatal period differs both quantitatively and qualitatively from the response in an older child or adult. The IgM response is predominant and tends to be persistent, whereas IgG and IgA antibody formation is relatively deficient. Functional studies comparing in vitro responses of neonatal B and T cells with those of adult cells implicated both T and B cells in the impaired capacity to produce IgG and IgA.[123] It appears that in addition to providing poor helper function, neonatal T cells are active suppressors.

It is generally accepted that maturational deficiencies of the immunologic system exist in the young infant and child. This may contribute to the increased susceptibility of this population to infections, including pulmonary infections, and to mechanisms related to the development of tolerance to infection and/or predisposition to atopy.

RESOLUTION OF INFLAMMATION

Although a great deal of information is available on both antigen-specific and nonspecific mechanisms that initiate and perpetuate inflammation in defending the lung, much less is known about resolution of this response.[128] What is clear is if injury to the lung is to be prevented, all of the processes involved in the production of inflammation must be reversed. There must be removal of the stimuli responsible for inciting inflammation; dissipation or destruction of proinflammatory mediators; cessation of granulocyte emigration from blood vessels; restoration of normal vascular permeability and removal of extravasated fluids; limitation of granulocyte secretion of proinflammatory and cytotoxic agents; removal of bacterial and cellular debris and granulocytes and macrophages; and, finally, repair of any injury to the constitutive epithelial and endothelial monolayers.[129]

The host has several mechanisms in place to contain an inflammatory reaction once it has been initiated. Systems known to exist for these purposes include chemotactic factor inactivator and circulating inhibitors of the neutrophil proteinases. Chemotactic factor inactivator, a major serum regulator of C5 fragment-induced neutrophil chemotaxis and neutrophil lysosomal enzyme release, may also markedly reduce the chemotactic activity caused by macrophages stimulated with phagocytic and nonphagocytic stimuli.[130] This mechanism may be important in limiting the neutrophilic component of an inflammatory response once it has been triggered. The major circulating inhibitors of neutrophil proteinases include α_1-proteinase inhibitor as well as α_2-macroglobulin, the tissue inhibitor of metalloproteinases, plasminogen activator inhibitor-1, α_1-antichymotrypsin, C1 esterase inhibitor, and the more recently discovered secretory leukocyte protease inhibitor (SLPI) and elafin.[58,131] In the lung, SLPI is produced by Clara and goblet cells of the surface epithelium, and the serous cells of the submucosal glands. SLPI is also possibly produced by neutrophils, mast cells, and macrophages. Besides its function as a potent inhibitor of neutrophil-derived elastase and cathepsin G, SLPI has been shown to inhibit the proinflammatory activity of bacterial products such as lipopolysaccharide, and regulates the activity of inflammatory cells. This has been suggested by observations that SLPI inhibits nuclear factor-κB (NF-κB), which is a transcription factor involved in the expression of proinflammatory genes.[131]

During resolution of inflammation, the accumulated neutrophils need to be safely removed; apoptosis plays an important role in eliminating such neutrophils from inflamed tissues. The mechanism by which apoptosis occurs has been reviewed.[132,133] The removal of apoptotic neutrophils is essential to prevent the release of cytotoxic intracellular contents during lysis. Although macrophages are well known for acting as scavengers in removing debris, these cells also contribute to the resolution of inflammation by recognizing and ingesting these apoptotic neutrophils. An important observation is that uptake of apoptotic neutrophils suppresses the

release of proinflammatory agents (e.g., TNF-α, IL-8, granulocyte macrophage colony-stimulating factor) from macrophages.[134] These macrophages further suppress the inflammatory response by releasing antiinflammatory mediators, transforming growth factor-β (TGF-β), and PGE_2. TGF-β has also been implicated in fibrosis, tissue repair, and regeneration, suggesting that removal of apoptotic cells in inflammation may also promote the resolution process. The mechanisms by which macrophages recognize and ingest apoptotic neutrophils are an area of active study. A number of receptors have been identified in vitro. These include the vitronectin receptor (αv β3 integrin) which is thought to cooperate with CD36 in binding to thrombospondin on the surface of the apoptotic cell, a phophatidylserine-specific receptor, and scavenger receptors.[134] Alveolar macrophages may also help maintain normal lung architecture through their ability to contribute to both matrix synthesis and degradation by releasing growth factors (e.g., TGF-β, insulin-like growth factor-I) and matrix-degrading metalloproteinases, as well as their inhibitors.[68]

The initial cellular processes involved in tissue repair include matrix accumulation, cell migration, and proliferation of fibroblasts; in the later phases of repair there may be transient proliferation of epithelial and endothelial cells, cellular differentiation, matrix degradation, decreased fibroblast proliferation, and finally apoptosis.[135] Apoptosis is an integral step in tissue repair because this is a likely mechanism for the elimination of granulation tissue. It may also rid the repairing alveolar epithelium of excess hyperplastic type II alveolar epithelial cells.[136] Proliferation of type II cells is thought to occur in the early phases of the repair process. With the elimination of excess type II cells, it will allow the spread and differentiation of the thinner type I cells, which is essential for optimal gas exchange. Although epithelial monolayers display a remarkable capacity to regenerate in the face of insult, if the injury is too extensive, particularly if the basement membrane structural integrity is lost, it is thought that the lesion will heal by an excessive fibrotic response.[137]

Many factors determine whether a pulmonary inflammatory response resolves after protecting the lung or persists and damages the host. A critical determinant is the nature of the insult. The physical characteristics of the agent also help determine how the inflammatory response is initiated (e.g., direct stimulation to lung parenchyma or immune or inflammatory cells, antigen presentation to immunocompetent cells, direct activation of complement). Other factors of importance include the concentration of the foreign agent as well as the length and frequency of exposure to it. In addition to inciting the inflammatory response via one of these pathways, the provoking agent certainly has an effect on the processes that control the progression and resolution of a normal inflammatory reaction. For example, inflammation may become chronic because of the persistence of the etiologic agent, such as when an intracellular parasite of low virulence survives and replicates, producing sustained inflammation. Other scenarios that lead to lung injury and influence the process of repair are discussed in Chapter 6.

CONCLUSIONS

The importance of an anatomically normal respiratory tract as well as intact humoral and cellular mechanisms for effective defense of the lung is readily apparent.[1,2,106] The pulmonary sequelae of an impaired or absent cough reflex (see Chapters 25 and 26), abnormalities of ciliary function (see Chapter 67), Ig deficiencies (see Chapters 36 and 51), and defects in oxidative metabolism in the neutrophil (see Chapter 51) all attest to the importance of these mechanisms in defending the lung against invading organisms. In general, the body is well equipped to handle challenges from the environment with a built-in redundancy in lung defense that helps ensure the integrity of the organ.

An important part of lung defense is the inflammatory reaction that can be initiated by both antigen-specific and nonspecific mechanisms. Pulmonary inflammation is generally beneficial to the host and resolves without significant sequelae because of an extensive array of checks and balances. However, it is also important to realize that when part of the checks and balances is lacking (e.g., deficiency of α-proteinase inhibitor), inflammation may eventually harm the host (see Chapter 71). In addition, if this programmed response goes awry (see Chapter 44), is prolonged, or is inappropriate in magnitude (see Chapter 57), lung dysfunction and irreversible injury are produced. Given the variety of environmental insults to which the lung is continuously exposed and the complexities of the processes that defend the respiratory tract, it is remarkable that lung disease is the exception. Indeed, most children never experience significant pulmonary disease because of the efficiency of these elaborate and complementary systems of defense.

ACKNOWLEDGMENTS

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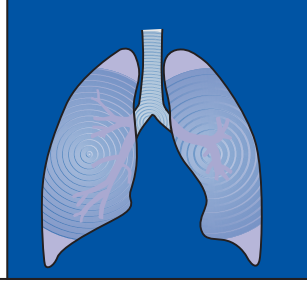

CHAPTER 6

Mechanisms of Acute Lung Injury and Repair

Kevin C. Doerschug and Gary W. Hunninghake

TEACHING POINTS

- Acute lung injury represents a common pathway of cellular and chemical processes despite a wide array of underlying causes.
- Inflammation causes alveolar permeability and leads to extravasation of protein-rich fluid into the alveolar space.
- Leukocytes, endothelium, and epithelium all actively contribute to the injury process.
- Mediators of injury are also mediators of host defense, which makes physiologic studies (and treatment) complex.

BACKGROUND

The term *acute lung injury* (ALI) refers to a syndrome of diffuse pulmonary inflammation and increased capillary permeability that manifests in acute refractory hypoxemia and lung infiltrates. Although references date through the last century, the first formal description of the syndrome is attributed to Ashbaugh in 1967.[1] Historically, reports of the syndrome have included terms such as *adult respiratory distress syndrome* and *shock lung*, thus emphasizing specific patient populations or predisposing conditions. More recently, hyaline membrane disease of newborns has been recognized as sharing the same radiographic and histologic findings, and being mediated by the same cellular and soluble factors, as the syndrome seen in adults with septic shock. To incorporate all continuums of patient populations and the vast variety of primary insults that lead to the final common pathway of diffuse pulmonary parenchymal damage, the more inclusive terms acute lung injury (ALI) and *acute respiratory distress syndrome* (ARDS) are now favored. The first American European Consensus Conference[2] defined ALI as (1) acute onset of bilateral infiltrates consistent with pulmonary edema; (2) the absence of evidence for left atrial hypertension; and (3) reduced ratio of arterial oxygen tension (PaO_2) to the fraction of inspired oxygen (FIO_2), PaO_2/FIO_2. The syndrome is called ALI when PaO_2/FIO_2 >300 and ARDS when this ratio falls below 200. The consensus definitions of ALI/ARDS have allowed for extensive clinical and translational research into the mechanisms of lung injury and repair.

STRUCTURE AND FUNCTION

Radiographic and Pathologic Aspects

Acute lung injury's hallmark finding of noncardiac pulmonary edema from alveolar capillary disruption usually appears several hours after an initial predisposing insult, but may not be detected for up to 72 hours. Clinical aspects of ALI are covered in more detail in Chapter 19. The syndrome of ALI has been attributed to an extensive and broad list of inciting causes that are frequently divided into direct (or primary pulmonary insult) and indirect (extrathoracic insult with systemic involvement) insults. A direct insult to the lung stimulates alveolar macrophages to produce a cascade of cytokines including tumor necrosis factor-alpha (TNF-α) and interleukins (IL),[3-5] which in turn recruit further cellular and biochemical responses that characterize the clinical effects of acute lung injury including fever, epithelial injury, and increased endothelial permeability.[6] The pulmonary response to an indirect insult is commonly considered to be part of the so-called *systemic inflammatory response syndrome* (SIRS), and mediated by migration of proinflammatory cytokines[7,8] and microbes[9-11] through the systemic circulation. Many of the local and systemic mediators of ALI are included in Table 6-1. Regardless of the nature and anatomic location of the initial insult, the clinical physiology and pathologic findings within the lungs are remarkably similar, indicating a common final pathway of injury.

The acute phase of lung injury is also characterized by reduced respiratory system compliance and pulmonary hypertension. The latter, in conjunction with increased capillary permeability, leads to pulmonary edema, which is contrasted to congestive heart failure by the finding of protein-rich fluid in the alveoli of those with ALI.[12] Despite vast differences in the molecular characteristics of noncardiogenic edema fluid, chest radiograph findings are indistinguishable from those depicting cardiogenic pulmonary edema[13]—ranging from asymmetrical patchy infiltrates to dense consolidation and may also include pleural effusions.[14,15] Chest computed tomography indicates heterogeneous involvement of injured lungs with a dependent gradient of consolidation that results in reduced effective alveolar surface area.[16] This consolidation relates to prognosis in that the percentage of lung units that can be recruited by increasing ventilatory support correlates with mortality.[17] In parallel, measure-

Table 6-1
Mediators of Acute Lung Injury

Factor	Class	Main Cell of Origin	Major Effects
Tumor necrosis factor-alpha (TNF-α)	Cytokine	Macrophage	Activate endothelium Induce nitric oxide synthesis Stimulate IL-1 production Fever, mobilize metabolites
Interleukin-1β (IL-1β)	Cytokine	Neutrophil, endothelial cell	Activate endothelium Stimulate IL-6 production Local tissue destruction Fever, mobilize metabolites
IL-6	Cytokine	Macrophage, endothelial cell	Activate lymphocytes Stimulate antibody production Fever
IL-8	Cytokine	Many	Stimulate neutrophil transmigration Degranulate neutrophil (oxidative burst)
IL-10	Cytokine	Many	Suppress proinflammatory cytokine expression
Vascular endothelial growth factor (VEGF)	Soluble protein	Many	Activate endothelium Induce permeability Stimulate adhesion molecules
Intracellular adhesion molecule (ICAM)	Adhesion molecule	Endothelial cell	Attract leukocytes to injured endothelium
Vascular adhesion molecule (VCAM)	Adhesion molecule	Endothelial cell	Attract leukocytes to injured endothelium
Nuclear factor kappa-B (NF-κB)	Transcription factor	Many	Increase transcription of proinflammatory mediators
CD14	Cell surface receptor	Macrophage	Bind bacterial endotoxin Activate macrophage
Toll-like receptor (TLR)	Cell surface receptor	Macrophage	Bind bacterial endotoxin Activate macrophage

ments of physiologic dead space correlate inversely with the prognosis of patients with acute lung injury.[18] It is important to note that lung areas that appear radiographically normal exhibit significant biochemical abnormalities on analysis of bronchoalveolar lavage fluid.[19]

Post-mortem examination of lungs from ALI patients reveals heavy, congested, and atelectatic lungs. The majority of autopsy organs show evidence of infection[20] even though pre-mortem studies reveal pneumonia at a much lower rate[21-23]; whether this is due to sampling errors or antibiotic effects on clinical evaluation is not clear. During the acute or exudative phase of ALI, biopsies display hyperemia and evidence of both epithelial and endothelial cell injury.[24,25] Endothelial cells are swollen, with decreased cell-cell adhesion leading to extravasation of microthrombi and polymorphonuclear neutrophils (PMNs) into the interstitium. Denudation of the alveolar epithelium leads to flooding of the alveoli with proteinaceous fluid, immune cells (largely PMNs) and red blood cells. Alveoli may be atelectatic and hyaline membranes are seen on the epithelial side of the basement membrane. The exudative phase of ALI usually persists for several days, after which many patients have rapid clinical improvement with resolution of parenchymal injury. This resolution is marked by a return of macrophages as the prominent luminal cell,[26] whereas type II pneumocytes re-epithelialize the alveolus, differentiate into type I pneumocytes, and restore epithelial barrier function. Other patients develop a prolonged fibroproliferative phase characterized by the absence of type II pneumocytes and the proliferation of myofibroblasts, fibronectin, and collagen within the alveoli.[27] It is not clear what triggers this prolonged recovery phase in some individuals with ALI, but these findings on lung biopsy signal an ominous prognosis. Attempts at reducing or reversing the fibroproliferative phase with corticosteroids showed initially promising results,[28,29] but ultimately corticosteroids have yet to be proven beneficial in larger studies of patients with ALI.

CELL-MEDIATED LUNG INJURY

Neutrophils

Biopsy and bronchoalveolar lavage specimens from patients with ALI are dominated by neutrophils, and intense investigations into the function of these cells during clinical illness have uncovered numerous processes mediated by PMNs. Neutrophils are recruited to injured sites by the expression of adhesion molecules including intracellular adhesion molecule (ICAM)-1 and E-selectin on activated endothelial cells, and plasma levels of these adhesion molecules correlate with the degree of organ dysfunction.[30] Once recruited to the alveolus, neutrophils in patients with ALI demonstrate activation of the transcriptional regulatory unit nuclear factor kappa-B (NF-κB), which in turn increases neutrophil expression of IL-1β and other proinflammatory mediators implicated in tissue injury. Accordingly, both the persistence of alveolar neutrophils and the activation of NF-κB within neutrophils[31] correlate inversely with survival. Following activation, neutrophils orchestrate a process of oxidative burst which generates hydrogen peroxide and other reactive oxygen and nitrogen species that destroy invading pathogens. This free-radical stress also culminates in oxidized host phospholipid membranes that alter mitochondrial and cellular function and compound tissue injury. Neutrophils may play a key role in the apoptosis (or programmed cell death) of immune cells in the lung through regulation of phosphatidylinositol-3 kinase (PI-3K) pathways.[32]

The association of neutrophil number and activation with outcome provides strong evidence of the involvement of these leukocytes in the injury pathways, yet tremendous controversy persists regarding the importance of PMNs in the pathophysiology of ALI. Attempts to mediate neutrophil

activation have led to conflicting results, raising questions regarding PMN function. This controversy is at least in part due to the recognition that these processes contribute to organ injury but are also key mediators of host defense. For these reasons, clinical and translational research continues in this important area.

Macrophages

The predominance of neutrophils in lung specimens obtained during ALI has drawn attention away from monocytic cell lines, including the macrophage. Alveolar macrophages are the resident immune cell in the lung, and represent the innate host defense system and as such initiate many of the processes leading to the intense inflammatory response of ALI (Fig. 6-1). Importantly, key macrophage activity may precede the clinical recognition of the disease. Alveolar macrophages recognize pathogens or their products through various cell surface receptors. In the most well-characterized system, pathogens or their products initially bind to CD14 which in turn recruits Toll-like receptor (TLR) subtypes that are specific for the toxin.[33-35] Together, toxin binding to CD14/TLR leads to activation of the macrophage and a subsequent intense inflammatory response. In addition to CD14 on the cell surface, macrophages release a soluble form of the receptor, sCD14, which activates cells that do not express CD14 (most notably endothelial and epithelial cells). The importance of sCD14 is demonstrated by the finding that the concentration of this protein in alveolar fluid is highly associated with the number of neutrophils in the lung.[36]

Once stimulated, macrophages display mobilization of NF-κB to the cell nucleus.[37] In contrast to neutrophil activation, macrophage activation is more characterized by the production of TNF-α[38] although certainly IL-1β is secreted as well. Like the macrophages themselves, TNF-α levels peak[38] and wane early in the disease process, making investigations, or manipulations, of TNF-α-mediated processes in humans difficult. In addition to TNF-α, the secretory products of activated macrophages form a list that is extensive,[39] redundant, and interactive in function, and summate to sequester and stimulate neutrophils in the lung early in ALI.[38]

The return of macrophages as the dominant alveolar cell line signals resolution of ALI,[26] supporting the notion that macrophages are also involved in the regulation of tissue injury. Further support is garnered by findings that alveolar macrophages possess surface receptors for neutrophil proteases,[40] and can scavenge hydrogen peroxide and limit oxidant-mediated injury.[41] Finally, macrophages phagocytose neutrophils in vitro in a time-dependent manner that corresponds to the clinical time course of resolution.[42] Taken together, these observations lend credence to the importance of alveolar macrophages in the resolution of ALI.

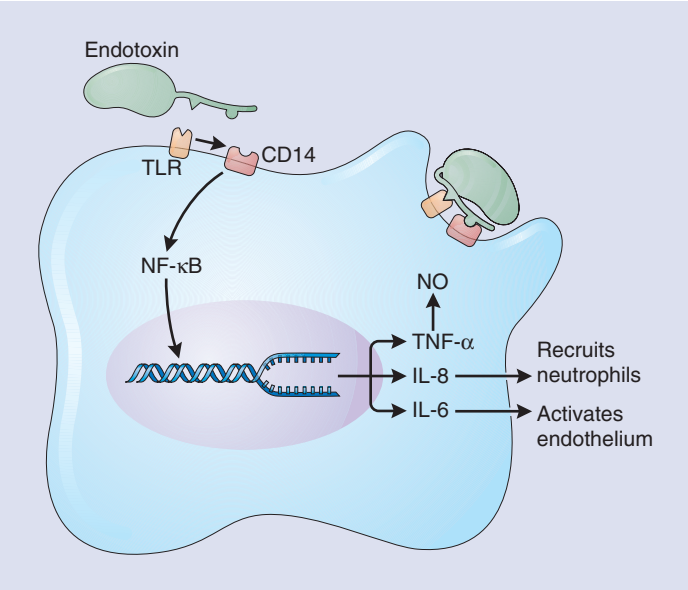

Figure 6-1 The alveolar macrophage in acute lung injury. Pathogenic bacteria are recognized by a family of Toll-like receptors (TLRs) which present the pathogen to the cell surface receptor CD14. Together, these receptors mobilize NF-κB to the nucleus where it facilitates gene transcription of several proinflammatory factors. Tumor necrosis factor-alpha (TNF-α) stimulates other immune cells and leads to the production of nitric oxide, which promotes both killing of engulfed bacteria as well as tissue injury. Stimulated macrophages also produce interleukin (IL)-6, which activates endothelial cells, and IL-8, which recruits neutrophils to the site of injury.

Endothelial Cells

The histology of ALI clearly documents altered capillary endothelial cells, and some consider ALI as a continuum of "panendothelial disease" resulting from the systemic inflammatory response syndrome.[43] This not only pertains to indirect, but also direct causes of ALI, as alveolar TNF-α affects the adjacent endothelium.[44] Once considered a relatively static cell line, the endothelium is now recognized as an active tissue that regulates blood flow, immune function, and solute transport. Whether the noted changes represent an injury to the endothelial cell or an activation of this cell line is controversial. Most likely, there is a continuum of altered endothelial processes that, if allowed to persist unabated, lead to irreversible loss of normal function. Because endothelial cell changes in ALI involve a loss of normal cell function and the extent of endothelial changes is related to the severity of disease, the term *endothelial injury* will be used throughout this chapter. This view is exemplified by findings that von Willebrand factor antigen (vWf, normally found in large concentrations only within endothelial cells) is released from injured cells into the vessel lumen and into the alveolar space. The extracellular concentrations of vWf are predictive of the development of ALI in those at risk,[45] and of outcome in patients with established ALI.[46,47]

Systemic inflammation leads to the secretion of vascular endothelial growth factor (VEGF) from many different cell lines. VEGF, also known as *vascular permeability factor*, induces many of the endothelial changes seen in ALI. Once injured, the endothelium transforms from a flat monolayer with tight intracellular junctions to an irregular surface of rounded endothelial cells and a loss of cell-cell interactions. This state creates a permeable surface such that fluid can escape capillaries into the interstitium and ultimately the alveoli. Extravascular lung water is clearly deleterious to gas exchange, but the injured endothelium also allows plasma proteases to exit the vessel and impair alveolar surfactant function and contribute to atelectasis.[48]

The role of endothelial cells in lung injury extends beyond a passive loss of barrier function leading to extravasation of vessel contents into the alveoli. VEGF stimulates the expres-

sion of several adhesion molecules on the luminal surface of endothelial cells, particularly intracellular adhesion molecule (ICAM), vascular adhesion molecule (VCAM), and the selectin family of glycoproteins. Together, these adhesion molecules function to slow neutrophil transport within the vessel and initiate rolling and adhesion of neutrophils on the endothelial surface (Fig. 6-2). Additional chemotactic molecules on the basolateral surface and beyond then promote transmigration through the permeable endothelium. VEGF is downregulated by endothelial-derived factors and this function is lost during sepsis; hence, the loss of normal endothelial function contributes to further endothelial injury. Importantly, manipulations to decrease expression of VEGF lead to decreased organ injury and improved mortality in live-infection models of sepsis, demonstrating the importance of VEGF and the related adhesion molecules in the progression of disease.[49] Consistent with these findings, the concentrations of endothelial-neutrophil adhesion molecules are more strongly associated with mortality in humans than are measures of neutrophil activation.[30]

Beyond neutrophil recruitment, endothelial cells propagate the inflammatory response by secreting cytokines, including IL-1 and IL-6. These inflammatory mediators further stimulate endothelial cells to decrease tissue-type plasminogen activator and increase plasminogen activator inhibitor activities[50] as well as decrease thrombomodulin secretion,[50] and thus induce the procoagulant state found in the alveolar fluid of patients with ALI.[51] Injured endothelial cells have diminished capacity to secrete endogenous vasoconstrictors and vasodilators necessary to regulate blood flow.[52] Endothelial cells exhibit injury that is evident on pathologic studies, but they clearly mediate the injury pattern and contribute to the morbidity and mortality of ALI.

Epithelial Cells

Histologic analysis shows diffuse alveolar damage during clinical ALI, and altered epithelial structure is evident. The lung epithelium has many functions during health, and many of these functions are lost during acute inflammatory processes. Epithelial damage clearly contributes to the pathogenesis and morbidity of ALI.

Increased capillary permeability may present a conduit for vascular contents to extravasate into alveoli, but there is a growing body of evidence describing ineffective clearance of alveolar fluid by epithelial cells leading to the clinical findings of noncardiogenic pulmonary edema. The epithelial surface is lined mainly with type I pneumocytes that maintain the structural integrity of the alveolus through barrier function. The remaining cells in the lung epithelium are type II pneumocytes, whose diverse functions include ion transport regulation, surfactant production, and regeneration of type I pneumocytes. Defects in epithelial function lead to alveolar fluid accumulation in two ways—increased permeability and decreased fluid transport out of the alveoli. However, the epithelial barrier is less permeable than the endothelium, even after injurious exposure,[53] suggesting that defects in alveolar liquid clearance play a large role in the accumulation of extravascular lung water. Indeed, the rate of alveolar fluid clearance is impaired in patients with ALI, and inversely related to prognosis.[54] Transepithelial transport of fluid occurs in several fashions, the best described being along an osmotic gradient formed by active transport of sodium via a Na^+/K^+-ATPase on the basolateral surface of type II pneumocytes.[55] Experimental evidence shows that hypoxia leads to displacement of the Na^+/K^+-ATPase from the basolateral surface—a condition that is rapidly reversible with alveolar instillation of the beta-adrenergic agonist, terbutaline.[56] Although the role of Na^+/K^+-ATPase in human ALI is still unclear, beta-agonist administration decreases total lung water in ALI patients, lending support to this hypothesis. Alveolar fluid clearance is impaired by several factors in addition to hypoxia. The generation of reactive oxygen and nitrogen species, possibly caused by free-radical deactivation of transport proteins, diminishes epithelial fluid transport.[57,58] Epithelial function is likely impaired through a loss of epithelial cells through the process of apoptosis.[58]

With the progression of ALI and loss of epithelial integrity, inflammatory mediators and bacteria normally contained by

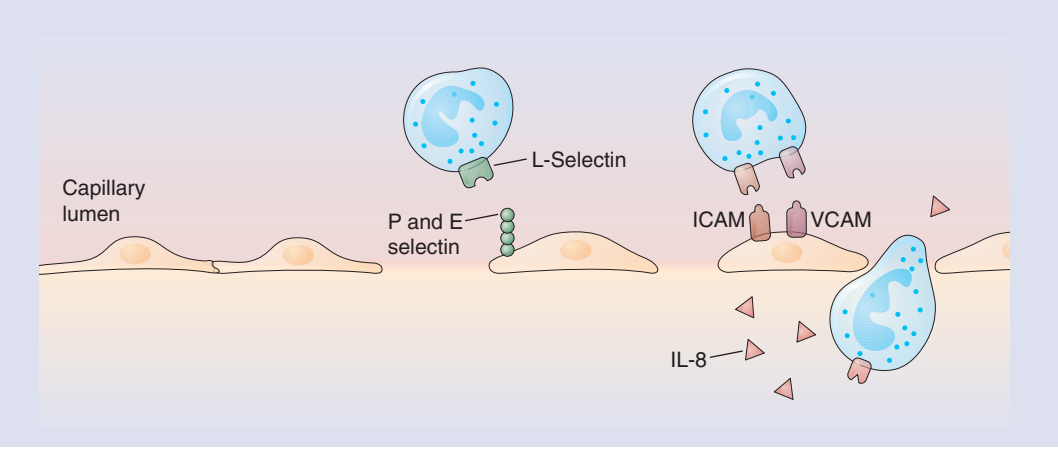

Figure 6-2 Endothelial-neutrophil interactions in acute lung injury. Endothelial cells become activated through a variety of factors, including tumor necrosis factor-alpha, angiotensin II, and vascular endothelial growth factor. Once activated, endothelial cells lose cell-cell interactions and the monolayer is permeable. Activated endothelial cells express P- and E-selectins which form weak interactions with passing neutrophils (via L-selectin) and initiate leukocyte rolling. Stronger interactions with intracellular adhesion molecule (ICAM) and vascular adhesion molecule (VCAM) function to adhere leukocytes to the monolayer, where chemokines such as interleukin-8 (IL-8) stimulate transmigration into the tissue.

the intact epithelium can enter the lung parenchyma and circulation.[59] The importance of this phenomenon is highlighted by a study showing that mortality-lowering ventilator strategies reduce the incidence of bacteremia in animal models.[60] However, compelling data of translocation across human lung epithelia are lacking. In contrast, there is a significant body of evidence that surfactant, a secretory product of the epithelium, is altered in composition and function in human ALI. Normal lung surfactant is composed of phospholipids, neutral lipids, apoproteins, and the surfactant proteins (SP)-A, B, C, and D. During ALI, the total amount of surfactant phospholipids is reduced, with marked decreases in phosphatidylcholine and phosphatidylglycerol[61,62]; these changes are associated with increased surface tension of surfactant liquid[61] and the severity of respiratory failure.[63] In addition to deficiencies in phospholipids, there is marked depletion of SP-A and SP-B during ALI. The net deficiency of proteins and phospholipids is due to decreased production by type II pneumocytes as a result of inflammation[64] and increased destruction by oxidant stress[65] and proteolytic cleavage.[66] The findings of abnormal surfactant composition and function have led to more than 200 clinical evaluations of exogenous surfactant,[67] yet no trial has provided a convincing mortality benefit. Several variables in previous trials of exogenous surfactant therapy include issues of dose, timing, and composition of the applied therapy—leading to continued debate regarding the future of this mode of treatment.

Soluble Mediators of Inflammation

CYTOKINE-MEDIATED LUNG INJURY

Cytokines are low-molecular-weight soluble proteins that transmit signals within cells; therefore they mediate many of the interactions between immune cells and lung tissue in the pathogenesis of ALI. Despite the intense effort spent in researching the role of cytokines in the pathogenesis of ALI, criticism of human studies has evolved and some consideration of sampling techniques must be mentioned. In most instances, cytokines participate in cell signaling through interaction with cell surface receptors and in this regard may have very localized effects. In parallel, because various anatomic barriers compartmentalize the immune response,[68] cytokine concentrations may be quite different in the serum, alveolar space, or lung parenchyma. Furthermore, systemic cytokines may represent "the tip of the iceberg"[69] or overflow of cytokines from various sources,[70] making interpretation of these factors complex. There is evidence, however, that the alveolar compartment is disrupted during intense inflammation and airway sampling yields cytokine concentrations that are similar to more invasive sampling.[71] With this in mind, as well as the capacity to perform repeated measurements in patients safely and easily, most regard bronchoscopic sampling of alveolar fluids as the best method available to assess the role of cytokines in ALI.[72]

Investigations into the role of cytokines in ALI initially focused on TNF-α and IL-1β—primarily because bacteria stimulate production of these molecules, whereas in the absence of bacteria, these cytokines are capable of initiating an inflammatory response identical to ALI. TNF-α has been identified in BAL fluid in some, but not all, studies of human ALI. This discrepancy may be related in part to timing of samples because this cytokine may be prevalent in the airway fluid for less than 24 hours. TNF-α exerts its effects through interaction with TNF receptors I and II on the surface of macrophages and other immune cells,[73] or is shed as a soluble receptor. TNF-α interactions with these soluble receptors are complex because the receptors may either potentiate TNF-α effects by stabilizing the cytokine, or attenuate TNF-α effects by interfering with TNF-α binding to active receptors.[74] The local effects of TNF-α collectively function to increase inflammation within the tissue by activating endothelial cells, thereby increasing vascular permeability and allowing the passage of immune cells, immunoglobulin, and complement into the tissue. In addition to these effects, TNF-α also stimulates the production of itself and IL-1β and thus further stimulates inflammation.

Like TNF-α, IL-1β has been identified in lavage fluid obtained during ALI, and through binding to the interleukin-1 receptor (IL-1r)—a potent stimulator of vascular endothelium. This cytokine also activates lymphocytes and as such has many of the same effects as TNF-α. However, IL-1β is commonly thought to be more responsible for tissue destruction than is TNF-α, as evidenced in a study that showed that inhibition of IL-1β decreased endothelial activation caused by BAL fluid from ALI patients, whereas inhibition of TNF-α had no effect.[75] In addition to the effects on tissue injury, IL-1β stimulates the production of IL-6. It has been proposed that IL-6 integrates the inflammatory response through diverse actions including differentiation of lymphocytes, induction of immunoglobulin production, and induction of many proteins found during the acute phase of inflammation.[76] Unlike TNF-α and IL-1β, IL-6 is found in the BAL of patients throughout the course of ALI, but the concentrations of the latter cytokine also inconsistently predict outcome.[72,77] All three of these early cytokines can be detected in the blood of patients with ALI, and may be responsible for systemic disease.

While TNF-α, IL-1β, and IL-6 have local and systemic effects, the effects of the chemotactic cytokine IL-8 are largely local in nature. This cytokine is the most abundant product secreted by alveolar macrophages followed by bacterial toxin stimulation, and it is the predominant neutrophil chemoattractant in BAL fluid.[78,79] It is worth noting, however, that although IL-8 concentrations correlate with BAL neutrophil concentrations, this strength of relationship varies over time, and IL-8 concentrations at any time are poor predictors of outcome. This observation clearly indicates that additional neutrophil chemoattractants are involved in the pathogenesis of ALI.

Immune cells also secrete a number of anti-inflammatory cytokines that regulate inflammation. In keeping with its role as an integrative cytokine, IL-6 reduces the effects of TNF-α and IL-1β by inhibiting their production[80] and stimulating their natural antagonists.[81] However, the most widely described anti-inflammatory cytokine is IL-10. This counter-regulatory protein is synthesized in lymphocytes and monocytic cells in response to bacteria and inflammatory cytokines, and inhibits inflammatory cytokines, inhibits class II major histocompatibility protein expression, and suppresses monocyte procoagulant activity in experimental systems. IL-10 is found in BAL fluid during ALI, and lower levels of this cytokine are associated with a poor prognosis.[82] Although this suggests that failure to decrease inflammation leads to

increased injury, increasing IL-10 in pneumonia models leads to impaired bacterial clearance and increased mortality.[83]

Tremendous efforts have been made to identify which cytokines may be primary mediators of inflammation during ALI. Although these studies provide irrefutable evidence of the involvement of many biochemical and cytologic processes, none has clearly prevailed as primary mediators amenable to therapy in human disease. Attempts at blocking or reversing suspected agents in patients have been generally unsuccessful and, at times, lethal. At least four issues may explain this apparent inconsistency. First, ALI induces a complex and redundant inflammatory milieu, and ameliorating any one factor is unlikely to stop the cascade of events. Second, inflammation and organ injury likely begin hours or days prior to the clinical recognition of the disease such that the primary mediators are no longer actively involved at the time of therapy. Third, the inflammatory process is, in fact, a reaction to a primary inciting event; a reduction in inflammation impairs host defense mechanisms. Fourth, and related to the latter issue, the host response is a tightly controlled response involving an initial proinflammatory response rapidly followed by an exuberant anti-inflammatory response. Both responses are increased during the first days of lung injury; however inflammatory antagonists predominate in the alveoli within 24 hours of disease onset.[84] It is becoming clear that the balance of inflammatory agonists and antagonists in patients at risk for lung injury may be more important than any one factor.[85,86] Further, exogenous attempts at altering inflammation may disrupt this balance and lead to either excessive inflammation or impaired host defenses, both of which may increase mortality.[87]

In summary, cytokine measurements in the BAL fluid of patients with ALI have provided insight into the complexity of interactions between lung epithelium, endothelium, and immune cells. However, despite intense research we have yet to discover a consistent pattern of cytokine regulation in ALI. Further research into cohesive groups of cytokines, coupled with markers of epithelial and endothelial barrier injury, is needed to provide a more comprehensive understanding of immune regulation in ALI.

RENIN-ANGIOTENSIN MEDIATED INJURY

The emergence of the severe acute respiratory syndrome (SARS) and the subsequent identification of an angiotensin converting enzyme (ACE) subtype as the receptor for the causative coronavirus have increased our understanding of the role of the renin-angiotensin-system (RAS) in the pathogenesis of ALI. Briefly, renin is produced by a variety of stimuli, including decreased glomerular pressure as encountered during shock. Renin cleaves angiotensinogen to angiotensin, which is subsequently transformed to angiotensin II (Ang II) by ACE subtype I (ACE-1). Ang II then exerts multiple effects through interactions with the AT1 receptor, including vasoconstriction and sodium resorption, that counteract the hemodynamic state during shock.

The association of the lung and RAS was first recognized anatomically and may be traced to findings that ACE-1 is produced extensively on the luminal surface of pulmonary capillary endothelial cells, and thus the lungs are a major source of systemic Ang II.[88] Furthermore, ACE-1 is found in lung lavage fluid during experimental lung injury[89] and as well as in serum from patients with lung diseases not typically associated with shock. These findings were initially explained as a demonstration of shedding of ACE-1 from injured endothelium, but there has been gradual acceptance that RAS is actively involved in the process of acute lung injury. Certainly RAS is upregulated in critical illness and patients have increased concentrations of Ang II in serum. It is also clear that this peptide mediates many of the pathogenic processes implicated in lung injury. Ang II promotes inflammation through activation of the NF-κB pathways,[90] as well as through the recruitment of immune cells via increased expression of VEGF[91] and of intercellular adhesion markers.[92] Furthermore, through the AT-1 receptor, Ang II promotes collagen formation in lung fibroblasts[93] and apoptosis in epithelial cells[94] and hence is responsible for features seen during the fibroproliferative phase of ALI. Most strikingly, AT-1 receptor blockers may decrease neutrophil infiltration, improve oxygenation, and prolong survival in an animal model of ALI.[95]

The lungs are a significant source of Ang II during critical illness as evidenced by increased concentrations found in arterial compared to mixed venous blood[96-98]; presumably this is related to an increase in ACE-1 activity within the lungs. In fact, patients with ACE-1 polymorphisms associated with increased ACE-1 activity appear to have an increased risk of both the development of ALI as well as mortality from the syndrome.[99] ACE-1 activity is not limited to pulmonary endothelial cells as previously thought—alveolar macrophages, neutrophils, and alveolar epithelial cells also produce ACE-1. These additional sources of Ang-II may, in fact, be more clinically relevant during critical illness because endothelium-bound ACE-1 activity is actually decreased in patients with ALI.[100] Because inhibition of ACE-1 attenuates endothelial activation[101] in patients at risk of ALI and decreases TNF-α activation in animal models,[102] persistent expression of angiotensin I is likely to contribute to the pathogenesis of ALI.

Recently, a homologue of ACE-1, or ACE-2, was discovered. This subtype of ACE cleaves Ang I and Ang II to additional angiotensin species that do not act through the AT-1 receptor. In so doing, ACE-2 appears to be protective in ALI; loss of ACE-2 activity via genetic manipulation of experimental sepsis leads to increased vascular permeability, lung edema, and neutrophil accumulation.[103] The finding that ACE-2 is an essential receptor to the coronavirus responsible for SARS, a severe demonstration of clinical ALI, lends clinical credence to the protective function of this enzyme.

CLINICAL APPLICATIONS

Decades of research have provided insight into many mechanisms of the pathogenesis of ALI, but have failed to identify disease-specific mechanisms that are amenable to therapy. As such, therapy is considered supportive, and most patients require some form of mechanical ventilation, parenteral fluids and nutrition, and intensive monitoring. The largest clinical trials of ALI[104-106] have described excessive mortality and morbidity because of the supportive care that allows patients to survive beyond the first several hours of disease. Patterns of injury related to ICU therapy should, therefore, be discussed.

Ventilator-Associated Lung Injury

Soon after the initial description of ALI and its pathology, many animal models of positive-pressure mechanical ventilation have demonstrated that high peak inspiratory pressures induce injury in previously normal lungs, including changes in pulmonary mechanics,[107] alveolar integrity,[108] and histology[109] that are identical to those seen in ALI. Subsequently, investigators found that limiting chest wall excursion during high pressure ventilation reduced the magnitude of this injury, demonstrating that the high lung volumes induced by high inspiratory pressures are responsible for this injury.[110] Furthermore, low tidal volume strategies decrease the translocation of bacteria[60] and toxins[111] from the lungs to the systemic circulation, showing that high tidal volumes contribute to a loss of epithelial barrier function. Edema and atelectasis in ALI could culminate in a significant decrease in effective alveoli, the so-called "baby lung,"[112,113] such that standard tidal volumes produce overdistention and alveolar wall shear stress and injury of the remaining functional lung.[114]

Clinical investigations of patients with ALI demonstrate that those ventilated with lung-protective strategies that included limited tidal volumes had lower concentrations of neutrophils and inflammatory cytokines in BAL fluid and decreased systemic inflammatory cytokines compared to those ventilated with traditional settings.[115] An early study of lung-protective ventilation strategies showed mortality lower than that predicted by severity of illness scoring,[116] but the initial randomized controlled trials of lung-protective ventilatory strategies that followed were small and produced conflicting results.[117-120] However, in the largest clinical trial of ventilator strategies in ALI, the group of patients ventilated with small tidal volumes (6 mL/kg) experienced lower mortality than those ventilated with higher tidal volumes (12 to 15 mL/kg).[105] Although there is controversy regarding both the choice of control group strategy and whether a tidal volume between the two strategies would be even more effective, experimental and clinical evidence clearly shows that mechanical ventilation with high tidal volumes contributes to lung injury and mortality.

Extravascular lung water is a hallmark finding in ALI, and as mentioned, indicates both increased alveolar-capillary permeability and impaired resorption of alveolar edema. In addition, hydrostatic pressure[121] and loss of capillary oncotic pressure owing to hypoproteinemia[122] contribute to non-cardiogenic pulmonary edema. Logically, decreasing capillary hydrostatic pressure may decrease edema and improve outcomes. Conversely, impaired left ventricular stroke volume from inadequate filling pressures may contribute to the inflammatory state resulting from inadequate organ perfusion.

Several studies have examined the relation between extravascular lung water and outcomes in ALI. An early study showed that patients managed with attempts to decrease extravascular lung water had more ventilator-free days than those whose fluid management was based on pulmonary capillary wedge pressures[123]—whether this was an effect of net fluid management or of the monitoring techniques was unclear. Increasing plasma oncotic pressure while decreasing total body water by co-infusing furosemide and albumin may also improve ICU-related outcomes.[124] The large ARDSnet Fluid and Catheter Treatment Trial utilized a 2 × 2 factorial design including conservative or liberal fluid treatment strategies guided by either central or pulmonary artery catheters.[104,106] Patients who were randomized to conservative fluid management experienced more ventilator-free days and fewer ICU days—this effect was true regardless of how fluid management was monitored. Although mortality did not differ between the two catheter groups, those managed with pulmonary artery catheters experienced more complications, illustrating the potential for iatrogenic complications in ALI. Taken together, multiple trials have shown that minimizing hydrostatic pressure improves physiology and ICU-related outcomes; the assuredness of this conservative fluid management is likely more important than the methods used to achieve it. These findings add support to the significance and complexity of pathology leading to the accumulation of non-cardiogenic pulmonary edema fluid in ALI.

CONCLUSION

Acute lung injury is a syndrome resulting from a variety of causes that involves diffuse inflammation leading to proteinaceous alveolar edema. The mechanisms involved in the injury are remarkably similar regardless of the underlying etiology, leading to damage of both epithelial and endothelial surfaces. These surfaces are not only passively injured, however, and along with leukocytes contribute to the pathogenesis of the syndrome. Considerable overlap exists between mediators of injury and mediators of host defense and repair such that attempts at intervening in the injury pathway have been troublesome.

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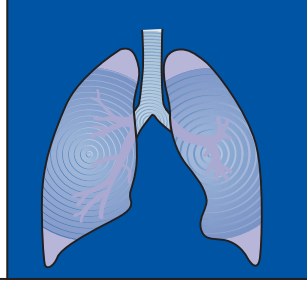


CHAPTER 7

Applied Clinical Respiratory Physiology

Peter D. Sly and Rachel A. Collins

TEACHING POINTS

- Lung volume is actively maintained by muscle activity, glottic "braking," or increases in respiratory rate in the presence of lung disease.
- Hyperinflation comes at the cost of an increase in work of breathing and putting respiratory muscles at a mechanical disadvantage.
- The presence of wheeze implies that expiratory flow limitation exists.
- Cough is a natural forced expiration and its characterization is an essential component of examining the respiratory system.
- The functional anatomy of the respiratory tract largely determines the physiology.
- An understanding of basic respiratory physiology aids understanding of the alterations of normal function that occur in diseases.

BACKGROUND: BASIC PHYSIOLOGIC PRINCIPLES

Functional Anatomy of the Respiratory System

RIB CAGE

The rib cage is formed by the 12 thoracic vertebrae, the 12 pairs of ribs, the sternum, and the costal cartilages. Posteriorly, the ribs articulate with the vertebral bodies. The head of the first, tenth, eleventh, and twelfth ribs each articulate with a single vertebra. The other ribs articulate with two vertebrae across the intervertebral disk. There is an articular surface on the tubercle of ribs 1 through 10, through which the ribs articulate with the transverse process of the vertebra to which it corresponds numerically.

Anteriorly, the first seven ribs are connected directly to the sternum via the costal cartilages and are called *true ribs*. The remaining five ribs are called *false ribs* because they are not attached directly to the sternum. The cartilages of ribs 8, 9, and 10 are joined to the cartilage of the rib above, and ribs 11 and 12 are free anteriorly. These are often called *floating ribs*.

The axis of rotation of the rib changes progressively down the thoracic cage (Fig. 7-1). The upper ribs have a pump-handle movement, with the anterior end swinging upward and outward. The lower ribs have a bucket-handle movement, with the ribs moving laterally and upward; the lowest ribs have a caliper movement, with the entire rib swinging laterally. These combinations of movements lift the rib cage as well as expand it in the anteroposterior and lateral directions. Such movement increases the transverse diameter of the rib cage, particularly at its lower end, and increases its volume. An understanding of how the ribs move is fundamental to understanding how the muscles of respiration expand the rib cage during breathing. This point is highlighted in sections discussing the individual muscle groups. The consequences of abnormalities in the rib cage are dealt with in Chapter 66.

MUSCLES OF RESPIRATION

The basic contractile unit of the skeletal muscle fiber is the *sarcomere*, consisting of thin actin filaments anchored at one end to the Z disk and thick myosin filaments that overlap between adjacent sets of actin filaments (Fig. 7-2). Contraction of the muscle is thought to occur when cross-bridges form between the actin and myosin filaments and the actin filaments slide progressively along the myosin filaments. Muscle shortening is thought to be limited when the Z disks limit further sliding of the filaments. Myofibrils are made up of multiple sarcomeres, and form the contractile apparatus of muscle fibers. Each muscle fiber is covered in a fine tubular sheath known as the *sarcolemma*.

When muscle excitation occurs, a propagated action potential is initiated across the sarcolemmal membrane of the muscle fibers, which travels in both directions away from the centrally located myoneural junction. The action potential is an ionic current flow resulting from sequential increases in membrane sodium and potassium conductance. The action potential also spreads inward along the transverse tubular system (which is an extension of the sarcolemmal membrane). The action potential causes calcium ions to be liberated into the tubular space. During rest, muscle interaction between actin and myosin is inhibited by the troponin-tropomyosin complex, thus preventing muscle contraction. The influx of calcium ions is thought to initiate muscle contraction by combining with troponin, releasing actin and myosin from the inhibitory influence of the troponin-tropomyosin complex. The sliding filament paradigm, which has been proposed to explain skeletal muscle, explains muscle contraction in terms of the thick (myosin) and thin (actin) filaments sliding over one another, forming attachments known as *cross-bridges*. During this process, adenosine triphosphate is converted to adenosine diphosphate, with the accompanying release of energy. The cross-bridges are not

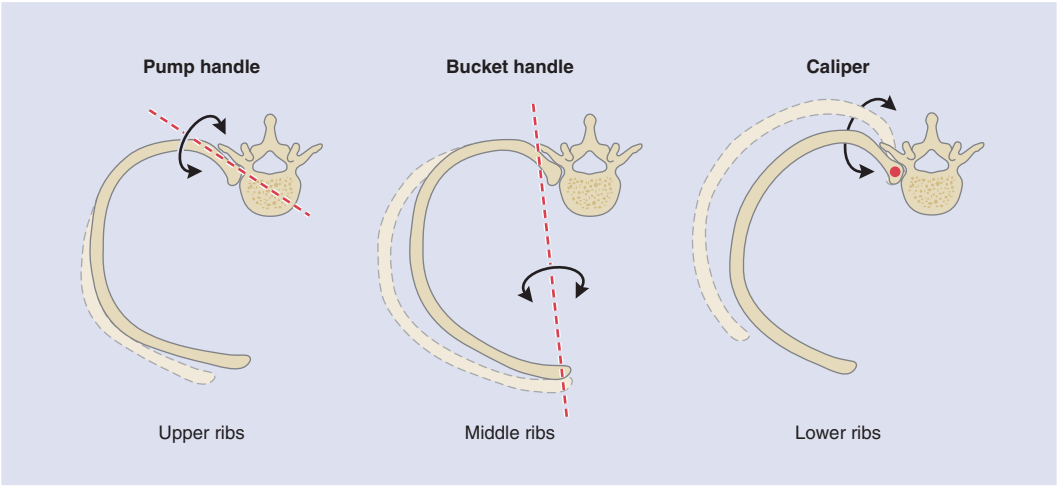


Figure 7-1 Schematic representation of rib motion around its axis. The *dotted lines* represent the upper and middle ribs, and the *red dot* represents the lower ribs.

static connections but actively cycle (attaching, detaching, and reattaching) during a contraction. Relaxation occurs as a result of the active transport of calcium ions into longitudinally oriented elements of the sarcoplasmic reticulum and a reversing of this process. Skeletal muscle cells typically bridge their attachment points on the skeleton. As a result, each cell is independent; the force of contraction can be increased by recruiting more cells for contraction.

The muscle fibers supplied by a single nerve fiber are known as a *motor unit*. A muscle is made up of many individual motor units, each unit consisting of many different muscle fibers. The number of muscle fibers in a motor unit varies widely among different muscles but can be as low as 2 to 10 fibers in small muscles used for delicate movements (e.g., laryngeal and extraocular muscles) and as many as 2000 fibers for large muscles such as the gastrocnemius muscle. Fibers from a single motor unit are not packed into one region of the muscle but are scattered throughout the muscle.

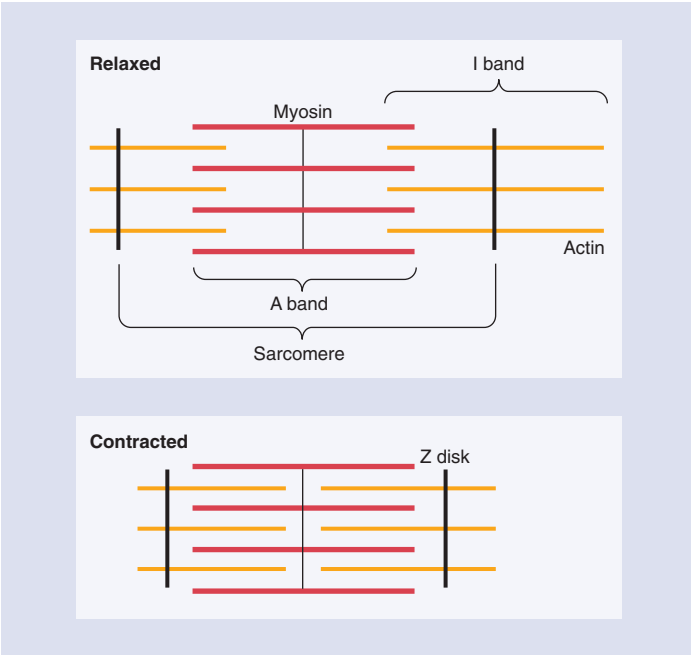


Figure 7-2 The sarcomere in the relaxed and contracted state. Sarcomeric shortening occurs by sliding of actin over myosin filaments.

Muscles of Inspiration

Diaphragm. The diaphragm is the most important inspiratory muscle. It consists of three main parts: the costal diaphragm originating from the costal margin and inserting into the central tendon, the crural diaphragm originating mainly from the vertebral column and also inserting into the central tendon, and the central tendon itself. The fibers of both muscular parts are directed axially; the costal part is apposed directly to the inner surface of the rib cage (zone of apposition).

Stimulation of the costal fibers causes a fall in pleural pressure and inflation of the lungs. Abdominal pressure rises, and the abdomen is displaced outward. The rib cage is also displaced outward. The force generated by the costal diaphragm is partly transmitted to the rib cage through the zone of apposition. This results in the rib cage being "pushed" upward and outward because of the axis of rotation of the ribs. Stimulation of the crural fibers also causes a fall in pleural pressure, a rise in abdominal pressure, and outward displacement of the abdominal wall, but there is no displacement of the rib cage.

External Intercostal Muscles. The external intercostal muscles connect adjacent ribs and slope downward and forward. When they contract, the ribs are pulled upward and forward, resulting in an increase in both the anteroposterior and lateral diameters of the thorax.

Accessory Muscles. The major accessory muscles are the scalene muscles, which elevate the first two ribs, and the sternocleidomastoid muscles, which elevate the sternum. These muscles play only a minor role in normal quiet breathing but contribute significantly at times of increased ventilatory requirements, such as during exercise or with obstructive diseases of the respiratory system (e.g., asthma). Other

muscles may also help inspiration; for example, the muscles of the alae nasi flare the nostrils and reduce nasal resistance, the small muscles of the head and neck can help raise the first rib, and the pectoralis major can be used to stabilize the rib cage.

Muscles of Expiration

Quiet expiration is usually passive, but at times of increased ventilatory requirement, expiration may become an active process.

Muscles of the Anterior Abdominal Wall. Contraction of the rectus abdominis muscle, internal and external oblique muscles, and transversus abdominis muscle causes the abdominal pressure to rise and the anterior abdominal wall to be displaced inward. This pushes the diaphragm upward and aids expiration. These muscles also contract forcefully during coughing, vomiting, and defecation.

Internal Intercostal Muscles. The internal intercostal muscles aid active expiration by pulling the ribs downward and inward. The muscles also stiffen the intercostal spaces and prevent them from bulging outward.

PLEURA

Each lung is covered by a serous membrane arranged in the form of a closed sac called the *pleura*. A part of this serous membrane (the visceral pleura) covers the surface of the lung and lines the fissures between its lobes. The rest of the membrane (the parietal pleura) lines the inner surface of the corresponding half of the chest wall, covers a large part of the diaphragm, and is reflected over the mediastinum. Between the two layers of the pleura is a potential space called the *pleural space*. The pleural space is 10 to 15 μ wide and contains a small amount of liquid. The lymphatic system opens directly onto the parietal pleura. Active transport of pleural liquid occurs from top to bottom and from costal to mediastinal surfaces. The pleural space "couples" the chest wall to the lungs; without the intact pleural space the lungs would collapse away from the chest wall (a pneumothorax).

LUNGS

Airways. The airways consist of a series of branching tubes that become narrower, shorter, and more numerous as they penetrate deeper into the lung. The trachea divides into the right and left main bronchi, which in turn divide into lobar bronchi, segmental bronchi, subsegmental bronchi, small bronchi, bronchioles, terminal bronchioles, respiratory bronchioles, alveolar ducts, and finally, alveoli (Fig. 7-3). At each division, or generation, the total cross-sectional area of the tracheobronchial tree increases. The division of airways does not occur symmetrically. The tracheobronchial tree is generally divided into two parts. The airways from the trachea (generation 0) to the terminal bronchioles (generation 16) are generally known as the *conducting airways* because they have no alveoli arising from them.

The airways from the respiratory bronchioles (generations 17 through 19) and the alveolar ducts (generations 20 through 22) have increasing numbers of alveoli budding from their wall and are known collectively as the *transitional* and *respiratory zones*. The portion of lung distal to a terminal bronchus forms an anatomic unit called the *primary lobule* or *acinus*.

Gas exchange occurs only within the acini and not in the conducting airways. The total volume of the conducting airways is approximately 150 mL in adults. During expiration, 500 mL of air is forced out of the acini and through the airways. Approximately 350 mL of this air is exhaled through the nose or mouth (together with the 150 mL of air in the conducting airways), but about 150 mL remains in the conducting airways. With the next inspiration, 500 mL of air enters the alveoli, but the first 150 mL is not atmospheric air but the 150 mL left in the conducting airways at the end of

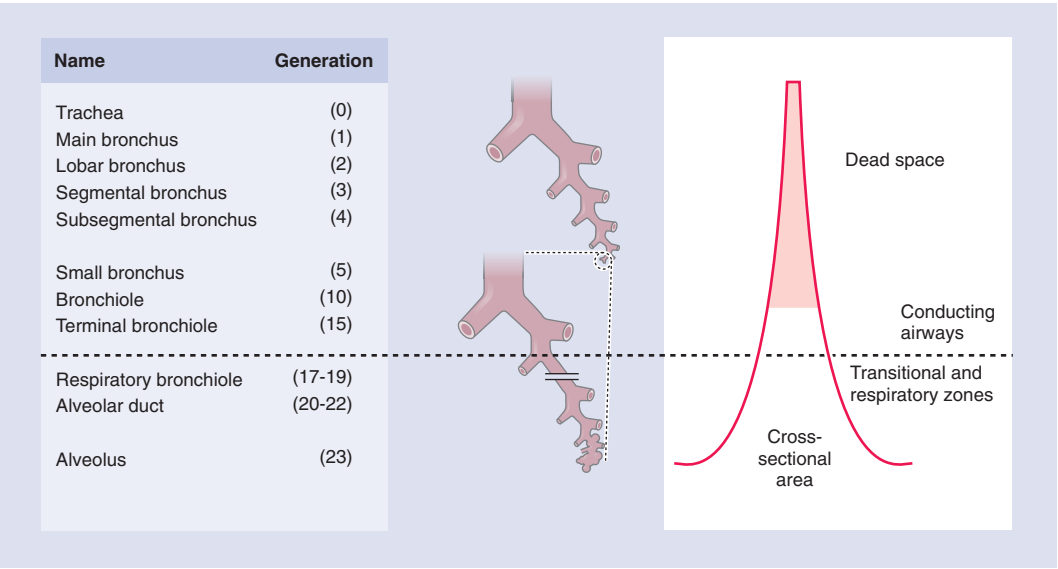


Figure 7-3 Airway generations. Individual airway size decreases with increasing generations but the total cross-sectional area increases. The conducting airways (generations 0 to 16) have no gas exchange and contribute to the amount of dead space *(shaded area)*.

the previous expiration. Thus, only 350 mL of new atmospheric air enters the alveoli during one inspiration. At the end of inspiration, 150 mL of fresh air also fills the conducting airways but cannot participate in gas exchange. The volume of the conducting airways is known as the *anatomic dead space*. The ratio of dead space volume to tidal volume (V_{DS}/V_T), together with the breathing frequency, determines the alveolar ventilation. It is the alveolar ventilation that is important for gas exchange. A decrease in V_T without a corresponding increase in breathing frequency, as may occur with central respiratory depression, leads to a decrease in alveolar ventilation. Similarly, an increase in V_{DS}, such as can occur in conditions that make the conducting airways more compliant (e.g., bronchiectasis), can also lead to alveolar hypoventilation. The cross-sectional area of the tracheobronchial tree increases with each division. This increase in area becomes very rapid in the respiratory zone (see Fig. 7-3).

During respiration, gas flows through the conducting airways by bulk flow, like water through a hose. Beyond that point, the cross-sectional area of the airways is so large that the forward velocity of the gas becomes very small. Diffusion of gas takes over as the dominant mechanism of ventilation in the respiratory zone.

Airway Smooth Muscle. In contrast to skeletal muscle cells, which are mechanically independent, smooth muscle cells must be mechanically coupled and their activation coordinated. Increases in force are produced by increases in the activation of all the coupled cells. The "tone" maintained in airway smooth muscle is an example of continuous partial activation.

There are similarities in ultrastructure, subcellular mechanisms, and contractile and regulatory proteins in striated and smooth muscle. However, there are differences in the way muscle function is regulated. For example, in smooth muscle, a calcium-sensitive regulation of contraction is mediated not via a tropomyosin-troponin system but by a calmodulin-mediated, myosin-linked light-chain phosphorylation mechanism. Smooth muscle has a random organization of filaments giving it a smooth appearance under electron microscopy. Smooth muscle thin filaments are anchored in dense bodies, in a similar fashion to the Z disks of skeletal muscle. Smooth muscle contraction is achieved by cross-bridge formation and interaction between actin and myosin.

Smooth muscle exists in the walls of airways, where it is oriented in a spiral fashion rather than a circular fashion around the airway. The smooth muscle has been reported to make an angle of approximately 30 degrees with the cross-sectional plane.[1] Thus, smooth muscle contraction results in both narrowing and shortening of the airways. The orientation of the smooth muscle could be important in determining airway responsiveness to various stimuli[2] (see Part 10).

Alveoli. The lung can be considered a collection of hundreds of millions of bubbles, each approximately 0.3 mm in diameter. The alveoli bring the air and blood into proximity to each other to facilitate gas exchange. The alveolar walls are thin and contain numerous capillaries. The alveolar-capillary membrane consists of four layers: the capillary endothelium and its basement membrane; a thin connective tissue layer; the alveolar epithelium and its basement membrane; and a surfactant lining. The alveolar epithelium consists of two types of cells: Type 1 cells, or squamous pneumocytes, are large, mature cells that do not divide, cover most of the alveolar surface, and are vulnerable to injury, and type 2 cells, or granular pneumocytes, are small, cuboidal cells packed with granules that store and synthesize surfactant. Type 2 cells differentiate into type 1 cells during growth and repair after injury.

The alveoli are inherently unstable. Because of the surface tension of the liquid lining the alveoli, relatively large forces develop that tend to collapse alveoli. The surfactant secreted by the type 2 cells profoundly lowers the surface tension of the alveolar lining fluid. This increases the compliance of the lung and reduces the work of expanding it with each breath. It also makes the alveoli more stable and less likely to collapse. Because the surface tension forces are greater within bubbles with a larger radius of curvature, there is a tendency for smaller bubbles to empty into larger ones (Fig. 7-4). This results in a reduction of alveolar surface area and a decreased ability for gas exchange. Surfactant reduces the surface tension more in smaller bubbles and prevents the collapse of smaller alveoli. Surfactant also helps keep the alveoli dry. Surface tension forces tend to suck fluid into the alveolar spaces from the capillaries. By reducing these forces, surfactant prevents the transudation of fluid.

Infants born prematurely may suffer from a condition known as *respiratory distress syndrome*. This syndrome is thought to result from a lack of surfactant and is characterized by stiff lungs (low compliance), areas of collapsed alveoli (atelectasis), and alveoli filled with transudate. The result is a decreased capability for gas exchange (see Chapters 28 and 29).

Connective Tissues. In addition to the airways and blood vessels, the lungs consist of a network of collagen and elastin fibers within a proteoglycan matrix. These fibers form a supportive network connecting adjacent airways and alveoli. They are partly responsible for the elastic recoil of the lung, help prevent the collapse of the alveoli and airways, and promote homogeneous emptying of the lungs. The elastin

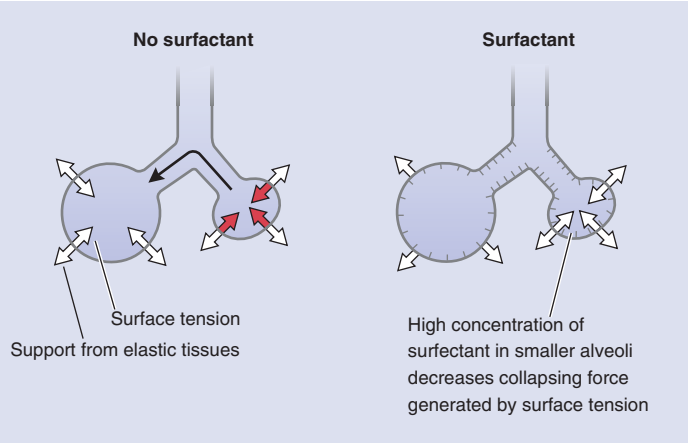


Figure 7-4 The presence of surfactant in the alveoli decreases surface tension and prevents alveoli with a high radius of curvature (small size) from emptying into larger alveoli. (Arrow size represents the magnitude of force.)

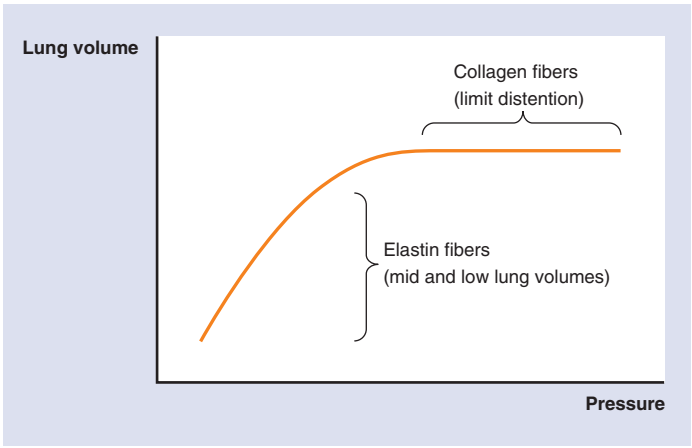


Figure 7-5 Pressure-volume relationship of the lungs. The influence of connective tissues at different lung volumes is demonstrated.

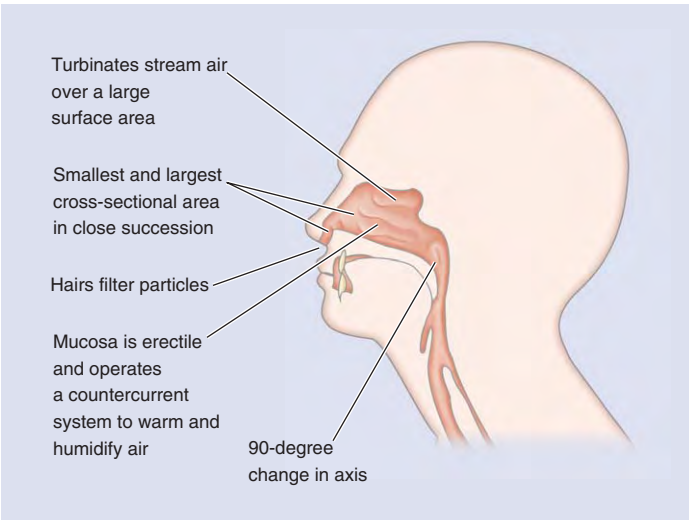


Figure 7-6 Air filtration and conditioning factors of the upper airway.

fibers are thought to be largely responsible for the distensibility of the lungs at volumes in the low to middle ranges. This distensibility is reflected in the slope of the static pressure-volume curve (a reflection of the compliance of the lungs). The collagen fibers are thought to be more involved in limiting distention of the lungs, which is reflected by the plateau in the static pressure-volume curve (Fig. 7-5). Proteoglycans act to stabilize the collagen-elastin network within the connective tissue matrix and contribute to lung elasticity and alveolar stability at low to medium lung volumes.[3] Alterations in proteoglycan content have been shown to alter the distensibility of the lung parenchyma in animal models. The collapse of alveoli or airways in one area tends to pull on adjacent alveoli and airways. The adjacent structures resist this pull, which in turn tends to resist the tendency for the alveoli or airways to collapse. This relationship is known as *mechanical interdependence*.

PULMONARY CIRCULATION

The pulmonary circulation begins at the main pulmonary artery, which receives the mixed venous blood pumped by the right ventricle. The pulmonary artery divides in a manner corresponding to the division of the tracheobronchial tree. Pulmonary arteries accompany the bronchi as far as the terminal bronchioles. Beyond that, they break up to supply the capillary bed, which lies in the walls of the alveoli, where gas exchange occurs. The oxygenated blood is collected by the small pulmonary veins that run between the lobules and eventually unite to form four large veins that drain into the left atrium. The blood supply to the lungs comes from the bronchial circulation, which is formed by systemic arteries and veins and is separate from the pulmonary circulation. The pulmonary circulation is a low-pressure system, and the arteries have thin walls containing little smooth muscle. This lessens the work of the right side of the heart as much as is feasible for efficient gas exchange to occur in the lung. If the pulmonary arteries are subjected to chronic hypoxia, the muscle in the wall hypertrophies and narrows the lumen. This increases the resistance to blood flow through the pulmonary system and results in increased pulmonary artery pressures and an increased strain on the right side of the heart (see Part 9).

UPPER AIRWAY

The upper airway consists of the passages for airflow between the larynx and the airway opening. Ordinarily it is composed of the nasal passages (from the nostrils to the posterior termination of the nasal septum), the nasopharynx (from the end of the nasal septum to the lower border of the soft palate), and the pharynx (from the palate to the larynx). When a person breathes through the mouth, it also includes the mouth. The nasal airway consists of two passages, each with turbinates projecting from the lateral wall into the lumen. In adults, the surface area of the functional (turbinated) portion of the nasal mucosa is around 120 cm^2, approximately double that of the trachea. The blood vessels in the nasal mucosa, especially that covering the turbinates, are arranged to provide an erectile capacity comparable to that of the male genitalia.

The following are the main anatomic features that allow the nasal passages to perform their specialized function:

1. The axis of the nasal airway is oriented at 90 degrees to that of the trachea.
2. The cross-sectional area increases from the smallest area in the respiratory tract (anterior nares) to the relatively large turbinated airway and then decreases again in the nasopharynx.
3. The anatomic arrangement of the turbinates concentrates the airflow into a relatively small stream.
4. The surface area of the turbinated airway is large.
5. The extensive vascular network gives the body the ability to vary the width of the nasal airway.

All of these features allow the nasal airway to function as an efficient air filtering and conditioning unit (Fig. 7-6).

Air Conditioning. Blood flow in the nasal mucosa is arranged in a countercurrent fashion such that air entering the nose is progressively brought to body temperature and humidity. This usually means that the air is warmed to 37° C and fully saturated with water. The transfer of heat (by turbulent convection) and water (by evaporation) to the air cools the mucosa. During expiration, some of the heat and water vapor return to the mucosa from the alveolar gas. If the nasal

airway is bypassed, the mouth and pharynx can perform these air-conditioning functions almost as well as the nose. The trachea and bronchi cannot. During strenuous exercise, the nasal airway is usually bypassed, and increased minute ventilation may exceed the conditioning capacity of the mouth and pharynx. This causes drying and cooling of the lower airways and may provoke exercise-induced asthma in susceptible individuals.

Filtration and Cleansing. Hairs in the anterior nares block the passage of very large particles into the nose. Once inside the nose, the air is forced to pass in narrow streams close to the mucosa. The turbulent flow through the nasal airway and the changes of air stream direction force many particles to become trapped in the mucus lining the nasal mucosa. Particles with diameters greater than 10 μ are almost completely removed from the inspired air in the nose. The nasal mucosa is also capable of removing some toxic gases, especially those that are water soluble; for example, sulfur dioxide in concentrations up to 25 ppm can be removed by the nasal mucosa.

Mechanics of the Upper Airway. The nose accounts for approximately one half the total respiratory resistance to airflow, but the absolute value shows marked variation among subjects. Nasal resistance varies with changes in nasal vascular congestion, posture, exercise, ambient air conditions, pharmacologic agents, and disease.

Almost all of the nasal resistance is contributed by the first 2 to 3 cm of the nasal passage (i.e., the anterior constriction [the nares and the tip of the inferior turbinate]). The turbinated passage contributes little to resistance under normal circumstances. However, if the nasal mucosa is engorged with blood, the turbinated passages can make a significant contribution to the total resistance.

The nasal vasculature is under autonomic control, reflexively responding to changing ambient air conditions. Small fluctuations occur in response to the temperature of inspired air; there is a significant increase in nasal resistance resulting from vascular engorgement when the temperature of inspired air falls below 7° C. Changes in body posture alter resistance through hydrostatic effects on the vasculature. Changing from a standing or sitting to a recumbent position increases nasal resistance. Nasal resistance is often higher through one nasal passage than the other because of differences in the degree of vascular engorgement. The high-resistance changes from one side of the nose to the other occurs in 3- to 4-hour cycles. This cycle may allow one nasal passage to recover from injury suffered in filtering and conditioning inspired air.

The most compliant region of the upper airway is the pharynx. The negative pressures generated during inspiration tend to collapse the pharynx. This region is usually protected from collapsing by the tone of the upper airway muscles, which also contract during inspiration. During rapid-eye-movement sleep, this tone can be markedly decreased, making the upper airway vulnerable to collapse during inspiration. If other factors combine to make the upper airway more prone to collapse, the syndrome of obstructive sleep apnea may be seen (see Chapter 65). Some infants are born with relatively small upper airways. This may be part of a recognized syndrome or may be a familial trait. A small upper airway has a higher resistance and may necessitate the generation of greater negative pressures to produce sufficient inspiratory flow. This results in a greater tendency for the upper airway to collapse. The same syndrome is seen in adults, especially those who are grossly obese. These people probably have deposits of fat around the upper airway that effectively "load" the upper airway and make it more likely to collapse during inspiration. Heavy alcohol use can also precipitate upper airway obstruction during inspiration, probably by decreasing the tone of the upper airway muscles that are responsible for stabilizing the upper airway.

ELASTIC PROPERTIES OF THE RESPIRATORY SYSTEM

The respiratory system is composed of a collection of elastic structures. When a force is applied to an elastic structure, the structure resists deformation by producing an opposing force to return the structure to its relaxed state. This opposing force is known as *elastic recoil*. In the respiratory system the pressure generated by the elastic recoil is known as the *elastic recoil pressure* (P_{el}). The force required to stretch an elastic structure depends on how far it is stretched, not on how rapidly it is being stretched. Similarly, the pressure required to overcome the elastic recoil of the lung depends on the lung volume above or below the elastic equilibrium volume (EEV) (i.e., the volume at which the outward recoil of the chest wall balances the inward recoil of the lungs [see later section]). The P_{el} divided by the lung volume gives a measure of the elastic properties of the respiratory system and is called *elastance*, as follows:

$$E = Pel/V \qquad \text{Eq 7.1}$$

When lung volume is plotted on the ordinate and P_{el} is plotted on the abscissa, the slope of the static pressure-volume curve is equivalent to the reciprocal of elastance, called *compliance*. Elastance and compliance are discussed more fully in Chapters 12 and 13.

HYSTERESIS

The static pressure-volume curves of the respiratory system, lungs, and chest wall are not the same during inspiration and expiration. This phenomenon is called *hysteresis* (Fig. 7-7). Hysteresis is the failure of a system to follow identical paths of response on application and withdrawal of a forcing agent. Hysteresis in the respiratory system depends on viscoelasticity, such as stress adaptation (i.e., a rate-dependent phenomenon) and on plasticity (i.e., a rate-independent phenomenon). In the lungs, hysteresis is due mainly to surface properties and alveolar recruitment-derecruitment, whereas in the chest wall, it seems mainly related to muscles and ligaments because both skeletal muscles and elastic fibers exhibit hysteresis. Hysteresis is negligible for volume changes such as those occurring during quiet breathing. This is functionally desirable because the area of the hysteresis loop represents energy lost from the system.

Muscles of the Respiratory System

BASIC CONCEPTS OF SKELETAL MUSCLE MECHANICS

Muscle Fiber Type. The three basic types of muscle fibers are distinguished by their histochemical and morphologic

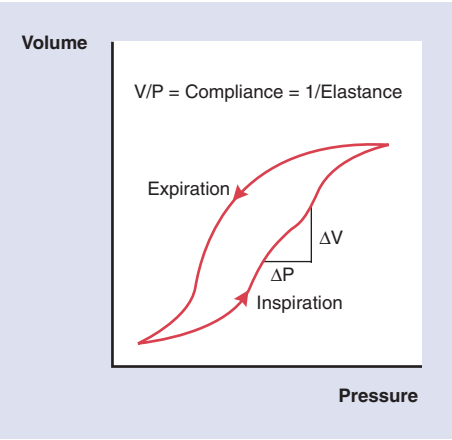


Figure 7-7 Hysteresis in the pressure-volume curve of the lung. The area contained within the curve represents energy lost in the system. P, pressure; ΔP, change in pressure; V, volume; ΔV, change in volume.

Table 7-1
Properties of Muscle Fiber Types

Properties	FOG	FG	SO
Synonym	Fast-twitch red	Fast-twitch white	Slow-twitch red
Presence of myoglobin	Positive	Negative	Positive
Isometric-twitch contraction time	Short	Short	Long
Myosin adenosine triphosphatase activity	High	High	Low
Glycolytic enzyme system	Reasonable	Good	Poor
Mitochondrial oxidative system	Good	Poor	Good
Resistance to fatigue	Good	Poor	Very good
Movements	Sustained, phasic	Brief, rapid, powerful	Sustained, tonic

FG, fast-twitch, glycolytic; FOG, fast-twitch, oxidative, glycolytic; SO, slow-twitch, oxidative.

properties and their time course of contraction: fast-twitch, oxidative, glycolytic (FOG); fast-twitch, glycolytic (FG); and slow-twitch, oxidative (SO). The concentration of myoglobin in the FOG and SO fibers makes them red, so these fibers are also known as *fast-twitch red* and *slow-twitch red fibers*, respectively (Table 7-1). The FG fibers have minimal myoglobin and are known as *fast-twitch white fibers*.

Within a species, white fibers are frequently larger in diameter than fast red fibers, with slow red fibers intermediate in size. FG fibers are used for short-term, fast, powerful activity in which endurance and resistance to fatigue are not required. FOG fibers are used for sustained phasic activity in which resistance to fatigue is desirable. The SO fibers are sluggish but are economical contractile units most suitable for sustained tonic activity (such as the maintenance of posture, in which resistance to fatigue is of prime importance).

Most mammalian muscles contain a mixture of the three types of muscle fibers. Each motor unit of a mixed muscle is composed of a single fiber type. The contractile properties of a mixed muscle are determined by the predominant fiber type. Although three types of muscle fiber are recognized, classification of muscle based on their mechanical properties alone yields two types of muscle: fast-twitch, including both FOG and FG fibers; and slow-twitch muscle, composed of predominantly SO fibers.

The following factors are important in determining the twitch characteristics of muscles:

1. The speed of sarcomere shortening, which is proportional to the specific activity of myosin adenosine triphosphatase (ATPase) activity (which varies with myosin isotype).
2. The neural supply to the muscle: If a motor nerve that normally innervates a slow muscle is transplanted into a fast muscle and time is allowed for nerve regeneration, the muscle changes its properties from those of a fast muscle to those of a slow muscle, and vice versa.
3. The stage of muscle development: Differentiation into fast and slow fibers takes place somewhat late in development. In species in which the young are born mature (e.g., guinea pig), the differentiation occurs before birth, whereas in species in which the young are born immature (e.g., mouse, rat, human), the differentiation occurs after birth. The differentiation seems to involve changes in the biochemical and morphologic properties of the sarcoplasmic reticulum and transverse tubular system, which effect changes in the excitation-contraction coupling.
4. Training: Any training, particularly endurance training, can alter fiber composition and characteristics.

Thus, the composition of a muscle is a dynamic property that can be altered to suit the requirements of the muscle at the time.

Muscle Mechanics. Skeletal muscle has been most successfully modeled as the following interacting components (Fig. 7-8):

1. A contractile component responsible for force generation and muscle shortening
2. A lightly damped series-elastic component representing an internal load that the muscle must overcome
3. A parallel-elastic component responsible for the passive tension produced as the muscle is stretched

During contraction, the actin and myosin filaments slide over one another, shortening the sarcomere. The force generated is a function of the degree of sarcomere shortening. As the filaments slide over one other, cross-bridges form between the fibers. These cross-bridges are independent, force-generating elements, and the force produced is a function of the number of active cross-bridges.

Length-Tension Relationship. Measurement of the force developed with activation over a range of lengths provides information about the ability of the muscle to stiffen and support loads. The "resting tension" curve is the tension produced when the muscle is passively stretched. The shape of this curve is typical of noncontractile biological tissues and results primarily from the presence of elastin and collagen. With activation of the muscle at a given length, the tension rises to a level shown by the "total tension" curve. The difference in tension between the total and resting tension

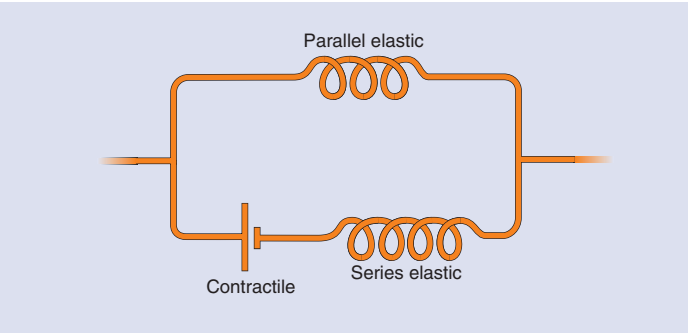


Figure 7-8 Circuit diagram representing the mechanical properties of skeletal muscle.

curves represents the activity of the contractile element or force generator of the muscle and is known as the *active tension.* The length at which the active tension is maximal is defined as the optimal length of the muscle. The resting length of the muscle is defined as the maximal length the muscle can be stretched before passive tension develops. This length generally corresponds to the muscle's resting length in the body. When the resting muscle is stretched beyond optimal length, it exerts a passive tension that increases exponentially as a function of increasing muscle length. When the muscle is maximally stimulated at varying lengths, an isometric length-tension curve can be drawn. The *active tension* of the muscle is defined as the difference between the total tension measured and the passive tension at that length. There is an optimal muscle length, usually between 100% and 120% of the length at which isometric tension is maximal during tetanic stimulation. Comparing the tension-generating capacity of one muscle with another muscle of a different size requires expression of tension in relationship to the amount of contractile material active in parallel with the muscle. This is usually done by expressing tension in terms of force per unit of a cross-sectional area of the muscle. The cross-sectional area is only roughly related to the amount of contractile material acting in parallel because it ignores variations in the density with which myofibrils are packed within individual fibers and it ignores differences in extracellular space that occupies 8% to 25% of the cross-sectional area in different muscles. When expressed this way, fast and slow muscles show no major differences in the intrinsic strength of their contractile material.

Force-Velocity Relationship. A light weight can be moved very rapidly by a muscle, whereas a heavy weight must be moved slowly. This fundamental property of muscle is known as the *force-velocity relationship.* There is an inverse curvilinear relationship between the force produced by a muscle and the velocity with which the muscle can shorten while producing that force. This can be expressed by Hill's equation, which describes a hyperbolic relationship between force and velocity, as follows:

Eq 7.2
$$(P + a)(V + b) = (P_0 + a)b$$

where P is the instantaneous force of contraction, V is the velocity of shortening, P_0 is the force of contraction at zero velocity (i.e., the isometric force of contraction), and a and b are constants. The position of the force-velocity curve depends on the initial length of the muscle.

The shortening velocity of a muscle (appropriately normalized for fiber cross-sectional area and so on) reflects the average cross-bridge cycling rates, which in turn are functions of the load and the isoform of myosin expressed in that particular muscle cell.[5,6]

BASIC CONCEPTS OF SMOOTH MUSCLE MECHANICS

Although smooth muscle does not have the same anatomic structure as skeletal muscle, biochemical and biophysical studies in the 1970s indicated that smooth muscles contract in a manner similar to skeletal muscle. The "sliding filament" paradigm in which the active cycling of cross-bridges is responsible for the amount of force developed (number of cross-bridges) and the force-velocity relationship (cycling rate) of muscle, however, cannot adequately explain the "force maintenance" properties of smooth muscle. This leads to the description of "latchbridges." *Latch* refers to a state in which force is maintained, despite a reduced cross-bridge cycling rate, by calcium-dependent cross-bridge phosphorylation.[5] Although the term *latchbridge* tends to imply that the actin and myosin filaments are locked together, this is not the case.

In a review of the regulation of smooth muscle contraction, Murphy[5] suggested that the unique properties of smooth muscle derive from a covalent regulatory mechanism whereby phosphorylation of cross-bridges is obligatory for attachment and cycling and that the fundamental myosin "motor" whose behavior is described by the sliding filament/cross-bridge hypothesis is the same in smooth and striated muscle. Murphy presented evidence suggesting that covalent regulation in smooth muscle allows four rather than two cross-bridge states: free, attached, phosphorylated, and dephosphorylated. This hypothesis seems to explain the special properties of smooth muscle.

Length-Tension Relationship. Although skeletal muscle usually has a resting length approximating the optimal length, it has not been established whether this is also true for airway smooth muscle. Some investigators have found that airway smooth muscle is close to optimal length at the end of tidal expiration. The contractile elements of smooth muscle can develop approximately the same force as those of skeletal muscle. Skeletal muscle can shorten to approximately 65% of optimal length, whereas tracheal smooth muscle can shorten to about 10% of optimal length. The reason for this difference is not known. The ratio of myosin to actin is less in smooth muscle than in striated muscle, and well-defined sarcomeres are not present. It has been speculated that the lack of limiting Z bands allows the myosin filaments to "crawl" farther along a set of relatively long actin filaments.

Force-Velocity Relationship. Measurements of force at various velocities of contraction provide information regarding the ability of the muscle to not only support loads but also to shorten and thus do work. They also provide an index of power generation. Smooth muscle force-velocity curves are also hyperbolic and can be fitted by Hill's equation, as previously described. Force-velocity studies show that the force of contraction at zero velocity for smooth muscle is

similar to the force of contraction for striated muscle but that maximum velocity values are much smaller. The maximum velocity is a convenient index of the contractility of smooth muscle as long as the shortening is limited to less than 25% of optimal length.

When a muscle is forcibly lengthened, the load may exceed the force of contraction at zero velocity. This may be the case for airway smooth muscle during inspiration. Thus a muscle that is being actively elongated may be stronger than the same muscle that is shortening. An elongating muscle also consumes less energy than the shortening muscle at equivalent velocities.

Influence of Breathing Movements on Smooth Muscle Mechanics. As diameters of airways change with inspiration and expiration, it is important to know how the smooth muscle behaves when its length is externally forced. When the muscle length is changed with amplitudes and frequencies similar to those occurring during respiration, considerable force-length hysteresis occurs. The tension in the muscle depends not only on the pattern of the imposed length cycles but also on their timing. During repeated muscle stretching, increased time between cycles equates to greater initial tension in the muscle.

INDIVIDUAL RESPIRATORY MUSCLES

The mechanical task of the respiratory muscles differs from that of a typical limb muscle because the respiratory muscle must overcome primarily elastic and resistive impedances, whereas limb muscles contend principally with inertial impedances. Usually, respiratory muscles must repeatedly perform relatively sustained tension-generating and shortening actions, whereas limb muscles are usually required to generate short bursts of tension and shortening in executing the usual rhythmic motions of the limbs. This difference can be a determining factor for the contractile and endurance properties of the respiratory muscles. The changes in lung volume that occur during breathing indicate that different muscles are asked to begin contracting from different lengths.

Diaphragm. The diaphragm is a mixed muscle made up of approximately 21% FOG, 55% SO, and 24% FG fibers. The number of fatigue-resistant SO fibers increases in the diaphragm during infancy and has been reported to be approximately 10% in premature infants, 25% in full-term infants, and reaching the adult level (around 55%) by 2 years of age. In all species studied, including humans, the diaphragm is functionally intermediate in its rate of tension generated between fast and slow muscles. The diaphragm fibers are thought to be at optimal length at supine functional residual capacity (FRC), although maximal tension seems to occur at somewhat longer lengths.

Intercostal Muscles. The composition of the intercostal muscles is similar to that of the diaphragm. Also, the percentage of fatigue-resistant fibers is substantially reduced in premature infants and, to a lesser extent, full-term neonates, reaching adult levels by 2 years of age.

Scalenus Muscles. The scalenus muscles insert into the first rib, and contraction elevates the first rib during inspiration. These muscles have generally been regarded as accessory muscles of respiration, but they appear to contract, as indicated by the presence of action potentials, during resting breathing and should be regarded as primary respiratory muscles. There are no published data about their fiber type distribution or contractile properties.

Sternocleidomastoid Muscle. The sternocleidomastoid muscle is clearly an accessory muscle of respiration because it usually does not contract unless breaths are considerably deeper than resting tidal breaths. It appears to be made up of 65% fast-twitch and 35% slow-twitch fibers.

Abdominal Muscles. The respiratory actions of the abdominal muscles are twofold. They are primary expiratory muscles because of their direct action on the rib cage and their ability to compress the abdominal contents, forcing the diaphragm upward. They also appear to facilitate the inspiratory action of the diaphragm by contracting toward the end of expiration, pushing the diaphragm upward and optimizing its fiber length for generating tension during the subsequent inspiration. This action of the abdominal muscles occurs during the postural change from supine to upright, during voluntary hyperventilation, and during exercise.

Dynamics of Breathing

Ventilation of the lungs involves motion of the respiratory system, which is produced by the forces required to overcome the flow-resistive, inertial, and elastic properties of the lungs and chest wall. Under normal circumstances, these forces are produced by the respiratory muscles.

FLOW RESISTANCE

The force required to move a block of wood over a surface is determined by the friction between the block of wood and the surface and by the speed with which the block is moving. It is not, however, determined by the position of the block. Similarly, the pressure required to produce flow between the atmosphere and alveoli and thus to overcome the frictional resistance *(fr)* of the airways is proportional to flow $\dot{V}$ (i.e., the rate at which volume is changing), as follows:

$$P_{mouth} - P_{alv} = P_{fr} = \alpha\dot{V} \qquad \text{Eq 7.3}$$

The pressure required to produce a unit of flow is known as the *flow resistance (R)*, as shown by the following:

$$R = P_{fr}/\dot{V} \qquad \text{Eq 7.4}$$

If the respiratory system is modeled as a single compartment with a single constant elastance *(E)* and a single constant resistance *(R)*, then the equation of motion describing the balance of forces acting on the system is as follows:

$$P = EV + R\dot{V} + I\dot{V} \qquad \text{Eq 7.5}$$

The inertance *(I)* is usually negligible and therefore ignored. During tidal respiration, approximately 90% of the pressure produced is required to overcome the elastic forces,

and approximately 10% is required to overcome the flow-resistant forces.

Traditionally, it was thought that the majority of the force developed during breathing was required to move gas through the airways and that little energy was dissipated by the tissues of the respiratory system. In recent years, however, it has become increasingly apparent that the viscoelastic properties of the respiratory system contribute significantly to the behavior of that system. The energy expended moving the tissues has been called *tissue viscance* or *resistance*, although it is a non-newtonian resistance. The anatomic structures responsible for the viscoelastic behavior of lung tissue are not known. Candidates likely to contribute to viscoelasticity include the air-liquid interface, collagen and elastin fibers, actin/myosin cross-bridges, contractile (Kapanci) cells within the interstitium, and smooth muscle in the alveolar ducts. Experimental evidence is consistent with the involvement of "contractile" elements because the stress adaptation seen after an airflow interruption (a manifestation of viscoelastic behavior) increases after "constrictor" stimuli[4,7-10] and decreases after "relaxant" stimuli. Alternatively, the viscoelasticity demonstrated in many animal studies may be a reflection of the immense complexity of the lungs, with no single structure responsible.[11]

Studies in animals have demonstrated that when measured during inspiration, tissue resistance increases and airway resistance falls with increasing lung volume. Tissue resistance contributes approximately 65% of respiratory system resistance at FRC in mechanically ventilated animals and increases to as much as 95% at higher lung volumes.[12] The contribution of tissue resistance to respiratory system resistance in humans, under the same conditions, is not known, but the overall behavior of the respiratory system appears to be similar.

DRIVING PRESSURES FOR RESPIRATION

Inspiration occurs when the respiratory muscles cause the alveolar pressure to be less than atmospheric pressure. Air then moves along this pressure gradient, and the lungs inflate, thus storing potential energy in the elastic structures. At the end of inspiration, the respiratory muscles relax, and the elastic recoil of the respiratory system causes the alveolar pressure to be positive relative to atmospheric pressure, and expiration occurs. Under resting conditions, expiration is usually passive. At times of increased ventilatory requirements, such as during exercise, contraction of the abdominal and internal intercostal muscles can aid expiration.

TIME CONSTANT OF EMPTYING

When the respiratory system is allowed to empty passively the time taken for the initial volume to be reduced by 63% is known as the *time constant* (τ) of the respiratory system (Fig. 7-9). If the respiratory system is modeled as a single compartment with a single, constant elastance and a single, constant resistance, then the following occurs:

Eq 7.6

$$\tau = R/E$$

Under these conditions, the volume-time profile can be represented by a single exponential decay.

In healthy adults the time constant of the passive respiratory system is approximately 0.5 second, which allows the lungs to empty to the EEV at the end of each expiration; the FRC and EEV are equal. This means that the respiratory system is relaxed at the end of expiration and that inspiration can begin as soon as inspiratory muscle activity commences. In obstructive airway diseases, such as asthma and chronic bronchitis, resistance is increased, and the expiratory time constant is longer. Therefore, a longer time is required for the lungs to empty and return the respiratory system to EEV. Patients with these diseases frequently have carbon dioxide retention and an increased respiratory drive. This results in an increased respiratory rate with a decrease in the time available for expiration. Thus, the respiratory system frequently does not have time to return to EEV before the next inspiration starts. This means that FRC occurs at a volume higher than EEV and that the respiratory system is not relaxed at the end of expiration but that there is a positive recoil pressure. This pressure has been called *intrinsic positive end-expiratory pressure*, or PEEPi. Before inspiratory flow can begin, the inspiratory muscle must produce enough force to overcome the PEEPi; thus this force is "lost" to producing inspiratory flow and represents a load that must be overcome by the inspiratory muscle. In patients with severe airway obstruction this pressure can be as high as 15 to 20 cm H_2O. The expiratory time constant is shorter in children, with values approximating 0.3 second reported in infants with normal lungs.[10] Infants with hyaline membrane disease have stiffer-than-normal lungs, with expiratory time constants reported to be as low as 0.1 second.[13]

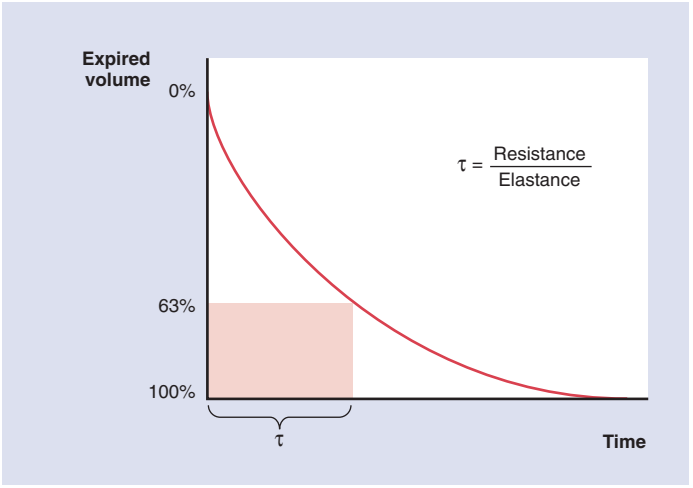


Figure 7-9 Time constant of lung emptying.

DYNAMIC CHANGE IN AIRWAY CALIBER DURING RESPIRATION

Airway caliber is partially dependent on the transmural pressure (Fig. 7-10). The external airway wall is subjected to interstitial pressure, which is approximately equal to pleural pressure for all intrathoracic airways. The external walls of extrathoracic airways are subjected to atmospheric pressure. The pressure inside the airway depends on the generation of the airway. During inspiration, pleural pressure is negative relative to atmospheric pressure. Alveolar pressure is approximately equal to pleural pressure, and pressure at the mouth is atmospheric. Thus, there is a pressure gradient from the

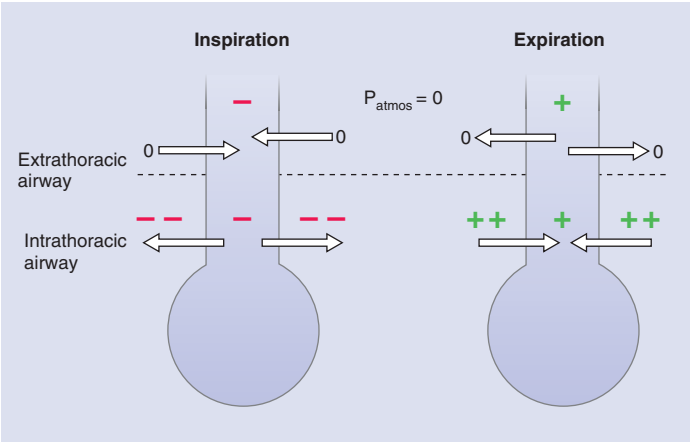


Figure 7-10 Transmural airway pressures during inspiration and expiration, with net forces illustrating one factor leading to extrathoracic narrowing on inspiration and intrathoracic narrowing on expiration. *Arrows* indicate net force on airway; plus and minus signs indicate pressure relative to atmospheric pressure (0).

mouth to the alveoli. Transmural pressure for the extrathoracic airways is positive, and there is a tendency for these airways to narrow during inspiration. The transmural pressure is negative for the intrathoracic airways, causing a tendency for these airways to dilate during inspiration. The degree of change in airway caliber depends on the magnitude of the transmural pressure and the airway wall compliance. At the end of inspiration, the inspiratory muscles relax, and the elastic recoil of the respiratory system produces positive pleural and alveolar pressures (relative to atmospheric pressure). Thus, there is a tendency for intrathoracic airways to narrow and extrathoracic airways to dilate during expiration.

Gas Exchange

The basic respiratory function of the respiratory system is to supply oxygen to the body and to remove excess carbon dioxide. The following are the basic steps involved in this process:

1. Ventilation, the exchange of gas between the atmosphere and the alveoli
2. Diffusion across the alveolar-capillary membranes
3. Transport of gases in the blood
4. Diffusion from the capillaries of the systemic circulation to the cells of the body
5. Use of oxygen and production of carbon dioxide within the cells (i.e., internal respiration)

VENTILATION

Ventilation is the process whereby fresh, oxygen-rich gas is delivered to the alveoli and carbon dioxide is removed. As discussed earlier, the volume of gas reaching the alveoli per unit time—not the volume of gas entering and leaving the respiratory system—is the important parameter for gas exchange.

GAS DIFFUSION

Gas diffusion is a passive process: Gases diffuse from a site of high partial pressure to a site of low partial pressure. The flux is proportional to the area available for diffusion and to the difference in partial pressure per unit length of the diffusion pathway. Conditions that thicken the alveolar wall, the main blood-gas barrier, can interfere with diffusion.

GAS TRANSPORT

Gas is transported in the blood via two primary methods: dissolved in plasma or combined with hemoglobin. Approximately 98% of oxygen transported in the blood is bound to hemoglobin. When oxygen combines loosely with the heme portion of hemoglobin in the lung, where the oxygen partial pressure is high, it forms oxyhemoglobin. When the oxyhemoglobin reaches the tissues, where oxygen partial pressure is low, the oxygen is released and diffuses to the cells. The binding of oxygen to hemoglobin is a nonlinear process, as demonstrated by the sigmoid oxygen-hemoglobin dissociation curve (see Chapter 14 for a more detailed discussion). When hemoglobin is 100% saturated with oxygen, large changes in the partial pressure of oxygen (Pa_{O_2}) are required before the arterial oxygen saturation (Sa_{O_2}) falls much. However, below a Sa_{O_2} of about 90%, the relationship between the fall in Pa_{O_2} and that in Sa_{O_2} becomes steeper. Increases in both body temperature and arterial pH shift the oxygen-hemoglobin dissociation curve to the right, facilitating the peripheral unloading of oxygen. Normal lungs have sufficient reserve capacity to overcome the increased difficulty in loading oxygen under these circumstances. However, in the presence of a marked $\dot{V}/\dot{Q}$ imbalance, rightward shifts in the oxygen-hemoglobin dissociation curve may become more significant.

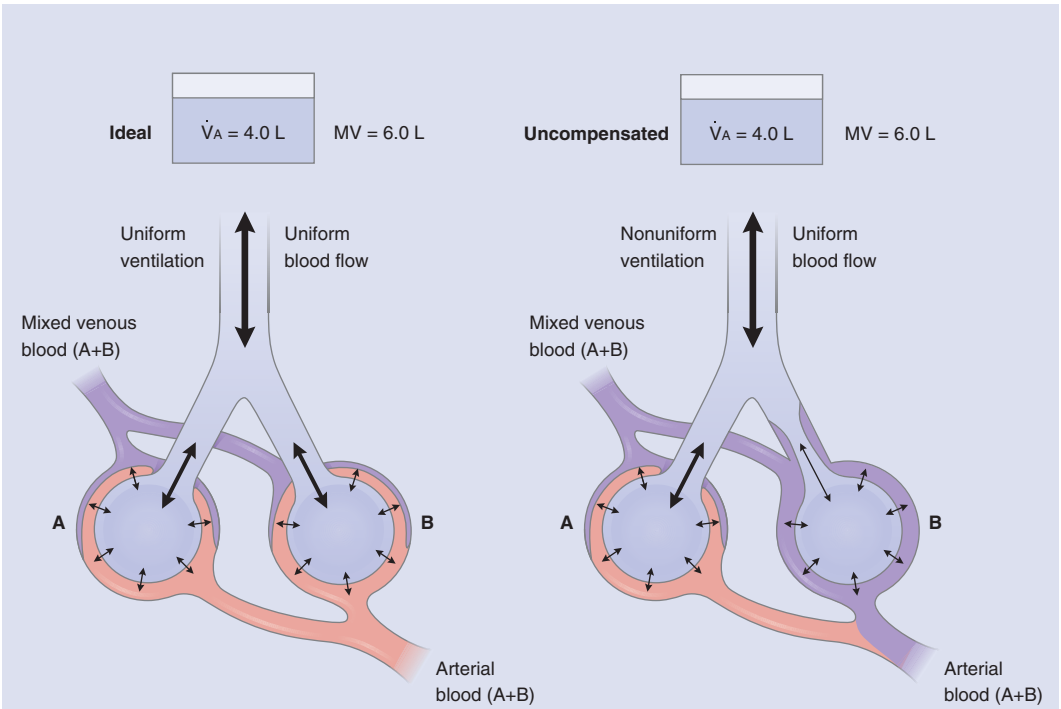
Carbon dioxide is transported more readily in the blood than oxygen because carbon dioxide, being a nonpolar molecule, is highly lipid soluble. Carbon dioxide is transported in the blood in the following ways, all of which begin with the gas being dissolved in the plasma after it has diffused into the systemic capillaries from the tissues:

1. As bicarbonate ions (60% to 70%)
2. Combined with hemoglobin to form carbaminohemoglobin (15% to 30%)
3. Dissolved in plasma and red blood cells (7% to 10%)

Carbon dioxide does not bind to hemoglobin at the same site as oxygen; instead it binds directly with some of the amino groups that form the hemoglobin molecule. The carbon dioxide-hemoglobin dissociation curve is less curvilinear.

VENTILATION/PERFUSION IMBALANCE

Inhomogeneity of the ventilation/perfusion ($\dot{V}/\dot{Q}$) balance in the lungs most commonly occurs in conditions that produce ventilatory inhomogeneity, such as obstructive airway diseases (e.g., asthma). $\dot{V}/\dot{Q}$ mismatch results in a decrease in the transfer of oxygen to arterial blood and a decrease in carbon dioxide elimination. However, the result is a lowering of Pa_{O_2}, with a lesser increase in Pa_{CO_2}. Several factors contribute to this phenomenon. The gas tension in an individual alveolar-capillary unit depends on the ratio of ventilation to perfusion in that unit. Well-ventilated units tend to raise the oxygen tension toward that of the inspired gas (about 150 mm Hg when breathing air), whereas well-perfused units tend to lower oxygen tension toward that of the mixed venous blood (normally about 40 mm Hg). For the same reasons, the



	A	B	A+B
Alveolar ventilation (L/min)	2.0	2.0	4.0
Pulmonary blood flow (L/min)	2.5	2.5	5.0
Ventilation/blood flow ratio	0.8	0.8	0.8
Mixed venous O_2 saturation (%)	75.0	75.0	75.0
Arterial O_2 saturation (%)	97.4	97.4	97.4
Mixed venous O_2 tension (mm Hg)	40.0	40.0	40.0
Alveolar O_2 tension (mm Hg)	104.0	104.0	104.0
Arterial O_2 tension (mm Hg)	104.0	104.0	104.0

	A	B	A+B
Alveolar ventilation (L/min)	3.2	0.8	4.0
Pulmonary blood flow (L/min)	1.3	2.5	5.0
Ventilation/blood flow ratio	75.0	0.3	0.0
Mixed venous O_2 saturation (%)	98.2	75.0	75.0
Arterial O_2 saturation (%)	40.0	91.7	95.0
Mixed venous O_2 tension (mm Hg)	116.0	40.0	40.0
Alveolar O_2 tension (mm Hg)	116.0	66.0	106.0
Arterial O_2 tension (mm Hg)		66.0	84.0

Figure 7-11 *Left,* Ideal $\dot{V}/\dot{Q}$ matching. *Right,* Nonuniform ventilation with uniform blood flow leading to mismatch. MV, respiratory minute volume; $\dot{V}_A$, alveolar ventilation. (From Comroe JH Jr, et al: The Lung: Clinical Physiology and Pulmonary Function Tests, 2nd ed. St Louis, Mosby, 1962.)

P_{CO_2} is higher in overperfused units and lower in overventilated units. The extreme case of overventilation and underperfusion results in an increase in dead space, whereas the converse results in an intrapulmonary shunt (Fig. 7-11). Mixing of the blood from units with different $\dot{V}/\dot{Q}$ balances does not compensate for the different oxygen and carbon dioxide tensions because, by definition, relatively more blood comes from the underventilated, overperfused units. This results in a difference between the gas tensions in the mixed pulmonary venous blood (which becomes the arterial gas tension) and the mixed alveolar gas (in reality the average tension) and is expressed as an alveolar-arterial difference. The alveolar-arterial difference is greater for oxygen than for carbon dioxide.

A lowering of the P_{aO_2} or an increase of P_{aO_2} results in an increase in respiratory rate via chemoreceptor stimulation. This increase can lower the P_{aCO_2} but cannot raise the P_{aO_2} to the same extent. This is because of the different shapes of the blood gas content-tension curves. Because the oxygen-hemoglobin dissociation curve is almost flat at high blood oxygen contents, increasing ventilation to well-ventilated units cannot increase the blood oxygen content but does remove extra carbon dioxide from the blood passing through the well-ventilated units. This means that increasing ventilation, in the face of $\dot{V}/\dot{Q}$ inhomogeneity, reduces the P_{aCO_2} toward or below normal but does not increase the P_{aO_2} to normal values.

Control of Breathing

The primary function of the respiratory system is gas exchange. This requires a precise regulation of blood gas concentrations, which allows for the varying requirements imposed by the different levels of demand encountered with differing levels of activity. This control system can be thought of as having two parts: a "feed-forward" component, which is related to the ventilatory requirements, and a "feedback" component, which tells the system how well it is performing. The feed-forward system includes factors such as cardiac output, carbon dioxide production, oxygen consumption,

input from muscle afferents, and input from higher brain centers. The feedback system consists of the partial pressures of carbon dioxide and oxygen and the hydrogen ion concentration reaching the respiratory centers. The feed-forward system is important because it allows the respiratory centers to "anticipate" the increased ventilatory requirements (e.g., during exercise). Without this anticipation, the ability to cope with the increased ventilatory demands is substantially reduced. This concept is expanded more fully in an article by Cunningham and colleagues.[14]

Although much of the knowledge about the interaction of changes in blood gases through control of breathing has come from studies in which the influences of carbon dioxide and oxygen have been studied separately, in the real world, these variables almost always change together. Changes in blood gas tensions are sensed by chemoreceptors located in the carotid bodies and central respiratory centers. The carotid body receptors respond to a change in either blood carbon dioxide or oxygen levels by a change in output. The impulses that reach the central respiratory control centers are identical, whether they are produced by changes in oxygen or carbon dioxide tensions. The carotid body chemoreceptors respond to a fall in PaO_2 or an increase in $PaCO_2$ with an increase in output, stimulating an increased respiratory rate. Changes in $PaCO_2$ also result in changes in hydrogen ion concentration, which also influences chemoreceptor output. The central chemoreceptors are influenced by the pH and carbon dioxide tensions in the cerebrospinal fluid. The output from the central chemoreceptors is thought to act independently on the respiratory control centers.

The relationship between ventilation $(\dot{V})$ and alveolar carbon dioxide partial pressure ($PaCO_2$) can be described as:

Eq 7.7

$$\dot{V} = S(PaCO_2 - B)$$

where S is the slope of the line or sensitivity of the relationship and B is the intercept with the $PaCO_2$ axis (Fig. 7-12).

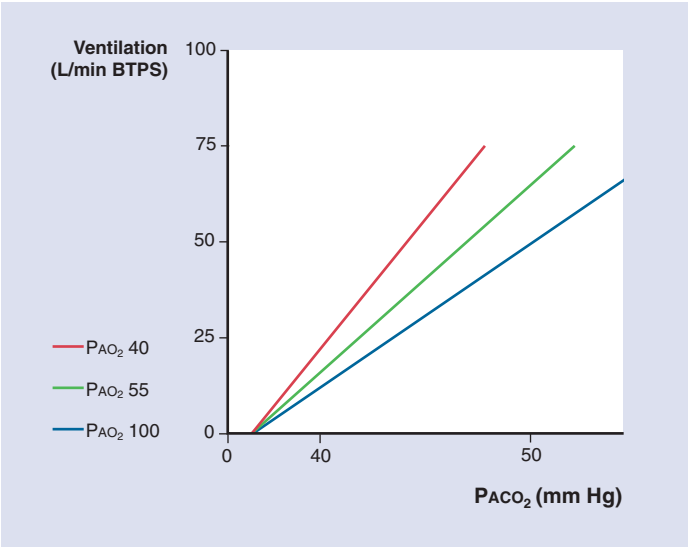


Figure 7-12 Carbon dioxide response curves at various fixed values for PaO_2. BTPS, Body temperature, pressure, saturated. (From Ganong WF: Review of Medical Physiology, 16th ed. Norwalk, Conn, Appleton & Lange, 1993.)

Hypoxia increases the sensitivity without altering the intercept. At very high levels of $PaCO_2$ and very low levels of PaO_2, respiratory depression occurs.

Studies investigating the control of breathing in infants have reported conflicting results, largely because of the methodologic difficulties inherent in studying infants. The major difference in the control of breathing between adults and infants is in the infants' ventilatory response to hypoxia. Despite the difficulties in using appropriate methodology, it is now generally agreed that the slope of the ventilatory response to carbon dioxide, when appropriately corrected for size in infants, is the same as that in the adult.

When exposed to low oxygen mixtures, newborns respond with a brief period of hyperpnea, followed by ventilatory depression. If the neonate has been allowed to cool (or is not in a neutral thermal environment), the period of hyperpnea is not seen. The ventilatory depression in response to hypoxia persists for about a week in full-term infants and for several weeks in infants born prematurely. The mechanism for this paradoxical response remains obscure. Recent evidence favors an immaturity of the central controlling centers rather than an immaturity of the peripheral chemoreceptors. Sleep state also seems to modify the ventilatory response to hypoxia, with the paradoxical response absent during rapid-eye-movement sleep. For an in-depth discussion of control of breathing in the fetus and newborn, see Bryan and coworkers.[15]

The state of the respiratory system is important in the translation of the signals from the respiratory center to alveolar ventilation and gas exchange. Diseases of the various components of the respiratory system are characteristically associated with increased mechanical loads. These loads may be elastic, resistive, inertive, or a combination thereof.

Diseases that increase the resistance against which the patient must breathe impose resistive loads. Increased intrinsic resistive loading occurs when the peribronchial forces that act to keep the airways patent are overwhelmed, resulting in airway narrowing; when gas flow becomes turbulent, increasing energy dissipation; or when high-viscosity or high-density gases are breathed. The most common example of increased intrinsic resistive loading seen in children is asthma, although this also occurs in other lung diseases such as chronic suppurative bronchitis and emphysema. The primary ventilatory response to these disorders is usually an alteration in V_T and respiratory timing indices, although many patients with severe disease appear to tolerate a chronic increase in $PaCO_2$ rather than respond appropriately, thereby conserving work of breathing. A breathing pattern with a prolonged expiratory phase is optimal for lung emptying and avoiding increases in lung volume (which would impose an increased elastic load), although a shortened inspiratory time would require higher inspiratory flows, adding to the increased resistive load.

Increased elastic loading occurs when the respiratory system is stiffer than usual; this occurs with hyaline membrane disease and interstitial lung diseases (increased lung stiffness); severe cases of obesity, ankylosing spondylitis, or kyphoscoliosis (increased chest wall stiffness); or conditions of decreased muscle performance (e.g., high quadriplegia, Guillain-Barré syndrome, botulism, muscular dystrophies). In these conditions, the ability to expand the thorax is decreased. The primary ventilatory response to these disor-

ders is usually tachypnea; hypoxia, and a relatively normal or even low $PaCO_2$ result. Rapid, shallow breathing, which minimizes the elastic load, may be seen.

STRUCTURE AND FUNCTION: APPLIED PHYSIOLOGY

Maintenance of Lung Volume

In healthy subjects at rest, FRC occurs at the volume at which the elastic recoil of the respiratory system is zero. This volume is known as the *EEV*, or the relaxation volume. The lungs and chest wall both contribute to the elastic properties of the respiratory system. The chest wall and the lungs are mechanically in series; thus the algebraic sum of the pressure exerted by the chest wall and lungs equals the pressure of the respiratory system. The EEV of the respiratory system occurs where the elastic recoil of the chest wall is equal and opposite to that of the lungs (Fig. 7-13). In isolation the relaxation volume of the lungs is zero; that is, there is always a tendency for the lungs to empty when there is gas in them. However, in practice, the lungs can never empty fully because small airways collapse before the lung volume becomes zero, thus trapping gas in the lungs. In healthy people the relaxation volume of the respiratory system is well above the volume at which the small airways close. Newborns have a more compliant (less stiff) chest wall. The chest wall thus has less elastic recoil to balance that of the lungs. This moves the static pressure-volume curve to the right, thus decreasing the relaxation volume of the respiratory system. Infants born prematurely also have stiff lungs. Thus at any given volume the P_{el} of the lungs is increased. This moves the static pressure-volume curve of the lungs, and hence that of the respiratory system, to the right, further reducing the EEV. This reduction may be marked enough so that the relaxation volume is less than the "closing volume" for small airways. This situation cannot be tolerated, and the infant remedies the situation by breathing at a higher volume than the relaxation volume. Thus FRC and relaxation volume are not necessarily interchangeable because they may not always be equivalent.

Hyperinflation

Hyperinflation refers to an increase in lung volume above that usually seen at rest. As previously discussed, the end-expiratory lung volume coincides with the EEV of the respiratory system in adults and older children with normal lungs. Hyperinflation occurs naturally in two primary settings: (1) in the presence of a significant increase in resistance and (2) in the presence of a significant decrease in elastic recoil. Both of these conditions result in an increase in the time constant of emptying of the respiratory system. If the respiratory rate required to satisfy ventilatory demands does not allow sufficient expiratory time, hyperinflation occurs. Another setting in which hyperinflation may develop is during mechanical ventilation. On theoretical grounds, an expiratory time equal to three times the expiratory time constant allows emptying of 95% of the end-inspiratory volume, whereas an expiratory time equal to five times the expiratory time constant allows emptying of 99% of the volume. In practice, if the expiratory time constant was less than three times the expiratory time constant, hyperinflation (manifested as the development of PEEPi) develops in ventilated infants.[13]

Hyperinflation does serve a useful purpose. The increase in lung volume is associated with an increase in airway caliber secondary to mechanical interdependence. The increase in lung volume also increases the tissue viscance.[16,17] The degree to which resistance and, therefore, the time constant of emptying depends on the balance between these opposing influences. A patient with severe airflow obstruction may have so

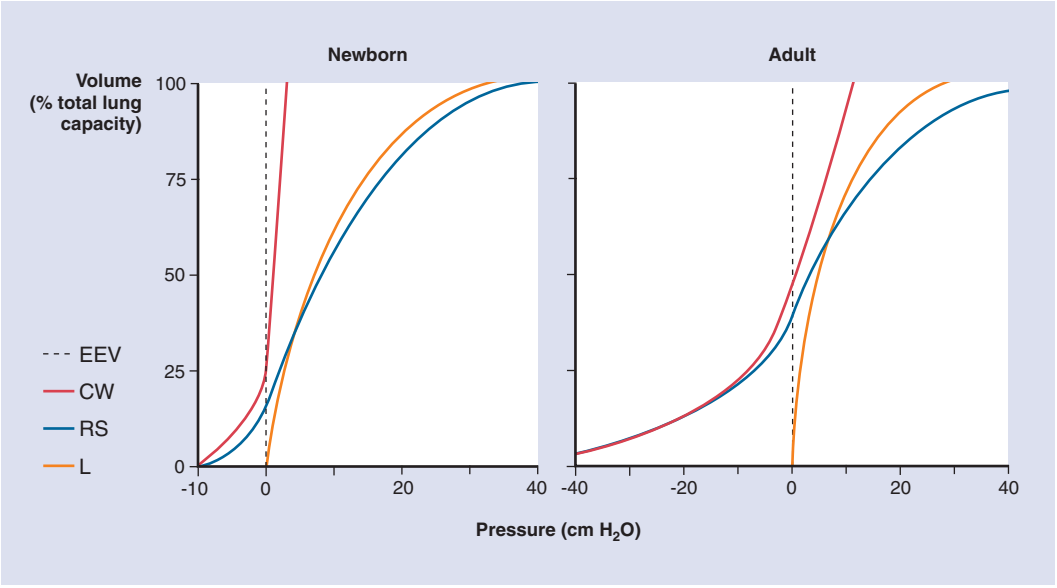


Figure 7-13 Pressure-volume curves of the newborn and adult respiratory system (RS) demonstrating the effect of lung (L) and chest wall (CW) compliance on elastic equilibrium volume (EEV). (From Agostini E: Volume-pressure relationships of the thorax and lung in the newborn. J Appl Physiol 14:909-913, 1959.)

much expiratory flow limitation that these values are, in fact, flow-limited during tidal breathing at rest. The only way that the expiratory flows can be increased at times of increased ventilatory demand, such as during exercise or febrile illnesses, is to increase lung volume, thus moving tidal breathing to a more advantageous part of the expiratory flow-volume curve. It is not surprising that hyperinflation has been found to be, at least partly, an active phenomenon.[18-20] Hyperinflation is achieved by tonic contraction of inspiratory muscles[19] and by expiratory "braking" by adduction of the vocal cords.[21]

The increase in expiratory flows made possible by hyperinflation does come at a cost. Hyperinflation puts the inspiratory muscles at a mechanical disadvantage, placing them at an inefficient part of their length-tension relationships. Under these conditions, the muscle excitation must increase to produce the same external work. This results in an increase in energy consumption and a decrease in efficiency. The work of breathing also increases because although the resistive work decreases and the total resistance is less, the elastic work increases and more than offsets any gain in resistive work. In addition, actively contracting muscles run the risk of limiting their own energy supply by narrowing the feeding arteries. These factors place the inspiratory muscles at risk of developing inspiratory muscle fatigue.

Two compensatory processes have been reported that have the potential to decrease the load on the inspiratory muscles. In patients with severe chronic airflow limitation, end-expiratory lung volume has been reported to increase during exercise, whereas the anteroposterior dimensions of the abdomen decrease because of expiratory recruitment of the abdominal muscles.[22] End-expiratory cephalad displacement of the diaphragm, secondary to contraction of abdominal muscles toward the end of expiration,[23] aids inspiration in at least two ways: It puts the muscle fibers of the diaphragm on a more favorable part of their length-tension relationship, and it stores elastic and gravitational energy in the abdominal compartment and releases it during the subsequent inspiration, performing inspiratory work and contributing to minute ventilation without increasing the activation of the diaphragm.

The expiratory braking, grunting, achieved by partial glottic adduction, "unloads" the inspiratory muscles by allowing hyperinflation to be maintained with less tonic activation of inspiratory muscles.

Forced Expiration

EXPIRATORY FLOW LIMITATION

Measurements during forced expiration are useful in detecting obstructive lung disease because during a forced expiration, expiratory flow is independent of the force driving the flow over most of the expired vital capacity as long as reasonable effort is made. This observation was made by plotting the pressure-flow relationships at isovolume points measured during expirations made with increasing effort (Fig. 7-14). This observation led directly to the description of the maximal expiratory flow volume curve, which emphasized that at most lung volumes, there was a limit to maximal expiratory flow. The peak flow depends largely on effort, and the flows near the residual volume may be effort-dependent because some people may not be able to maintain sufficient force to maintain flow limitation at this low lung volume.

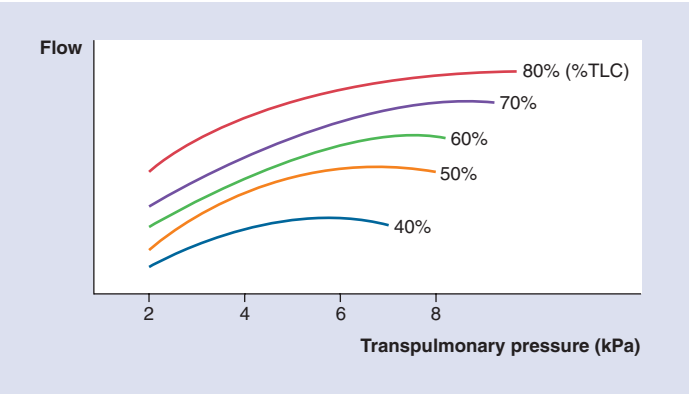


Figure 7-14 Isovolume pressure-flow curves in a normal adult at different proportions of total lung capacity (TLC). (From Tammeling GJ, et al: Contours of Breathing, 2nd ed. Burlington, Ontario, Canada, Boehringer Ingelheim Pharmaceuticals, 1985.)

The mechanism for expiratory flow limitation is complex. In fluid dynamic terms, a system cannot carry a greater flow than the flow for which the fluid velocity equals wave speed at some point in the system. The wave speed is the speed at which a small disturbance travels in a compliant tube filled with fluid. In the arteries, this is the speed at which the pulse propagates. In the airway, the speed is higher than this—mainly because the fluid density is lower. The wave speed *(c)* in a compliant tube with an area *(A)* that depends on lateral pressure *(P)* filled with a fluid of density *(ρ)*, is given by the following:

$$c = (A\delta P/\rho\delta A)^{1/2} \qquad \text{Eq 7.8}$$

where $\delta P/\delta A$ is the slope of the pressure-area curve for the airway. Maximal flow is the product of the fluid velocity at wave speed and airway area, as follows:

$$\dot{V}_{max} = cA \qquad \text{Eq 7.9}$$

At high lung volumes the flow-limiting site in the human airways is typically in the second and third airway generations. As lung volume decreases, flow decreases, and the flow-limiting site moves peripherally. At low lung volumes the density dependence of maximal flow is small, and the viscosity dependence is large and becomes the predominant mechanism limiting expiratory flow.

PHYSIOLOGY OF WHEEZING

Flow limitation in a compliant tube is accompanied by the "flutter" of the walls at the site of flow limitation. This flutter occurs to conserve the energy in the system because the driving pressure in excess of that required to produce $\dot{V}_{max}$ is dissipated in causing the flutter.[24,25] In the presence of airway obstruction, this flutter may become large enough to generate sound. This sound is heard as wheezing. Thus expiratory wheezing is a sign of expiratory flow limitation. However, although wheezing implies the presence of expiratory flow limitation, flow limitation can occur in the absence of

detectable wheezing.[24] Gavriely and associates[26] demonstrated that the transpulmonary pressures (as an indication of the effort required for breathing) required to produce wheezing were substantially greater than those required to achieve flow limitation. They concluded that this extra pressure was required to "induce flattening of the intrathoracic airways downstream from the choke point" and to induce oscillations in the airway walls.[26]

COUGH

Cough is the most common natural forced expiration. Most of the forced expirations measured by clinicians are artificially produced to satisfy the clinician's desires. Cough has several practical functions. It can be stimulated by various receptors in the respiratory tract; that is, irritant receptors in the large airways stimulate cough in response to mechanical irritation (e.g., inhalation of dust, cigarette smoke, aspirated material) or respiratory infections to help clear material from the respiratory tract; irritant receptors in the larynx prevent or minimize aspiration of foreign materials into the airways; or stretch receptors in the lung parenchyma, stimulated by application of high distention pressures to the lung, limit maximal inspiration, presumably protecting the lung from overdistention and mechanical disruption. Cough can also be initiated voluntarily.

Whether cough is initiated by voluntary means or by stimulation of receptors, the first action is usually inspiration of a variable volume of air. Next, the glottis is closed simultaneously with or just after the onset of forceful expiratory muscle activity that quickly raises thoracoabdominal pressures to 100 cm H_2O or more above ambient pressure. About 0.2 second after the glottis closes, it is actively opened; subglottic pressure falls, and expiratory flow begins. Intrathoracic pressures, however, usually continue to rise; thus peak pressure usually occurs after peak flow. Expiratory flow quickly rises to "maximal" flow as central intrathoracic airways collapse. Their narrowed cross-section is associated with high gas linear velocities and therefore with high shearing forces at airway walls and high kinetic energies. These conditions are probably important in suspending and clearing materials adherent to the walls. After a widely variable volume of air is expired, expiratory muscle activity diminishes abruptly, perhaps with the onset of antagonist activity of the diaphragm and other muscles; alveolar pressure falls toward ambient pressure, and flow drops toward zero, sometimes interrupted finally by glottic closure. Several coughs may follow in immediate series from high to low lung volume without intervening inspirations. This has the effect of "squeezing" secretions in the smaller airways more centrally to airways with high enough linear velocities to clear the secretions.

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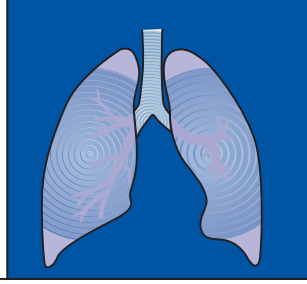

CHAPTER 8

Exercise Physiology

Alan R. Morton

TEACHING POINTS

- Exercise physiology is a branch of applied physiology concerned with the patient's responses to both acute and chronic exercise (training).
- Humans require regular physical activity to achieve optimal growth, optimal development of the heart and lungs, and optimal strength of bones, ligaments, tendons, and muscles.
- A sedentary lifestyle during adulthood, which is often the result of a childhood with restricted physical activity, may contribute to the development of various illnesses collectively classified as *hypokinetic diseases*. These diseases include coronary heart disease, obesity, diabetes, hypertension, colon cancer, and low back problems.
- Adenosine triphosphate (ATP), often referred to as the *universal energy currency*. is a molecule that contains adenosine plus three phosphate groups. Energy is provided by the phosphagen system, the lactic acid system (anaerobic glycolysis), or the oxygen (aerobic) system.
- The number of muscle fibers is determined at birth; however, the thickness of the fibers grows about fivefold from birth to adulthood. The increase in muscle girth is due almost entirely to hypertrophy or continued growth of existing muscle fibers and not by hyperplasia.
- When the body changes from a resting state to one of maximal exercise intensity, its energy expenditure may increase more than 23 to 26 times the resting value, and the metabolic demands of the most active skeletal muscles may increase by as much as 130 to 200 times the resting value.
- During exercise, the body's rate of oxygen consumption ($\dot{V}O_2$) may increase by more than 20-fold, exhibiting a linear relationship between $\dot{V}O_2$ and the intensity of exercise or rate of work.
- The child is not a miniature adult, and because there are important differences in physiologic responses to muscular activity, children should not be expected to perform in a manner similar to adults.
- During training and competition, repetitive stress on a muscle, bone, or joint produces adaptations, some of which may be undesirable.
- In sports, the different levels of performance at a given age are often the result of different levels of maturity rather than of skill.

The trend is for children to become involved with serious sports training at progressively younger ages, with some beginning as early as 6 years of age, and teenagers are performing at world championship level in many sports, particularly swimming, tennis, and gymnastics. It is important, therefore, that the clinician have a good understanding of the physiologic, psychologic, and sociologic responses of children to vigorous exercise, with emphasis on the benefits and possible detrimental outcomes.

Exercise physiology is a branch of applied physiology concerned with the patient's responses to both acute and chronic exercise (training). It is concerned with these responses under various climatic, hyperbaric, and hypobaric conditions as they differ between genders and among people of different ages. In a chapter of this size, it is impossible to describe all of the physiologic changes accompanying acute and chronic exercise; therefore the major metabolic and cardiorespiratory factors are discussed only briefly.

Unfortunately, most of the research in this relatively new discipline has been performed on adults, and as a result, many of the pediatric exercise physiology questions are either unanswered or only partly answered. The reason for the lack of evidence concerning children can be explained by the reluctance of parents and ethics committees to provide consent for many of the required invasive and noninvasive procedures, such as muscle biopsies and arterial and venous blood sampling (especially when performed on a serial basis), and exposure to harsh environmental conditions and prolonged or severe exercise for what is often misconstrued as "athletic curiosity." When cross-sectional studies are performed in an effort to compare athletic children with sedentary children, it is difficult to separate training effects from genetic endowment. Nevertheless, this chapter examines the general responses to exercise and, when information is available, compares the responses of adults to those of children. This comparison will indicate any advantages that the mature child, who more closely resembles the adult, has over the immature child. This maturity difference is often evident in children of the same chronologic age who are expected to compete against one another in sports.

Humans require regular physical activity to achieve optimal growth,[1] optimal development of the heart and lungs, and optimal strength of bones, ligaments, tendons, and muscles. The child needs to play and be on the move constantly and, until a generation ago, considered *rest* a four-letter word; however, this no longer appears to be true. For instance, studies in England[2,3] and Singapore[4] have indicated that the daily activity level of children today, as determined by continuous heart rate monitoring, is very low and that many children seldom undertake enough physical activity to appropriately stress the cardiopulmonary system. A sedentary lifestyle during adulthood, which is often the result of a childhood

with restricted physical activity, may contribute to the development of various illnesses collectively classified as *hypokinetic diseases*. These diseases include coronary heart disease, obesity, and low back problems.[5] In 1996 the Surgeon General of the United States published a most comprehensive review of the research on physical activity and health and the implications. This 278 page document, based on a vast number of studies, showed that a lifelong regimen of regular, moderate amounts of moderate or vigorous physical activity, will provide substantial health gains. Physical activity also reduces the risks of developing coronary heart disease, hypertension, colon cancer, and diabetes as well as maintaining a high quality of life.[6] Regular and frequent exercise is an important component in the prevention and treatment of obesity, a problem that has reached epidemic proportions among children and adults in the Western world. Many obese children and adolescents become obese adults.[7] Weight-bearing physical activity during childhood and adolescence is required to develop peak bone mass. This helps to prevent osteoporosis in later life. Sallis[8] suggests that improved psychological health may be one of the strongest health benefits of physical activity for young people. It is generally accepted that the foundation for the lifelong regular exercise habit should be laid down during childhood and depends on a competent school physical education program emphasizing motor skills, improvement and maintenance of fitness components, and the pleasure of participation in physical activities.[6]

It is impossible in this chapter to fully discuss the role of exercise in the prevention, management, and treatment of the various diseases. The reader is referred to the excellent text by Bar-Or.[7]

METABOLIC RESPONSES TO ACUTE EXERCISE

Energy Systems

The muscular system, as with other systems of the body, has one source of energy for metabolism (Fig. 8-1): adenosine triphosphate (ATP), often referred to as the *universal energy currency*. ATP is a molecule that contains adenosine plus three phosphate groups in the following format:

$$\text{ADENOSINE} - \text{Pi}^{-} \sim \text{Pi}^{-} \sim \text{Pi}^{-2} \qquad \text{Eq 8.1}$$

The last two phosphate radicals are attached by two high-energy bonds (.010), each of which releases 30.7 kJ (7.3 kcal) per mole of ATP when the bond is broken to change ATP to adenosine diphosphate (ADP) or ADP to adenosine monophosphate. The provision of ATP for metabolism occurs by at least one of three metabolic systems: the phosphagen

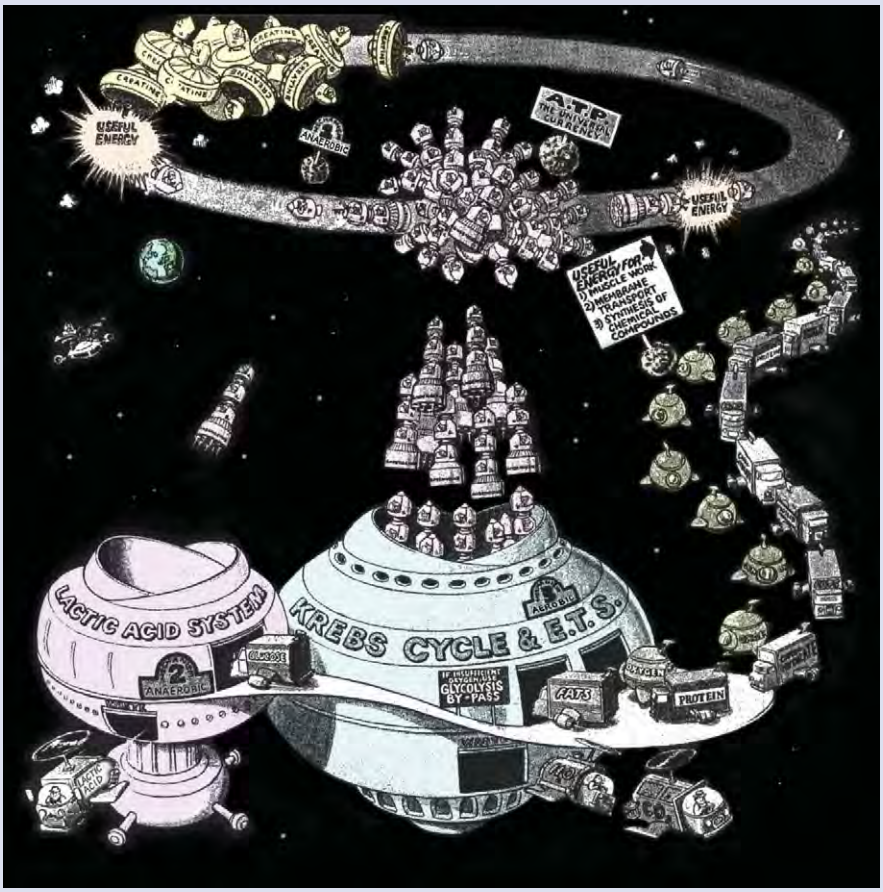

Figure 8-1 Representation of the body's energy sources.

system, the lactic acid system, and the oxygen (aerobic) system.

PHOSPHAGEN SYSTEM

The phosphagen system consists of the ATP store and the phosphocreatine (PC) (also called *creatine phosphate*) store (see upper section of Fig. 8-1). The ATP store in the body is small and is sufficient to allow maximal effort for about 1 to 2 seconds, but there are ways of providing more ATP to replace that being used during metabolism. Muscles cannot obtain ATP from the blood or other tissues, so they must manufacture it. To do this, they need ADP, inorganic phosphate (Pi), and energy from other chemical sources to reconstruct the ATP molecules by rephosphorylation of ADP, as follows:

Eq 8.2 $$\text{ADP} + \text{Pi (plus energy)} \rightarrow \text{ATP}$$

One method of providing more ATP is to break down another stored chemical containing a high-energy phosphate bond so that the energy released by its breakdown can be used to reconstitute ATP from ADP and Pi: PC (creatine .010 PO_3^-) decomposes to creatine plus a phosphate ion plus energy. The breaking of the PC bond releases 43.3 kJ (10.3 kcal) per mole, which is considerably more than that seen in the breakdown of the high-energy bonds in ATP, indicating that there is more than enough energy to reconstitute ATP. Unfortunately, the energy available from the store of PC is also limited and is enough for only about another 5 to 8 seconds of maximal effort. That is, the ATP and PC activity combined, referred to as the *phosphagen system*, can provide energy for less than 10 seconds of maximal activity. This phosphagen system is the most rapidly available source of energy and is often termed the *immediate energy source*. It is extremely important in explosive type efforts such as throwing, hitting, jumping, and sprinting.

The system is rapidly replenished during recovery; in fact, it requires about 30 seconds to replenish about 70% of the phosphagens and 3 to 5 minutes to replenish 100%. This means that during intermittent work (short periods of activity followed by rest periods), much of the phosphagen can be replenished during the recovery period and thus be used over and over again.

LACTIC ACID SYSTEM (ANAEROBIC GLYCOLYSIS)

Because the ATP-PC system can sustain intense activity for less than 10 seconds, other means of reconstituting the ATP molecule must be available. This is accomplished by the use of the other two energy systems, the lactic acid system and the oxygen system, both of which use the breakdown products of the foods ingested.

During the initial stages of exercise and during high-intensity effort, the body cannot provide sufficient oxygen to regenerate the ATP required. To allow for this, the ATP-PC and another system termed the *anaerobic glycolysis system* or *lactic acid system* provides the ATP.

The lactic acid system, also referred to as the *short-term energy source*, uses glucose or glycogen (carbohydrates), which break down to pyruvic acid; then if insufficient oxygen is available, the pyruvic acid breaks down to lactic acid. During the breakdown of glucose to lactic acid, a small amount of ATP is produced (see lower left section of Fig. 8-1). If this system is overworked, the hydrogen ions from the dissociation of lactic acid and the subsequent decrease in pH are associated with fatigue, and when the hydrogen ion concentration becomes high enough, it can decrease the contractile capacity of muscle. This system can sustain another 40 seconds of maximal work over and above that of the ATP-PC system. During glycolysis, which occurs in the cytoplasm of the cell, a complex series of enzymatic reactions occur to provide ATP. This is a slower process than in the phosphagen system. The lactic acid system results in two or three ATP molecules being made available, depending on whether glucose or glycogen is used. This system is inefficient compared to the oxygen system, which can provide 38 molecules of ATP; however, the lactic acid system can provide these two or three ATP molecules even when the supply of oxygen to the muscle is absent.

Lactic acid can be removed during rest periods, but this is a slow process compared to the replenishment of the phosphagen stores. In fact, a large accumulation of lactate may take at least an hour to be removed.

The lactic acid system provides the majority of energy during bursts of vigorous activity that can be maintained for only 1 to 2 minutes; for example, people doing long sprints (200-, 400-, and 800-meter runs) rely largely on the lactic acid system, although during these events, some energy would be provided by all three systems. Neither the ATP-PC system nor the lactic acid system requires oxygen to be present, so they are classified as *anaerobic energy systems*.

OXYGEN (AEROBIC) SYSTEM

If the level of activity is light enough to be performed for a considerable length of time, sufficient oxygen will be available to prevent pyruvic acid from breaking down to lactic acid after glycolysis. Instead, the pyruvic acid breaks down to acetylcoenzyme A, which enters the Krebs cycle and the electron transport system and is eventually processed to form water plus carbon dioxide plus a large amount of ATP. Oxygen is required in this process, and the carbon dioxide produced is then transported to the lungs for removal from the body. Fat and protein can also be used aerobically to provide ATP (see lower section of Fig. 8-1). The aerobic system, also termed the *long-term energy source*, is the important energy system for activities lasting longer than 2 minutes (all-out efforts lasting 2 minutes receive one half of their energy aerobically and one half anaerobically). The higher the maximal oxygen uptake (aerobic power) by the muscles, the higher the work rate that can be sustained.

The contribution of the various energy sources during a given event or sport can be gauged by the duration of the event or effort phases in the sport. For instance, events lasting less than 6 to 10 seconds rely almost exclusively on energy provided by the ATP-PC system. In events lasting 10 to 60 seconds, most of the energy is provided via the anaerobic glycolytic pathway (lactic acid system). As the event increases to about 2 to 4 minutes, the reliance on the anaerobic pathways becomes less important, and aerobic (oxygen system) metabolism increases in importance. Events performed at a low level of intensity for prolonged periods of time, such as a marathon, use the oxygen system almost completely because

the ability to provide oxygen is adequate to cover the oxygen requirements.

SUMMARY OF ENERGY SOURCES

During glycolysis, four molecules of ATP are formed from a molecule of glucose; however, two of these are expended to initiate the process by the phosphorylation of glucose, leaving a net gain of two ATP molecules. During the use of the oxygen system, there is a maximal gain of 38 molecules of ATP: 2 via glycolysis and 36 via the Krebs cycle and electron transport system.

Although most of this discussion concerns carbohydrate use, fat and protein can also be used to provide ATP aerobically; however, only carbohydrate can be used anaerobically. Triglycerides are digested to fatty acids; fatty acids are activated in a process called β-*oxidation,* which prepares fatty acids for entrance into the Krebs cycle by modifying them to acetylcoenzyme A. Protein is used as a substrate only in small amounts, unless the available carbohydrates and fats are seriously depleted.

The use of a gram of fat as the energy substrate produces $2^1/_4$ times as much energy (37.7 kJ or 9 kcal) as 1 g of carbohydrate (16.7 kJ or 4 kcal). However, about 8% less oxygen is required to produce a given amount of energy when using carbohydrate compared to fat.

MUSCULAR SYSTEM

It appears that the number of muscle fibers is determined at birth; however, the thickness of the fibers grows about fivefold from birth and adulthood.[8] The increase in muscle girth is due almost entirely to hypertrophy or continued growth of existing muscle fibers and not by hyperplasia. In male patients, this increase is facilitated by the secretion of testosterone after sexual maturation.[9]

At birth, about 20% of the muscle fibers are type IIc (undifferentiated), whereas by the age of 6, the distribution of types I, IIa, and IIb fibers is identical to that of adults.[10] There are almost no type IIc fibers found after a child has reached 1 year of age.

Muscular strength, or the ability to exert force, is highly related to the cross-sectional area of the muscle and to lean body mass. According to Malina,[11] muscle strength increases linearly with chronologic age from early childhood to about 13 to 14 years in boys. This is followed by a period until about 20 years of age, during which there is considerable acceleration of the increase in muscular strength. The muscular strength of girls increases linearly until about 15 years of age, after which it tends to plateau with very little additional increase.

CARDIORESPIRATORY RESPONSES TO ACUTE EXERCISE

The cardiorespiratory system plays an important role during exercise because its response to the exercise-induced increase in metabolic rate allows the muscles to be supplied with increased oxygen, glucose, and free fatty acids to support the increase in metabolism and to remove waste products (particularly carbon dioxide and heat). This system also transports hormones, vitamins, and amino acids to their target areas so that they can help regulate the body's activities during performance at an increased metabolic rate. When the body changes from a resting state to one of maximal exercise intensity, its energy expenditure may increase more than 23 to 26 times the resting value, and the metabolic demands of the most active skeletal muscles may increase by as much as 130 to 200 times the resting value. That is, the body's rate of oxygen consumption ($\dot{V}O_2$) may increase by more than 20-fold, exhibiting a linear relation between $\dot{V}O_2$ and the intensity of exercise or rate of work. The increase in $\dot{V}O_2$ is accomplished by the following:

1. An increase in cardiac output ($\dot{Q}$)
2. An increase in the oxygen extraction rate by the muscles ($a - \bar{v}O_2\Delta$)
3. A redistribution of the $\dot{Q}$ so that more blood is channeled to the active tissues (skeletal and cardiac muscle) and to the skin for heat dissipation, and so that reduced amounts are channeled to organs such as the gut and kidneys while maintaining the absolute flow rate to the brain (although decreased relative to the increased $\dot{Q}$)
4. An increase in ventilation
5. An increase in the lung diffusion capacity resulting from an increase in blood flow to the lungs (particularly to the upper portion) and the opening of closed alveoli
6. An increase in hematocrit because of the redistribution of fluid from the plasma to the interstitial space (hemoconcentration), thus increasing the oxygen-carrying capacity of the circulating blood

The magnitude of many of these responses changes as a result of regular, frequent, endurance-overload training sessions (chronic exercise). These changes in responses result in an increase in the maximal work capacity and a decrease in the myocardial oxygen demand for a given level of submaximal work.

Cardiovascular Responses to Acute Exercise

The increase in $\dot{Q}$ during maximal work may be as much as four to five times the resting $\dot{Q}$, is linearly related to the increase in the $\dot{V}O_2$ and therefore to the work rate, and is a result of an increase in both the heart rate and the stroke volume. When the body changes from rest to a given level of submaximal exercise, the heart rate and oxygen consumption increase rapidly and reach a steady state in about 3 or 4 minutes; with cessation of exercise the heart rate decreases rapidly at first and then more gradually until the resting level is reached (Fig. 8-2A and C). The steady-state heart rate increases linearly, $2^1/_2$-fold to 3-fold, with an increase in $\dot{V}O_2$ from the resting level to the maximal heart rate. Maximal heart rate has for many years been estimated at 220 minus the age of the individual, but more recently it has been more accurately estimated by the formula HRmax = 208 − (0.7 × age).[14]

Stroke volume increases rapidly with an increase in work rate but usually plateaus at about 40% to 60% of the maximal oxygen consumption ($\dot{V}O_2$max) and represents approximately a twofold increase. This is assuming that the exercise is performed in an upright position because the maximal stroke volume during upright exercise is very similar to the resting stroke volume in the supine position. When the body changes

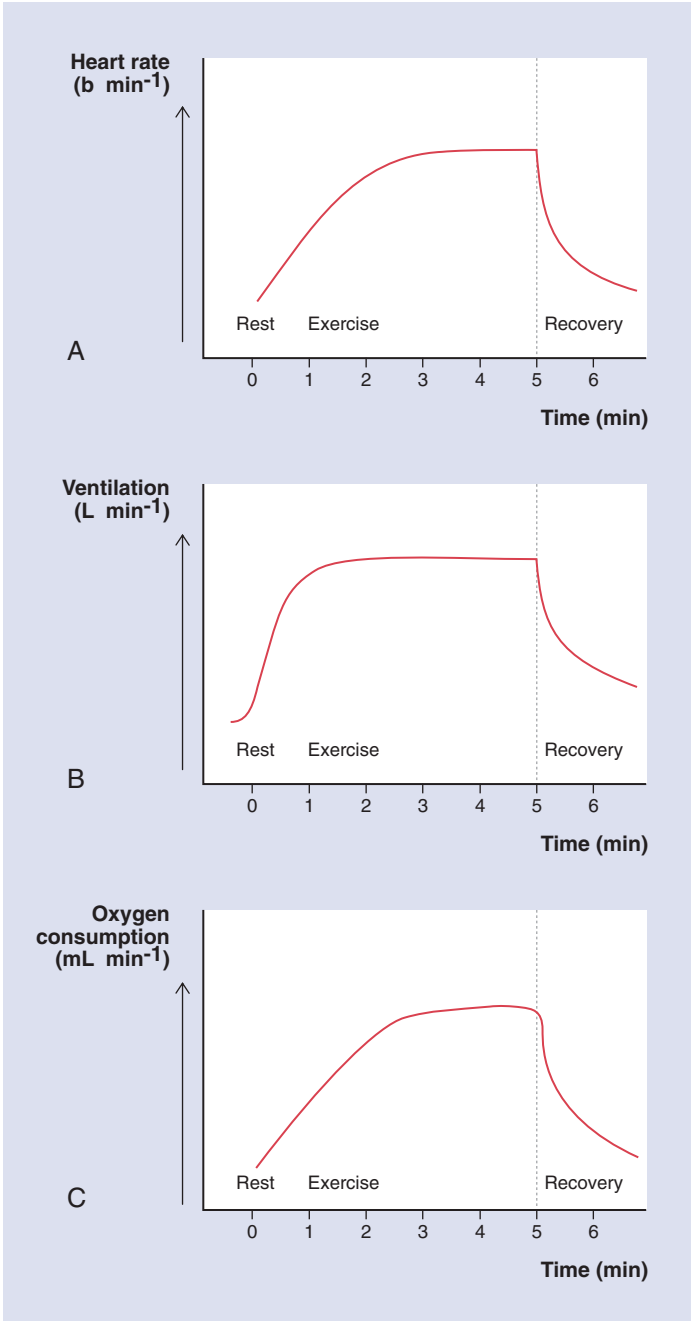

Figure 8-2 Responses of selected cardiorespiratory parameters when the body changes from rest to a given level of submaximal exercise followed by a recovery period.

from resting to maximal exercise while in the supine position, there is little increase in the stroke volume. At rest, a change from supine to standing results in a drop in stroke volume resulting from the effects of gravity, which tends to cause the blood to pool in the legs. This pooling decreases the central blood volume and venous return, thus reducing stroke volume.

The approximately threefold increase in $a - \bar{v}O_2\Delta$ from resting to maximal exercise is attained by increasing the number of patent capillaries, by increasing the oxygen partial pressure gradient between blood and active tissues (which results from the use of oxygen by active cells in accordance with the characteristics of the oxygen-hemoglobin dissociation curve), and by metabolically inducing an increase in blood temperature and acidity (the Bohr effect).

The blood pressure increases during exercise to ensure an adequate blood flow to critical areas such as the brain and the heart and to meet the increased requirements of the skeletal muscles. This increase occurs as a result of an increased $\dot{Q}$ value and the vasoconstriction in inactive tissues. It also occurs despite a large decrease in peripheral resistance.

The blood pressure during a given submaximal workload reaches a steady state within 3 to 4 minutes. When the steady-state blood pressure is plotted against $\dot{V}O_2max$ or the increasing workload, it follows a pattern indicating that the systolic blood pressure increases linearly, reaching a value about 1.5 to 1.6 times the resting level. Meanwhile, the diastolic pressure remains fairly constant or increases to about 1.1 times the resting value; under some conditions, it even decreases slightly. The mean arterial blood pressure, which is equal to the diastolic blood pressure plus one third of the pulse pressure, increases linearly to about 1.3 times the resting level.

The relatively small increases in arterial blood pressure caused by the large increase in $\dot{Q}$ is explained by the curvilinear decrease in the total peripheral resistance caused by the increasing workload. The total peripheral resistance can be reduced by about $4^1/_2$-fold. This decrease in total peripheral resistance results primarily from vasodilation of the arterial vascular beds in the active muscles as a result of the metabolites released during the increased metabolism of these muscles. These metabolites override the sympathetic vasoconstrictor effects.

The myocardial oxygen consumption ($M\dot{V}O_2$), like the heart rate, increases linearly with increasing workload. The $M\dot{V}O_2$ may increase fourfold to fivefold from rest to maximal exercise because of an increase in coronary blood flow and the $a - \bar{v}O_2\Delta$ of the cardiac muscle. The myocardial $a - \bar{v}O_2\Delta$ is very high at rest and increases only slightly during exercise, whereas the coronary blood flow increases about fourfold during maximal exercise. The heart, which is only about 0.5% of the weight of the body, receives about 5% of the $\dot{Q}$.

Ventilatory Responses to Acute Exercise

The increase in the ventilatory rate from rest to a given level of submaximal exercise is very rapid at first and then becomes more gradual until a steady state is attained. Similarly, when exercise is terminated, a rapid decrease is followed by a more gradual decline until the resting ventilatory value is reached (see Fig. 8-2B).

When exercise is increased from resting until maximal levels are attained, the minute ventilation increases linearly with the increase in workload up to approximately 50% to 60% of the $\dot{V}O_2max$, after which it becomes curvilinearly related, with the increase in ventilation being greater than the increase in workload. The increase in minute ventilation results from an increase in the breathing frequency, which varies from 10 to 15 breaths/min at rest to 45 to 70 breaths/min at maximal work (depending on age), and an increase in tidal volume, which may reach values as high as 50% to 60% of the vital capacity during maximal work. Both breathing frequency and tidal volume tend to increase linearly when

there is an increase in workload and $\dot{V}O_2$ during light to moderate work, whereas at heavier workloads and higher $\dot{V}O_2$, the tidal volume tends to level off, and the increases in ventilation become dependent primarily on an increase in breathing frequency. The increase in ventilation increases the elastic and flow-resistive work of breathing, which increases the energy required for breathing. The energy required by the muscles of breathing is very low at rest but may increase 50-fold during maximal exercise.[15]

The point on the ventilation-$\dot{V}O_2$ curve at which the relationship suddenly changes from linear to curvilinear is often referred to as the *respiratory compensation threshold*[16] or *ventilatory anaerobic threshold*.[17]

The ventilatory response during exercise, which increases the provision of oxygen for transport to muscle cells, also includes a threefold increase in the lung diffusion capacity. This is due primarily to an increase in the amount of blood flowing through the lung, particularly to the upper sections, as a result of more of the pulmonary capillaries becoming patent; thus the total surface area available for pulmonary gas exchange is increased. (Diffusion capacity is measured in milliliters of oxygen diffused for each millimeter of mercury of partial pressure difference between the alveolus and pulmonary blood.)

CARDIORESPIRATORY RESPONSES TO CHRONIC EXERCISE

Exercise sessions repeated every 2 or 3 days for weeks or months (endurance training) result in physiologic and morphologic adjustments that modify physical performance. Training increases the maximal work capacity, and the best measure of this capacity is the $\dot{V}O_2$. The $\dot{V}O_2$ depends on the ability of the body to take in oxygen from the environment, transport it to the active muscles, extract it from the blood, and use it for muscular work. That is, the $\dot{V}O_2$ is the maximum $\dot{Q}$ multiplied by the maximal arteriovenous oxygen difference ($a - \bar{v}O_2\Delta$).

The responses of the trained and sedentary individual differ in the parameters that modify maximal work capacity. The person in training has a higher maximal work capacity, higher $\dot{V}O_2max$, and greater maximum $\dot{Q}$; however, both the $\dot{V}O_2$ and the $\dot{Q}$ at rest and at any given level of submaximal work is essentially the same for both the trained and the sedentary individual.

The increased maximum $\dot{Q}$ is a result of an increased maximal stroke volume because the maximum heart rate is changed very little and, in fact, may decrease as a result of endurance training. The stroke volume at rest or at any given submaximal work rate is also higher in the trained person, and because the $\dot{Q}$ is essentially the same, it is evident that the heart rate at that workload must be considerably lower.

The pattern of response for $M\dot{V}O_2$ for the trained and sedentary individual is similar to that for the heart rate responses. That is, $M\dot{V}O_2$, which is highly related to the double product (heart rate multiplied by systolic blood pressure), which in turn reflects the work of the heart, is considerably lower in the trained individual at rest and at any given level of submaximal work, whereas the maximal attainable $M\dot{V}O_2$ is very similar for the trained and sedentary individual. This indicates that the trained heart is more efficient.

The $a - \bar{v}O_2\Delta$ and oxygen use in the trained and the sedentary individual is essentially the same at rest and for given levels of submaximal work; however, the maximal ability to extract and use oxygen from a given amount of blood is greater in the trained individual. This response pattern is similar to that of $\dot{Q}$ and $\dot{V}O_2$.

Systolic, diastolic, and mean blood pressures all tend to be reduced at rest or at submaximal work intensities after endurance training. The values at maximal work capacity are similar for the trained and the sedentary individual. There is a greater reduction in the peripheral resistance in trained versus sedentary individuals at rest and at all levels of exercise intensity.

The changes in ventilation with increasing workload after endurance training has a pattern similar to those in the sedentary individual; however, at any submaximal workload the ventilatory rate is reduced in trained individuals. The ventilatory rate is very similar at rest, whereas the maximal ventilatory rate is greater in the trained individual. The pattern of response for pulmonary diffusion capacity is similar in the trained and the sedentary individual except that the value is greater in the trained person at rest at any given submaximal workload and at maximal work capacity.

COMPARISON OF CHILDREN AND ADULTS

An examination of sports programs for children indicates that boys and girls are, for the most part, participating in games and events designed by and for adults. This is particularly true in school sports programs. The child is an "immature working machine," not a miniature adult, and because there are important differences in physiologic responses to muscular activity, children should not be expected to perform in a manner similar to adults.

Anaerobic Metabolism

ALACTIC ENERGY COMPONENT

The contribution of the phosphagen system to the energy used during the performance of a given physical activity is termed the alactic energy component. The concentration of the phosphagens (ATP and CP) are similar in children and adults. The rate of use of both phosphagens at workloads eliciting a given percentage of $\dot{V}O_2max$ is also similar in children and adults. Thus the alactic anaerobic processes do not differ significantly.[18-22]

LACTACID ENERGY COMPONENT

The contribution of the lactic acid system to the energy used during the performance of a given physical activity is termed the lactacid energy component. A child possesses lower concentrations of phosphofructokinase, the rate-limiting enzyme in glycolysis, than adults.[22] Furthermore, the child exhibits a lower maximal lactic acid level in both blood and muscle after maximal work and lower lactic acid levels at all submaximal workloads when compared to adults. This suggests that the child has a lower lactacid anaerobic capacity and is at a disadvantage in events requiring maximal use of this energy source.[19,23] Furthermore, development of this lactacid energy capacity and thus success in events dependent on this energy source are closely related to maturity level.

Aerobic Metabolism

The child's heart and lungs are smaller than the adult's when expressed in absolute terms, but the sizes are very similar if expressed relative to body size.[24] Aerobic capacity ($\dot{V}O_2max$), the usual index of endurance capacity and cardiorespiratory fitness,[25] depends on the $\dot{Q}$ and the $a - \bar{v}O_2\Delta$. The stroke volume of the heart is similar in children and adults when corrections are made for the difference in body size,[20] whereas the maximal attainable heart rate is slightly higher in children.[26,27] Because these are the components of $\dot{Q}$, it is evident that adaptation of the $\dot{Q}$ to aerobic work in the child is at least equivalent to that of the adult.

At any given level of submaximal exercise and at maximal exercise $\dot{V}O_2$ ($L\,min^{-1}$), $\dot{Q}$, stroke volume, lactate concentration, tidal volume, ventilation, respiratory exchange ratio (RER), and blood pressure are lower in children than in adults; however, $\dot{V}O_2$ ($mL{\cdot}kg^{-1}{\cdot}min^{-1}$), heart rate and ventilatory equivalent $\dot{V}E/\dot{V}O_2$) are higher.[28] The $a - \bar{v}O_2\Delta$ is higher in children at submaximal but not at maximal exercise. Blood flow to the exercising muscle is greater in children.[29]

Despite the fact that maximal $a - \bar{v}O_2\Delta$ normally depends on the hemoglobin concentration in the blood and that children have a lower hemoglobin concentration than adults, the maximal $a - \bar{v}O_2\Delta$ is similar for both adults and children.[20,26,27] Eriksson[19,30] claims that this is because the child's maximal $a - \bar{v}O_2\Delta$ comes closer to the blood's oxygen-carrying capacity as a result of more active enzyme systems.[31] Children also have the ability to shunt a greater percentage of the $\dot{Q}$ through the active tissues during exercise, thus exhibiting a lower $\dot{Q}$ at any given submaximal level of oxygen uptake. This may result from a decrease in the amount of oxygen demanded by the child's smaller viscera or a decreased need for blood flow to the skin which is caused by a more ready elimination of the body's heat.[31] Systolic, mean, and even diastolic arterial blood pressures are relatively lower in children than in adults.[32,33]

In absolute terms, the pulmonary diffusion capacity is smaller in children than adults because it is dependent on the area of the alveolar membrane available for gaseous diffusion. This changes, as do lung volumes, with body size, particularly with height.

The question of the equality of aerobic capabilities between adults and children, however, is one in which there is not complete agreement. For instance, Astrand[34] claims that the $\dot{V}O_2max$ in children is not as high as expected for their size and they do not have the aerobic power to handle their weight compared to adults. However, the 16- to 18-year-old boys in his study had a mean $\dot{V}O_2max$ of $3.68\ L{\cdot}min^{-1}$, which translated into $57.6\ mL{\cdot}kg^{-1}\ min^{-1}$, whereas 7- to 9-year-old boys had values of $1.75\ L{\cdot}min^{-1}$ and $57\ mL{\cdot}kg^{-1}\ min^{-1}$. This indicates that the oxygen uptake expressed relative to body weight was the same, although the adult did have a higher aerobic power reserve. This was indicated by the adult's ability to increase the basal metabolic rate 13.5-fold, whereas the 8-year-old children demonstrated a maximal increase of only 9.4-fold.

Bar-Or[10] plotted data from a large number of studies and showed that the maximal aerobic power for boys, when expressed in liters per minute, increased continually from age 5 to 18 years, whereas for girls the values, although always slightly lower than boys, increased at about the same rate until about 14 years of age, after which it leveled off and increased no further. Because $\dot{V}O_2max$ is related not only to maturity but also to body size, Bar-Or[10] also compared the maximal aerobic power of individuals of different body mass and showed that it remained fairly constant for boys 5 to 18 years when expressed relative to body weight, whereas for girls the values were similar but lower up to age 10 years, after which there was a continual decline with age. Bar-Or[10] suggested that this decline may reflect an increase in body adiposity of girls during adolescence. Somewhat similar results have been reported by Andersen and coworkers[35] and Kemper and Verschuur.[36]

The child requires a greater stride frequency than the adult when running at the same speed, and because this results in a more expensive use of energy per unit of time, the child requires a greater oxygen uptake per kilogram of body weight than the adult.[34] Providing that the child is competing only against those of similar maturity, the sporting implications are minimal.

However, the most recent view is that the aerobic capacity of children is at least equivalent to that of the adult. As Eriksson[30] claims, when participating in an aerobic activity lasting less than 1 hour, the child, like the adult, must carry and transport his or her own body weight; therefore the child is not at any real disadvantage compared to the adult.

In aerobic events requiring a work level of 70% $\dot{V}O_2max$ for longer than 1 hour, the child is at a disadvantage because of the smaller absolute and relative storage capacity for muscle glycogen.[19,20,22,37] Muscle glycogen depletion is associated with fatigue.

The mean maximal accumulated oxygen deficit, a measure of anaerobic capacity, is 58.5 and 39 mL $O_2{\cdot}kg^{-1}$, respectively, for men and women.[38] These values are higher than those found for boys ($35\ mL\ O_2{\cdot}kg^{-1}$) and girls ($40\ mL\ O_2{\cdot}kg^{-1}$).[39] Carlson and Naughton[39] express concern over the accuracy of the values that they obtained for girls because they indicated that the reliability of the data was poorer.

The ventilation required per liter of oxygen consumed (oxygen ventilatory equivalent) at maximal exercise decreases from 6 to 18 years. In children under 10 years of age the values for ventilatory equivalent are about 30 L/L O_2 consumed during light work and up to 40 L/L O_2 during maximal exercise. The resting adult ventilatory equivalent is 20 to 25 L/L O_2 and increases to 30 to 35 L/L O_2 during moderately heavy exercise and to 40 L/L O_2 during maximal exercise. This seems to indicate that the ventilatory system is less efficient in children—this inefficiency being more pronounced in younger children because they use smaller amounts of oxygen from given amounts of inspired air.

The respiratory frequency during maximal exercise is about 70 breaths/min in 5-year-old children. The respiratory frequency drops to 55 breaths/min and 40 to 45 breaths/min in 12-year-olds and adults, respectively.[13] The young child has a shallower breathing pattern with a tidal volume/vital capacity ratio lower than that in older children and adults.

Strength

Children are at a disadvantage in events relying largely on strength because not only are children weaker than adults but

they are also weaker relative to their body dimensions. According to Paterson,[40] this indicates the involvement of biological factors that modify muscular dynamics. Astrand[34] lists three factors that affect muscle strength in aging children: (1) the increase in size of the muscles; (2) the aging process itself, which may reflect maturation of the central nervous system; and (3) the development of sexual maturity, which probably plays a dominant role for boys. For this reason, it is not very productive to include weight training for the prepubertal boy or girl because the strength gains are small until the androgenic hormones are produced in amounts sufficient to permit muscle hypertrophy.[41] It is, therefore, more beneficial to spend the extra time on practicing skills.[42] However, there are few detrimental effects if performed correctly, and those using weight training will certainly become stronger.[43-47] Also, learning the correct techniques of lifting is valuable in performing activities of daily living. The value of weight training in children's training programs is still not completely resolved, and many questions remain. For instance, it may be that those who commence weight training early may develop greater strength as an adult. Based on a recent review, Tanner[48] has claimed that most children and adolescents, provided that they adhere to a well-supervised, progressive strength-training program, can improve performance in other sports. This view is supported in a comprehensive review of the risks and benefits of resistance training in children by Blimkie.[49]

Thermoregulation

The human body is about 20% to 25% efficient under the best conditions; therefore most of the metabolic activity is eventually converted to heat. During vigorous exercise, a considerable heat load is imposed on the body, and bodily mechanisms, including sweating, shunting of blood through the arteriovenous anastomosis in the skin, and cutaneous vasodilation, are initiated to increase the rate of heat dissipation by evaporation, conduction, convection, and radiation.

Vigorous prolonged exercise in high temperatures and humidity can increase body core temperatures to levels high enough to cause cell and tissue destruction, which are manifested as heat illnesses such as heat cramps, heat exhaustion, and heat stroke. To prevent heat illness, people exercising in the heat should drink plenty of fluids (remembering that thirst is not an adequate guide to fluid needs); select appropriate, loose-fitting, light clothing; and cease exercise if any of the early symptoms of heat illness occur. People organizing and administering sporting events should cancel endurance events if the environmental conditions are such that the wet bulb globe temperature exceeds 28° C.[50]

The child has a larger skin surface area/body mass ratio than the adult and is more susceptible to heat loss or heat gain from the environment. The child also has less mature sweat glands and is at a disadvantage and in possible danger when performing heavy, long-term activities in the heat and high humidity. Children are also at a disadvantage when competing in endurance swimming events in cold water. That is, children are disadvantaged when performing exercise under environmental extremes of heat or cold. Inbar and colleagues[51] have also postulated that children are prevented from deriving the full effect of exercise-in-heat acclimatization because of some as-yet-undefined age-related factors associated with the thermoregulatory system.

Application

The differences between children and adults are important in sporting events. For example, there is a need to modify adult equipment, adult facilities, the duration of events, the number of players per team, and the rules—and to use a physiologic basis for selecting the most appropriate activities for the various age groups.

For instance, when the type of activities most suitable for children are selected, evidence suggests that the child can handle short, intense (alactic) sprints or aerobic work of less than 1 hour's duration without undue stress. However, compared to adults, children perform poorly in lactacid sprint-type events lasting $1^1/_2$ minutes (e.g., 200- or 400-meter track events). Success in these events depends on the child's level of maturity, so children who mature late may suffer psychologically as a result of continual failure. There is no apparent reason to suggest that the child should not attempt to train this energy system.

Although the available scientific data are meager and inconclusive, the American Academy of Pediatrics has issued a position statement on children lifting weights.[52] It claims that an athlete should not attempt maximal lifts until growth is complete at about age 16 or 17; thus weight-lifting and power-lifting are contraindicated before this age. The position statement admits that a well-supervised weight training program involving submaximal resistance can enhance performance in most sports, especially after puberty. The Academy warns of the tendency for weight-lifting to result in a transient elevation of blood pressure and that lifting very heavy weights may cause epiphysial damage in preadolescents.

The recognition of these differences between children and adults has been responsible (at last) for the realization that adult equipment and playing fields and adult game rules are not suitable for small children. As a result, some sporting associations have introduced modifications. The fields have been reduced in size, as have goal posts, balls, bats, and other playing equipment, and the duration of play and rest periods has been modified to better suit the physiologic development of the players. A study by Elliott[53] showed the need to modify the size of tennis racquets to suit the size and strength of the child. He found that children approximately 8 years of age, because they are smaller in stature and have less strength, could not handle the increases in the moment of inertia involved with the use of a larger racquet, so performance deteriorated, primarily in the strokes such as the serve requiring greater total racquet movement.

EFFECTS OF TRAINING

General Outcomes

One of the common questions related to the training of children concerns the suggestion that if training occurs during the period of rapid growth (prepuberty and puberty), there is a more marked improvement in components, such as aerobic power, than can be attained in training during adulthood. Certainly some animal studies have shown that this occurs, at least with the rat.[54]

Although some human studies[18,20,55,56] indicate that training before and during puberty produces a greater increase in the size of organs of the cardiorespiratory system than training later in life, Eriksson[20] claims that the changes in $\dot{V}O_2$max are similar. He found that in 11-year-old boys training for running, $\dot{V}O_2$max expressed in $mL \cdot kg^{-1} \cdot min^{-1}$ improved 16%, which is similar to the increase found by Saltin and associates[57] for sedentary adults. However, improvement is easier the more unfit the subject is initially, and sedentary adults are probably more unfit than sedentary children. A review by Bar-Or[58] has shown that $\dot{V}O_2$max can be increased in children with training; however, the improvement in prepubescent children is not as great as it is in adults. This conflicts with the view of Shephard,[59] who claims that there is no immediate evidence that the training response of the prepubescent child is less than that in an older person. However, after reviewing Malina and colleagues[60] and Payne and colleagues,[61] it appears that whereas prepubescent children do improve aerobic performance, that improvement is less than in older children.

Another question that is frequently asked, particularly by parents, is whether hard training has any deleterious effect on the growing child. A study by Astrand and coworkers[55] showed that in 30 Swedish girl swimmers aged 12 to 16 years, who trained intensively up to 65 km/week over a number of years, the $\dot{V}O_2$max improved to a mean value of 52 mL $O_2 \cdot kg^{-1} \cdot min^{-1}$. This training also increased the size of the organs involved in the oxygen transport system, and there was no indication of any detrimental effects.

These same girls were studied for 10 years, during which time all ceased regular training and most regressed to a sedentary lifestyle. As a result, their $\dot{V}O_2$max decreased from a mean of 52 to 37 mL $O_2 \cdot kg^{-1} \cdot min^{-1}$ (29% decrease); however, the dimensions of the lungs and heart were relatively unchanged.[56] The implication of retaining the larger heart and lungs is unknown, but others[62] have reported increased heart volumes in former top-rated endurance athletes without any accompanying medical problems. It does suggest, however, that the functional capacity of the cardiovascular system declines more markedly than its dimensions after training is ceased. This hypokinetically induced drop in $\dot{V}O_2$max to levels lower than those of the average nonathlete creates concern regarding the long-term effects on attitude toward physical activity after participation in a demanding training program at an early age.

A representative sample of 16 of the original 30 girls then embarked, at a mean age of 23.9 years, on a 12-week retraining program to determine whether the $\dot{V}O_2$max could be improved in this now-sedentary group of former swimmers to a greater extent than the average sedentary woman.[63] The study showed that the 12-week program increased $\dot{V}O_2$max by 14% without an increase in heart volume and yet almost restored stroke volume to that computed for the girls during their competitive swimming period 10 years earlier. This suggests that the training effect on the pumping function of the heart may be more pronounced in former top athletes than in previously sedentary people. Although these increases in $\dot{V}O_2$max and stroke volume are larger in other studies,[64] the studies are not quite comparable, so it is still difficult to claim that previous training in early life is of definite advantage. In fact, Pollock[65] has reviewed a large number of training studies, and his summary table indicates that a 14% gain represents an average increase in $\dot{V}O_2$max.

Because the training participation by these girls was not as good as expected and because no control group was used, Eriksson and colleagues[66] repeated the study using the most elite girls from the 1961 study ($N = 4$). This study used a control group of women each of whom lived in the same neighborhood and was age-matched to one of the former swimmers.[66] After retraining, the former girl swimmers had a 19% increase in $\dot{V}O_2$max when expressed in liters per minute, whereas $\dot{V}O_2$max in the control group increased 12.5%. When $\dot{V}O_2$max was expressed relative to body weight, the former swimmers' increase was still 19% compared to 10% for the controls. Stroke volume of the heart increased in both groups, exhibiting a 33% and 26% increase for the former swimmers and the control group, respectively. This study gives some support to the hypothesis that a former athlete has a greater capability to increase aerobic power with training.

Another longitudinal study of 29 girl swimmers who started vigorous swimming at ages 8.6 and 13.7 years has been reported.[56,67] These girls were followed annually to age 16 years. At 15 years of age, 15 of the 29 were still training, thus allowing comparisons between those still in training and the 14 who had dropped out. The data showed that heart volume increased with growth in both groups; however, the girls who continued to train had larger hearts at each age. A similar pattern was evident for maximal oxygen uptake in which absolute values (in liters per minute) increased with age for both groups. However, when these values were corrected for growth, the training group again showed a slightly greater value than the nontraining group. Static lung volumes were larger than normal after only a few years of training and increased further only in relation to the increase in height.

Early training does not necessarily guarantee sporting success later in life. Nor is it a prerequisite for success. One of the conclusions drawn from the Medford Boys' Growth Study[68] was that outstanding elementary school athletes may not be outstanding in junior high school and outstanding junior high school athletes may not have been outstanding in elementary school. He found that 45% of those outstanding athletes in junior high school were not considered such in elementary school. Research has yet to provide clear evidence as to the effects of sport training on the growth of children.[69]

Possible Detrimental Outcomes

During training and competition, repetitive stress on a muscle, bone, or joint produces adaptations, some of which may be undesirable.[70] Extreme overuse may lead to bony and muscular hypertrophy[71] and create problems such as Little Leaguer's elbow, tennis arm, swimmer's shoulder, Osgood-Schlatter disease, Sever's disease, and stress fractures.[72] In the child, ligaments are stronger than the epiphyses, so injuries are more likely to involve epiphyseal problems rather than be simple sprains. This type of injury then will require a more definitive treatment, such as protection, until the epiphysis heals, but more importantly, epiphysial injuries are often undetected.

To prevent problems caused by overuse, many sporting associations limit the amount of time a player uses particular

muscle groups; for instance, U.S. Little League baseball limits the number of innings that young players can pitch to six per week. To be successful, this system still relies on the coach placing the child's welfare above everything else, limiting the number of pitches allowed during a training session, and educating the child so that he or she restricts throwing activities when not under supervision. Similarly, restrictions have been advocated to prevent the frequent back injuries in young "fast bowlers" in cricket[73] and to prevent running injuries by limiting competitive race distances for children of various ages.[74]

Larson and McMahon[75] reported on 1338 athletic injuries in the area around Eugene, Oregon; 20% of these injuries occurred in the age groups 14 years and younger, which consisted of 60% of the participants, whereas 40% occurred in the group 15 to 18 years old, which constituted only 15% of the participants. This study indicated that the 15- to 18-year-old group is the most vulnerable to athletic injury. They found that 1.67% (23) were epiphysial injuries but claimed that although growth deformity can occur afterward, this type of injury is the exception rather than the rule. Most cases of epiphysial displacement were easily reduced with traction and gentle manual pressure, and only rarely was open reduction necessary.

Australian studies by Davidson and coworkers[76] and Sugarman, reported by the Australian Football Schools Union,[77] also indicate the low incidence of injury in the younger children, even in collision sports such as rugby. It is only as the boys become mature, and develop the muscle bulk and speed which contribute to greater momentum and coordination and the desire to "hit" rather than tackle, that the incidence of injury becomes a real concern.

However, even if the number of injuries is less than once believed and even if, as Larson and McMahon claim, they can be successfully treated medically, prevention should be the aim. Prevention efforts will involve an adequate level of preseason conditioning and emphasis on skills to ensure correct mechanics. Tennis elbow in adults is certainly related to overuse and faulty stroke mechanics.[78] Thus all coaches should modify an activity (such as by using two-handed backhand) or reduce the number of repetitions of an activity that places too much stress on young bones and joints.

Based on reports on heel cord injuries, epiphysial growth plate injuries, and other chronic joint trauma as a result of long-distance running, the American Academy of Pediatrics[79] has, in the interest of prevention, issued the following statement:

> Long distance competitive running events primarily designed for adults are not recommended for children prior to physical maturation. Under no circumstances should a full marathon be attempted by immature youths (less than Tanner Stage 5 sexual maturity rating). After pubertal development is complete, guidelines for adult distance running are appropriate.

The Australian Sports Medicine Federation[74] recommended that the maximal permitted competitive running distances for children under 12 years, 12 to 15 years, 15 to 16 years, and 16 to 17 years of age be 5 km, 10 km, a half marathon, and 30 km, respectively. Those 18 years of age and older should be permitted to run a full marathon race. The Federation also recommended that the maximal weekly training distance be no more than three times the recommended race distances.[74]

There is not enough evidence to prove or disprove the need to limit the amount and intensity of vigorous training; however, it appears prudent to err on the side of caution until such studies are performed. After reviewing the injury risks to children in sports, Larson and McMahon[75] drew the following conclusion:

> A more vigorous type of life will produce more wear and tear on joint surfaces than a sedentary one. However, the benefits derived by children participating in athletics, such as physical fitness, learning to meet competition, and the discipline of an organized athletic program outweigh such an indefinite potential.

LEVEL OF MATURITY AND SPORTS PERFORMANCE

In sports, the different levels of performance at a given age are often the result of different levels of maturity rather than of skill. For instance, Cumming and associates[80] showed that the level of performance in track-and-field events was more closely related to skeletal age than chronologic age, height, or weight. Mero and colleagues[81] have also shown that endurance capacity and strength were greater in an athletic group than in a control group and that the athletic group demonstrated an advanced biological maturity. Clarke[68] found that the skeletal age of children who were aged 13 years chronologically varied from 8 years, 10 months to 15 years, 11 months.

Advanced maturity imparts not only an increased body size, lactacid anaerobic ability, increased ability to store glycogen, and increased strength and muscle bulk, but also an increase in speed and power. Speed, which increases with age at least to the age of 18 for boys and 14 for girls, is probably due to the maturation of the nervous system.[34] Speed is related more closely to maturity level than height because at any given age, the running speed is usually not different in children of different heights, except for boys around the age of puberty. Boys around 14 and 15 years of age have increased running speed with increased height, probably because the taller boys are more mature.

The rate of growth and development is as individual as physique, eye color, and other personal characteristics.[82] Therefore, because junior sports programs should try to provide optimal participation and fair competition with a minimal risk of injury, classification on the basis of chronologic age is not satisfactory. This is especially true in events in which speed, size, and strength are important for successful performance. Probably the best criteria for matching competitors in sports should include maturity, age, height, weight, skill, and, where indicated, gender. The five stages of genital development or pubic hair development as described by Tanner[83] are adequate means of scoring maturity, and certainly no one classified in stages 1 or 2 should compete against anyone classified in stages 4 or 5, regardless of chronologic age. Shaffer[82] suggests estimating maturity level simply by observing secondary sexual development, namely the axillary and pubic hair, rather than organ development. He also suggests that girls' date of menarche is often adequate for determining maturity level.

Although the early maturers may have a distinct advantage in sports at an early age, they may suffer long-term disadvantages compared to the late maturers. Late maturers who do not become "sporting dropouts" because of discouragement from continual failure often spend a great deal of time acquiring skill so that they may compete. Many of the early maturers, however, because they are bigger and stronger, spend little time developing skill. They are content to use bulk rather than finesse, and unfortunately this practice is encouraged by many so-called coaches, especially in collision sports. As a result, these early maturers often become relegated to the second team when the late maturers eventually reach a similar size and develop similar speed and strength. Because success usually promotes continued interest and effort, lack of success often leads to hatred of the specific sport and often all forms of physical activity; as a result, many early maturers terminate their sporting careers before reaching their 20s.

CONCLUSION

If the effects of regular frequent exercise are plotted on the y-axis against the amount of exercise on the x-axis, the graph would take the shape of an inverted U. That is, little or no regular exercise has detrimental effects on the child and may be associated with some of the hypokinetic diseases such as heart disease and obesity in later life. As the volume of regular exercise is increased, there are increasing benefits, including increased capacity and efficiency of the cardiorespiratory, muscular, and metabolic systems, leading to greater work capacity. If, however, the volume and intensity of regular exercise become excessive, detrimental effects, especially stress fractures, overuse injuries, and even chronic fatigue syndrome, are likely.

All children require regular exercise for normal growth and development and for the development of minimal levels of health and fitness. Although many children today have far too little exercise, there are others who begin very intensive physical training for sports at an early age. Many children in age-group sports participate in unfair competition because chronologic age alone is used as the means of classification. In collision sports, this can be dangerous for the late maturer.

The physiologic responses to acute exercise and to training are similar in children and adults, and for the most part, these responses are beneficial. The pediatrician must understand these responses and be aware of the role of exercise in the possible prevention and management of many diseases such as asthma, cystic fibrosis, diabetes mellitus, hypertension, obesity, and cerebral palsy. The pediatrician must realize that although no sport is risk free, sports-related injuries can be minimized with proper preparticipation medical screening, with supervision, and with the use of protective equipment. Activities such as weight training, weight-lifting, and long-distance running are becoming popular with children and teenagers; therefore the advice of pediatricians to parents, sport administrators, and participants concerning what is safe and what can be hazardous at various ages can be very effective in minimizing detrimental outcomes. The desirability of regular, appropriate, supervised physical training is not in question and should be recommended on the basis of improved health, fitness, and performance capabilities.

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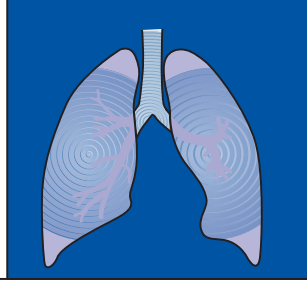

CHAPTER 9

Breathing in Unusual Environments

Michael A. Wall

TEACHING POINTS

- Ambient pressure increases most rapidly during the first 10 m of a dive. Thus pulmonary barotrauma can occur on ascent from relatively shallow depths.
- Children with obstructive lung diseases such as cystic fibrosis or bronchiectasis as well as children with any cystic lung pathology should not scuba dive.
- Children with asthma should be cautious about scuba diving. In general, children with current asthma, an exacerbation of asthma in the last 2 years, or a history of cold air induced bronchospasm should not dive. Others should be counseled on an individual basis.
- Most children with chronic lung disease who do not need supplemental oxygen on a daily basis will be able to take commercial flights without oxygen.
- Children with unilateral pulmonary hypoplasia are especially prone to the development of high altitude pulmonary edema.
- Children with CO poisoning may have extreme levels of tissue hypoxia yet will not be cyanotic. Thus, all children who are fire victims should be assumed to have CO poisoning until proven otherwise.

DIVING

A large number of medical conditions have been associated with breath-holding and scuba diving, and many texts and review articles on the subject are available as well as excellent websites.[1-5] This section concentrates on risk factors for injury that may be especially applicable to children with lung disease.

Diving Physics

The major health risks to divers (other than drowning) are related to the behavior of gases in conditions of changing ambient pressure. In essence, there are three ways that a human being can descend in the water (Fig. 9-1). In a submarine the hull resists compression, and the pressure inside the hull (and lungs) stays at about 1 atm. Thus for the crew, the situation is no different than breathing at sea level. During a breath-hold dive, the chest wall and lungs are compressed by ambient water pressure, pressure in the lungs increases to ambient pressure, and the volume of gas in the thorax decreases according to Boyle's law (in a closed system under conditions of constant temperature, the volume of gas is inversely proportional to the pressure applied to the system). On ascent, the ambient pressure around the thorax decreases, and the lungs re-expand to approximately their original volume when the diver reaches the surface. Thus, a breath-hold dive does not expose a diver to the risks associated with having the pressure in the lungs exceed ambient pressure. During scuba diving, however, one breathes compressed air at the ambient pressure of the water at any given depth and maintains relatively normal thoracic gas volume. The breathing of air at ambient pressure is made possible by the special features of scuba equipment. Typically this involves a two-stage regulator system. The first-stage regulator sits on top of the high-pressure tank and reduces the pressure in the scuba system from several thousand pounds per square inch to about 100 psi above ambient pressure. A second-stage regulator is located at the mouthpiece and reduces the gas pressure to ambient. This allows the diver to make a comfortable inhalation. At the end of inspiration, the pressure inside the lungs is equal to ambient as seen in Figure 9-1.

As a diver descends from sea level, the ambient pressure increases by 1 atm for every 10 m. Figure 9-2 depicts the relative changes in gas pressure and volume in a closed system as depth increases in increments of 10 m. For instance, as one goes from the surface to a depth of 10 m the absolute ambient pressure doubles and gas volume in a closed system will decrease by 50%. Gas volume does not decrease by another 50% until the diver reaches a depth of 30 m. Inspection of Figure 9-2 demonstrates that on a relative basis, the most change in ambient pressure occurs at the shallowest depths. This is why barotrauma caused by rapid expansion of gas often occurs as a diver ascends from relatively shallow depths.

The general principle to be understood is that local rupture is a risk if gas can get into an area under high pressure but cannot escape rapidly as it expands during ascent. Such conditions can arise if a diver holds his/her breath and ascends rapidly or if gas can get into a space but its egress is partially blocked (e.g., a partially blocked airway, a narrowed sinus opening, a partially blocked eustachian tube).

Another gas law particularly relevant to scuba divers is Henry's law. Henry's law states that the amount of gas dissolved in a liquid at a constant temperature is proportional to the partial pressure of that gas. Henry's law explains that as ambient pressure in the lungs increases during scuba descent, more and more oxygen and nitrogen (the major components of room air) dissolve into the blood. As long as the diver stays down, this is not a problem in regard to the risk for decompression illness. However, as the diver ascends

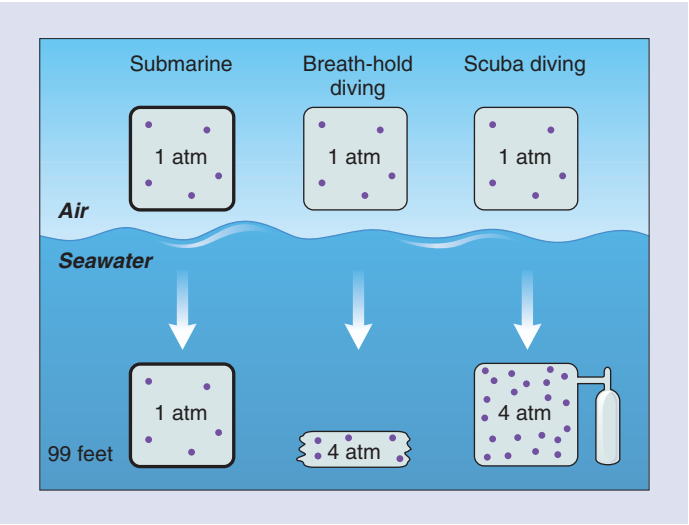

Figure 9-1 Impact of the three methods of submersion on intrapulmonary pressure and thoracic gas volume. Atm, atmosphere. (Redrawn with permission from Strauss RH [ed]: Diving Medicine, New York, Grune & Stratton, 1976.)

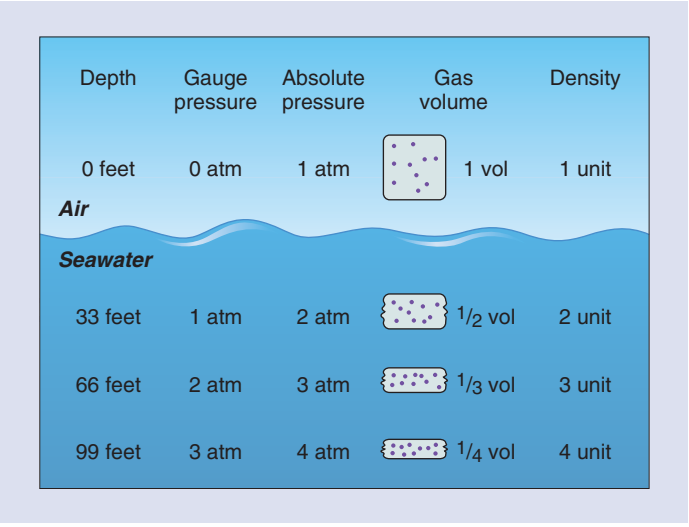

Figure 9-2 Effect of increasing depth on relative ambient pressure and gas volume. Atm, atmosphere. (Redrawn with permission from Strauss RH [ed]: Diving Medicine, New York, Grune & Stratton, 1976.)

and ambient pressure decreases, the gas that dissolved in the blood during descent is going to reverse direction and come out of solution (especially the inert nitrogen; most of the oxygen is metabolized). If ascent is too rapid, the gas coming out of solution will form small bubbles in the bloodstream that can lodge in crucial blood vessels and cause localized ischemia.

Pulmonary Barotrauma

CAUSE

Boyle's law explains one of the most potentially dangerous medical aspects of scuba diving: barotrauma associated with rapid ascent. Assume that a scuba diver is breathing tidally at a lung volume of 50% of total lung capacity (i.e., around functional residual capacity) at a depth of 30 m. The gas pressure in the lungs will be 4 atm (same as ambient). The diver then ascends to 10 m with the glottis and mouth tightly closed so that no gas can escape. At the new depth, the pressure in the lungs is still 4 atm, whereas the ambient pressure is 2 atm, and the thoracic gas volume doubles to total lung capacity. If the diver then continues to ascend with the mouth closed, the lung volume cannot expand to any significant degree and transpulmonary pressure increases. At total lung capacity, the transpulmonary pressure is usually 40 to 50 cm H_2O. When it reaches 80 to 100 cm H_2O, lung rupture ensues, leading to pneumothorax, pneumomediastinum, or air embolism. If a diver starts a closed-mouth rapid ascent at total lung capacity, which commonly occurs in panic situations, lung rupture occurs much sooner than if the ascent started at functional residual capacity. In fact, a rapid ascent from 2 m below the surface can cause lung rupture if one starts at total lung capacity.

For these reasons, scuba divers are instructed to ascend in one of two fashions. The usual ascent is made slowly while breathing in and out. During such an ascent lung pressure will equal ambient, so lung rupture is avoided. If an emergency ascent is required, divers are instructed to exhale actively or keep the mouth and glottis open all the way to the surface.

The same principles that cause pulmonary barotrauma can cause medical problems in other air-containing spaces. Rapid ascent can cause middle ear or sinus rupture if the diver ascends too quickly. This is especially true for children who have a history of recent middle ear or sinus disease.

SIGNS AND SYMPTOMS

Lung rupture may cause mediastinal emphysema, pneumothorax, air embolism, or any combination thereof. The signs and symptoms of mediastinal rupture include chest pain, dyspnea, subcutaneous crepitus, dysphagia, and voice changes. Pneumothorax presents initially as sudden chest pain with dyspnea. Because air in the pleural cavity continues to expand until one reaches the surface, tension pneumothorax with decreased cardiac output is common. Air embolism is thought to result from rupture into the pulmonary veins with subsequent carriage of air bubbles into the arterial system. The bubbles lodge in small arteries virtually anywhere in the body, with the cerebral and coronary systems being the common sites. Thus, air embolism may manifest as a sudden stroke with focal or global consequences or as a myocardial infarction.

TREATMENT

Mild mediastinal emphysema usually requires no treatment, although administration of oxygen may hasten its resolution. Divers thought to have a pneumothorax should be given oxygen in high concentration and transported to the nearest hospital for appropriate treatment, which may range from administration of oxygen to placement of a chest tube. Emergency, on-site relief of pressure from a tension pneumothorax may be required if cardiac output is severely impaired. Victims of suspected air embolism should be given high-concentration oxygen and transported in an emergent fashion to the nearest hyperbaric facility. In the United States, one can call the Divers Alert Network *(www.diversalertnetwork.org)* 24 hours a day for advice and consultation (1-919-684-8111).

Decompression Sickness

CAUSE

During descent, nitrogen and oxygen are breathed at ambient pressure and dissolve into the bloodstream and tissues. Much of the oxygen is consumed by metabolic demands, but the bulk of the nitrogen remains dissolved in a supersaturated fashion. The total amount of nitrogen dissolved in blood and tissues increases as a function of both depth and bottom time. Decompression sickness (the bends or caisson disease) is caused by the release of nitrogen bubbles into the tissues and arterial system on ascent. These bubbles may lodge anywhere and cause local ischemia. They have a particular predilection to lodge in cerebral, myocardial, and bone locations.

SIGNS AND SYMPTOMS

The signs and symptoms of decompression sickness may include pruritus, back and joint pain, neurological dysfunction such as spinal cord paralysis and stroke, and chest pain caused by myocardial infarction.

TREATMENT

As with barotrauma, prevention is of utmost concern. Detailed tables are available to advise divers of their safe bottom time at any depth. This is the time a diver can stay at any given depth and safely ascend to the surface without making stops to decompress along the way. The tables will also inform divers of the time they must stay on the surface before another dive. Treatment includes the immediate administration of oxygen, stabilization on return to shore, and transport to a hyperbaric chamber facility.

Recommendations for Children with Lung Disease

Patients with obstructive lung disease may be especially prone to lung rupture during ascent from scuba diving. The reason is that areas of the lung communicating only poorly with the airways may not have enough time to empty before regional transpulmonary pressure rises to a level that causes rupture. This phenomenon depends on the time constant of the area in question, the relative volume in the area before ascent, and the rate of ascent. Examples of lung diseases that could predispose a diver to lung rupture include cystic fibrosis, bronchopulmonary dysplasia, and current asthma. An additional group of patients who should avoid scuba diving are those who have had a previous spontaneous pneumothorax or who have a condition that might predispose to pneumothorax (e.g., Marfan syndrome, Ehlers-Danlos syndrome). Although these patients do not have obstructive lung disease, they are thought to be at risk because lung rupture may occur at a lower transpulmonary pressure than in people without such risk factors.

The most frequent question asked of pediatric pulmonologists in regard to scuba diving is whether to allow a child with current or past asthma to participate in the sport. The medical problems related to asthma and diving in adults have been reviewed.[6-8] About 8% to 10% of recreational divers claim a current and/or past history of asthma, which is no different than the general population. The consensus of the literature indicates that the odds ratio related to asthma for a diving related medical emergency (arterial gas embolism) is elevated to about 1.5 to 2.0; this did not reach statistical significance.[6-8] Scuba diving exposes the diver to the inhalation of cool, relatively dry gas. In addition, the diver may hyperventilate because of excitement, exercise, or panic. Divers often inhale small amounts of hypertonic water because of issues with their mask or a small leak around the mouthpiece. Thus, scuba diving certainly exposes the diver to an environment that is well known to stimulate asthma exacerbations in some children. An additional risk factor for a few children is latex in the rubber tubing of scuba equipment. Various medical and diving societies have different recommendations for allowing asthmatics to dive. It should be noted that there are no data pertaining to whether pretreatment with a beta-2 agonist before diving will prevent an asthma exacerbation during scuba diving. Given this information and the current state of the literature regarding asthma and scuba diving the following recommendations seem reasonable:

1. Preteens with a history of asthma should not scuba dive. There are no universally accepted laws concerning the age at which a child may be certified to dive. In general, most diving societies will allow children to begin to learn to dive at about age 10 to 12 years and will allow certification at about age 15. A major limitation for any child learning to dive is their response to panic and fear. Brief episodes of panic/fear are common for inexperienced divers and are caused by factors such as claustrophobia, inhaling some water, bumping into coral, seeing a predator fish, and so on. The issue is that divers need to have the mental capacity to recognize when panic is setting in and to remain in control. This mental maturity is lacking in most young children (and some adults). If a child adds hyperventilation or cold air-induced bronchoconstriction to a panic situation it can only make things worse. In addition, some children cannot recognize the early onset of airway constriction or may feel compelled to continue a dive for social reasons.
2. Children with current asthma or who have had a significant exacerbation in the past 2 years should not dive.
3. Children with a past history of asthma with current abnormal lung function should not dive. All asthmatic children should at least have spirometry performed prior to starting scuba training.
4. Children with a history of exercise, cold air, or hyperventilation-induced asthma should undergo a cold air challenge. If positive, they should not dive.
5. A child who requires controller medications to remain asymptomatic and who has a history of noncompliance should not be allowed to dive.
6. Children with a history of mild asthma who have had no exacerbations in the past 2 years, who have normal spirometry and cold air challenge if indicated, and who are compliant with medications, may be allowed to dive under strictly supervised conditions. This author would not sign a child's permission prior to a personal medical evaluation, an evaluation of the child's maturity and understanding of asthma, pulmonary function testing, and an in-depth discussion with the parents.

Other Medical Problems Associated with Diving

Patients with sinus disease may develop barotrauma on ascent in a fashion similar to pulmonary barotrauma. This usually manifests as pain over the frontal sinuses with epistaxis and responds to conservative therapy with decongestants.[2] Recurrent otitis or serous otitis is another contraindication to breath-hold or scuba diving because barotrauma may occur during descent or ascent. The signs and symptoms range from a feeling of pressure and pain to tympanic rupture, hematotympanum, conductive hearing loss, and vertigo.[3] The etiology is an inability to equalize middle ear pressure with ambient pressure, which is usually caused by blockage or swelling of the eustachian tube. Treatment ranges from decongestants to surgery—depending on the extent of injury.

ALTITUDE AND AIR TRAVEL

Air is much less dense than water, and a person must ascend to an altitude of about 5450 m (18,000 ft) before the ambient pressure decreases to 0.5 atm. The major potential problem of ascent above sea level for children with lung disease is hypoxemia. Barometric pressure decreases in an exponential fashion with altitude (Fig. 9-3), although from sea level to 4000 m the relationship is for all practical purposes linear. The most frequent questions concerning children with lung disease and altitude are about air travel during which the cabin is pressurized to an altitude of 1500 to 2400 m. The author has also been asked to give recommendations concerning hang gliding, skiing, and the feasibility of obtaining a pilot's license.

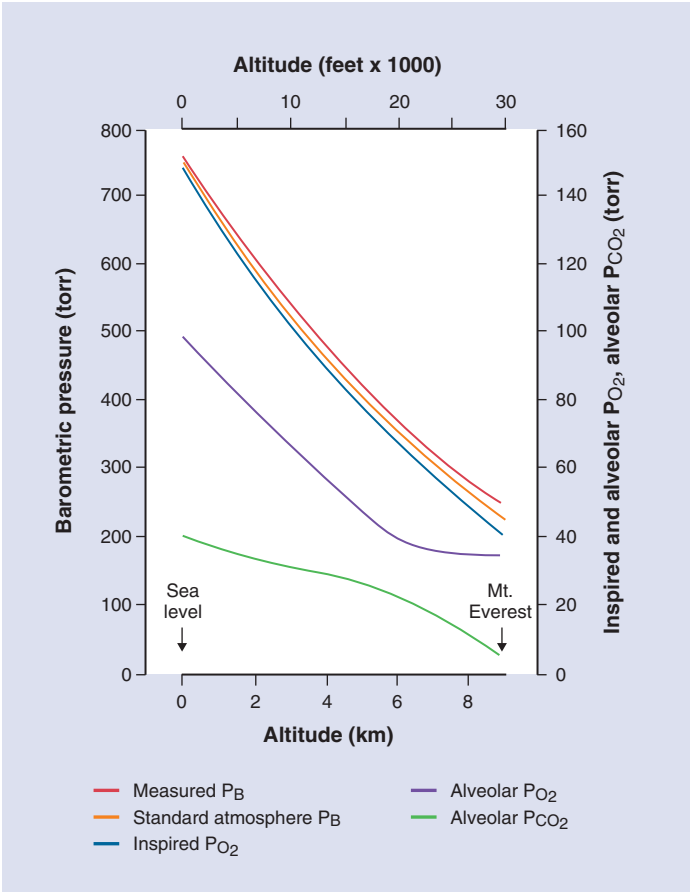

Figure 9-3 Effect of altitude on barometric pressure (Pb), the fraction of inspired oxygen, and alveolar P_{O_2}. (Redrawn with permission from West JB. In Crystal RG, West JB [eds]: The Lung. New York, Raven, 1991, pp 2093-2108.)

At 1500 m the alveolar oxygen partial pressure (P_{aO_2}) in a normal person will be about 74 mm Hg; at 2400 m, it will be about 60 mm Hg. Assuming a normal alveolar-arterial oxygen gradient, arterial P_{aO_2} should be in the range of 67 to 55 mm Hg. However, normal people hyperventilate somewhat at this range of P_{aO_2}, so the actual arterial P_{aO_2} is usually slightly higher. For any patient with chronic lung disease, a precise prediction of arterial P_{aO_2} when going from sea level to altitude is difficult because there is considerable variation in terms of ventilatory control mechanisms and mechanical ability to hyperventilate. Nonetheless, many patients with a sea level arterial P_{aO_2} of 55 to 75 mm Hg will show decreases in P_{O_2} to the range of 38 to 50 mm Hg as they ascend to 2400 m. Regression equations have been published relating ground-level arterial P_{aO_2} and the 1-second forced expiratory volume to P_{aO_2} at altitude that can serve as guidelines for clinical decision making.[9]

Several papers have been published reporting the effect of transient, altitude-related hypoxemia in adults with chronic obstructive pulmonary disease (COPD). The majority of these patients were elderly, and many had cardiovascular conditions that would not be present in children. In one study, 18% of adults with COPD who flew in commercial aircraft without supplemental oxygen had transient symptoms, but none had a serious medical incident.[10] In another study the same research group showed that 12 of 18 COPD patients exposed to hypobaric pressure simulating an altitude of 2400 m had a P_{aO_2} of less than 50 mm Hg, but none developed serious medical problems.[11] In an experimental setting, patients with cystic fibrosis have the same decrease in P_{aO_2} as adults with COPD.[12]

Patients already requiring preflight oxygen therapy will need at least the same amount of oxygen during air travel and perhaps more. For patients who do not require preflight oxygen, the situation is not as clear. The majority of young patients whose P_{aO_2} is greater than 55 mm Hg can tolerate the cabin altitude of air travel without supplemental oxygen with minimal discomfort. Patients whose P_{aO_2} is less than 55 mm Hg may need to arrange for in-flight oxygen.

In the United States, there are no standard policies or procedures for obtaining oxygen from an airline or for the delivery system to be used. Passengers are generally not allowed to use their own delivery systems but exceptions are made especially for those patients using ventilators. At this point, the best suggestion is to contact the particular airline in question well in advance of the flight to determine its rules. Many of the airlines have their oxygen regulations posted on their website. Virtually all airlines charge a fee for oxygen. A physician's prescription will be required and must state the flow to be maintained. It should be noted that airlines will not provide oxygen in the terminal. Other suggestions for travelers needing oxygen include: arrange for wheelchair assistance in advance; try to get an aisle seat; bring extra long cannula tubing; and make sure the vendor is set to deliver oxygen at the destination.

Barotrauma may be a concern for patients who have cystic lung disease or areas of the lung that communicate

poorly with the airways. The latter is almost purely theoretical because it would take a very rapid ascent to overcome even a very slowly emptying time constant. If a patient had a noncommunicating cyst at sea level that was fully expanded with a regional transpulmonary pressure of 40 to 50 mm Hg, then rupture would theoretically be possible on ascent to cabin altitudes of 4000 to 8000 ft. Reports of such events are exceedingly rare but the author reminds patients with advanced cystic fibrosis or other cystic lung diseases about the symptoms of pneumothorax as they prepare for air travel.

The author has received many questions from teenagers and young adults with cystic fibrosis concerning the potential altitude-associated risks of snow skiing. The summits of many resorts in the western United States are at altitudes where even sedentary patients may experience some discomfort, and with exercise, such patients may become quite dyspneic. The author advises patients with moderate to severe obstructive lung disease that they may become somewhat uncomfortable skiing at high altitudes but note that many have chosen to ski anyway with no long-lasting consequences. Teenagers and young adults with cystic fibrosis have also asked the author whether they would be able to obtain a private pilot's license. In the United States, all people who wish to obtain a pilot's license must pass a physical examination administered by a Federal Aviation Administration–approved physician. In the guide for examiners, no specific statements disqualify someone with a childhood lung disease, although moderate to severe asthma and bronchiectasis are both listed as relative contraindicators.[13] Each case is considered on an individual basis by the examiners. It has become the author's policy to advise hypoxemic patients that they probably would not pass the medical examination and that their medical history and laboratory results will be forwarded on request.

Acute Altitude-Related Problems

At altitudes above approximately 2500 m, even young, well-conditioned athletes may begin to experience altitude-related problems. Above 4000 m the incidence increases to about 40% to 50%. Acute mountain sickness is a syndrome in which headache is a universal feature; other signs and symptoms include lassitude, nausea, anorexia, and palpitations.[14] Acute mountain sickness may be accompanied by all the features of acute cerebral edema. The etiology of acute mountain sickness has not been completely elucidated but appears to include factors related to hypoxia, increased cerebral blood flow, fluid retention, and capillary leak.[14] Slow acclimatization is the best preventive measure and the best "treatment" for acute mountain sickness is descent. Various medications can help in prevention and treatment and have been recently reviewed.[14]

Acute high-altitude pulmonary edema is noncardiogenic in origin and may manifest in the context of acute mountain sickness or as an isolated phenomenon. Slow acclimatization can help reduce the incidence of high-altitude pulmonary edema but does not eliminate it. Unilateral pulmonary hypoplasia may be a particular risk factor for children.[15] The signs and symptoms usually start with dry cough and proceed to dyspnea; orthopnea; diffuse crackles; pink, frothy sputum; and cyanosis. The only definitive treatment is rapid descent, although administration of oxygen and continuous positive airway pressure will help. Nifedipine may be efficacious for prevention and treatment.[14]

CARBON MONOXIDE POISONING

Carbon monoxide (CO) is an odorless, colorless gas present in minute quantities in the atmosphere. CO is produced by incomplete combustion of carbon-containing compounds such as wood, hydrocarbons, and coal. Lethal concentrations of CO can be found in the blood of 50% of fire victims, and all burn victims should be assumed to have CO poisoning until it is proved otherwise. In addition to house fires, children can be exposed to high levels of CO via indoor heaters, wood stoves, indoor grills, automobile exhaust, and other sources.

Disease Mechanisms

Traditionally CO has been thought to cause poisoning by producing a functional anemia and by decreasing tissue oxygen availability. CO has a binding affinity for hemoglobin 240 times that of oxygen, so the competition for binding sites is heavily weighted toward CO. Thus, CO poisoning causes a functional anemia because any hemoglobin site bound by CO is virtually unavailable for oxygen binding. CO poisoning leads to tissue hypoxia because the presence of carboxyhemoglobin in the blood causes a leftward shift in the oxyhemoglobin dissociation curve (Fig. 9-4). This leads to increased binding of oxygen to hemoglobin so that at any given Pa_{O_2} the amount of oxygen released to tissues is decreased. However, current evidence suggests that the pathophysiology of CO poisoning is much more complex than initially thought. For instance, carboxyhemoglobin levels in the blood correlate

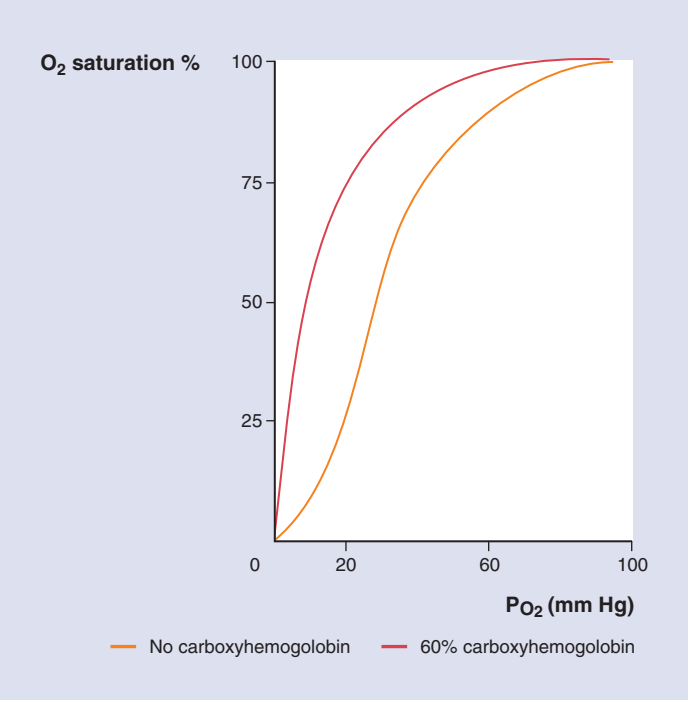

Figure 9-4 Effect of carboxyhemoglobin on the shape of the oxygen-hemoglobin dissociation curve. Note that at an arterial Pa_{O_2} of 20 mm Hg, 75% of the bound oxygen has been released to tissues in curve A versus only 25% in curve B.

poorly with clinical symptoms,[16] and in cross-transfusion experiments the presence of moderate levels of carboxyhemoglobin does not lead to toxicity.[17] CO binds to the cytochrome oxidases and other proteins involved in the intracellular oxygen-transport system, and the weight of evidence suggests that CO toxicity is probably mostly due to disruption of intracellular oxidative mechanisms.[16]

Clinical Manifestations

The initial signs and symptoms of CO poisoning are diverse and may be confused with viral illness. The first symptoms often include headache, nausea, dizziness, and blurred vision. As toxicity increases neurologic and cardiovascular symptoms predominate and include confusion, syncope, seizures, dyspnea, and hypotension. In the end stages, signs and symptoms include myocardial infarction, coma, and cardiopulmonary arrest.

Assessment

As noted earlier, all fire victims should be assumed to be suffering from CO poisoning until proved otherwise. Because the early symptoms are nonspecific, a high degree of suspicion is required. A history of potential exposure should be obtained for children presenting with viral-like symptoms but no fever. Because carboxyhemoglobin is well known to be "cherry red," cyanosis is not a reliable physical finding. Spectrophotometric measurement of carboxyhemoglobin concentration is the most reliable method of diagnosis. Co-oximetry is required to measure "true" oxygen saturation in the setting of CO poisoning. The standard measures of oxygenation used in most emergency rooms and intensive care units are of limited use in determining CO poisoning. Arterial P_{O_2} is usually normal in CO poisoning because this test measures only oxygen dissolved in the plasma. Oxygen saturation as determined by a pulse oximeter also needs to be interpreted with caution. The standard pulse oximeter uses only the wavelengths required to measure levels of oxyhemoglobin. However, the critical wavelength for carboxyhemoglobin is very close to that of oxyhemoglobin and thus, standard pulse oximetry measures the percent saturation of both molecules. In fact, the gap between oxygen saturation measured by co-oximetry and pulse oximetry will be very close to the carboxyhemoglobin level.[16]

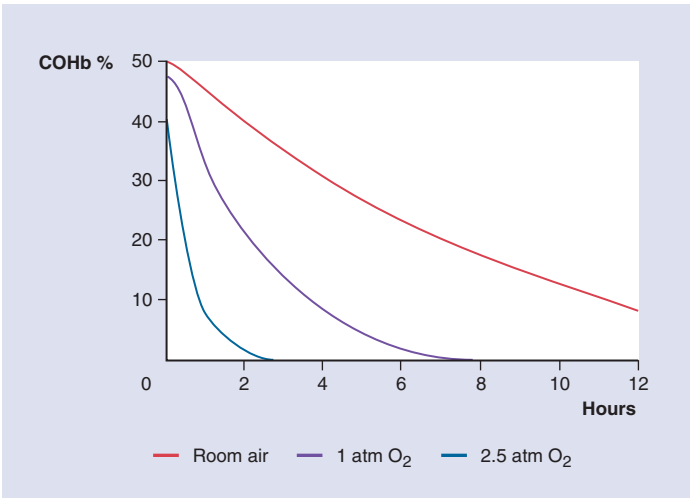

Figure 9-5 Effect of oxygen at varying concentrations and ambient pressure on the elimination of carboxyhemoglobin. (Redrawn with permission from Winter PM, Miller JN: Carbon monoxide poisoning. JAMA 236:1502-1504, 1976.)

Therapy

The only definitive therapy for CO poisoning is administration of oxygen. Oxygen significantly reduces the biological half-life of CO and should be administered in high concentration via a nonrebreathing mask to all burn victims until a carboxyhemoglobin level is obtained. Hyperbaric oxygen therapy offers two theoretical advantages. As seen in Figure 9-5, increasing the pressure at which oxygen is administered further reduces the half-life of carboxyhemoglobin. In addition, hyperbaric therapy increases the amount of oxygen dissolved in the plasma to levels that can almost sustain life even in the absence of hemoglobin. However, a recent Cochrane review concluded that there is no good evidence to support its use in reducing adverse neurologic outcomes.[18] In addition, hyperbaric oxygen is available only in a few locales, and bedside intensive care is virtually impossible in a hyperbaric chamber, so for most patients, such therapy is impractical.

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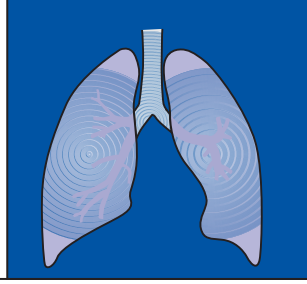


CHAPTER 10 Clinical Assessment and Diagnostic Approach to Common Problems

Mark A. Brown, Erika von Mutius, and Wayne J. Morgan

TEACHING POINTS

- Adapting the mnemonic device PQRST (provocation/palliation; quality; radiation or associated symptoms; severity; timing) may be helpful in systematically characterizing respiratory symptoms.
- The respiratory examination involves thorough inspection, palpation, percussion, and auscultation of the chest, as well as the relevant components of several other body areas, including the upper airway. It is not sufficient to merely listen to the chest.
- Frequent cough without colds should not be seen in healthy, normal children and thus deserves further evaluation.
- Extrathoracic airway obstruction leads to worsened obstruction on inspiration. Progression of upper airway obstruction to biphasic (inspiratory and expiratory) obstruction is a sign that critical airway obstruction is developing.
- In the absence of palpitation and/or syncopy, chest pain in children is rarely due to a cardiac etiology.
- The diagnosis of chronic bronchitis should occur in two phases. The first is consideration and identification of several well-defined respiratory disorders according to a staged management protocol. The second but simultaneous phase is elimination or modification of exogenous factors that produce or maintain the child's illness.

For millennia, the mark of the healer or physician was the ability to discern the nature of a patient's illness through careful questioning, observation, and examination. However, over the past half century or more, practitioners have for a variety of reasons come to rely more and more on technologic means of diagnosis. Although always important, the art of physical diagnosis will likely reassume greater importance in clinical practice in the future because of the growing emphasis on cost containment and the likelihood of limited access to certain technologies. This chapter focuses on clinical assessment of the respiratory system in children. There is much overlap between the respiratory examination and that of other systems, and it is assumed that the reader has mastered basic physical examination skills. Several excellent resources for the general physical examination are listed in the references.[1,2]

HISTORY

The extent and focus of the history (and physical examination) are dictated by the patient's pressing complaint. With few exceptions, there is no such thing as a "routine history and physical," both those activities being tailored to fit the particular complaint that the patient has. An extended history may not be necessary in every case. For example, it would not be necessary to inquire into the stool characteristics of a patient presenting for evaluation of snoring. Careful attention should be paid to the patient's narrative, followed by probing, nonleading questioning and clarification of key points. The exact order of elicitation is not as important as a consistent general routine covering all aspects pertinent to the patient's complaint.

Most physicians begin with the history of present illness, although in younger pediatric patients, it may be appropriate to begin with the antenatal and birth histories. Often the first step is to elicit the chief complaint with an open-ended statement or question. It is generally better not to accept a diagnosis as the reason for seeking consultation. The clinician should insist on hearing the symptoms that promoted concern in the patient's own words. Obviously, information such as the circumstances at onset, frequency, duration, and severity is important. Adapting the mnemonic device PQRST (provocation/palliation; quality; radiation; severity; timing) may be helpful in systematically characterizing a symptom. Associated symptoms such as fatigue, exercise induction or intolerance, and viral syndrome are important to note as well. The results of prior evaluations should be solicited and every effort made to obtain the actual reports or images of previous procedures, including those from pulmonary function tests. Information about previous therapies used and the response or lack thereof can provide important clues as to possible etiologies and may allow an assessment of adherence as well.

The antenatal, birth, and neonatal histories in general should be reviewed; the detail that is necessary depends on the individual. The duration of the pregnancy, together with any complications, including maternal medications and substance use or abuse (including tobacco), should be noted.

Previous respiratory problems, including respiratory illnesses, hospitalizations, and pulmonary injuries (e.g., chest trauma or surgery, smoke inhalation), should be explored in

detail, especially as they relate to airway instrumentation (e.g., endotracheal intubation, bronchoscopy). A history of recurrent pneumonia may suggest immunodeficiency, cystic fibrosis, anatomic abnormality, dysfunctional swallowing, or bronchiectasis. The child with a history of tracheoesophageal fistula repair is prone to tracheomalacia and gastroesophageal reflux–related disease.[3] Survivors of adult respiratory distress syndrome initially have restrictive lung disease, followed later by peripheral airway obstructive disease.[4,5] Evidence of atopy, such as eczema, atopic dermatitis, hay fever, or known allergies, may be important in the child with chronic cough or recalcitrant asthma. A history of frequent infections, blood product transfusion, parental substance abuse, or poor growth may be a clue to an underlying immunodeficiency. Risk factors for human immunodeficiency virus infection, both iatrogenic and behavioral, should be carefully explored because this is the most common cause of immunodeficiency in many countries.

The family history may provide valuable information. It is often fruitful to probe using a variety of terms; for example, *chronic bronchitis*, *wheezy bronchitis*, and *asthmatic bronchitis* are all frequently used to describe asthma. There may be terms in the local vernacular, especially in areas where segments of the population use traditional healers, with which the practitioner should become familiar. It is also important to elicit a family history of illnesses unlikely in the child, such as a parent or grandparent with recent lung cancer, because this may disclose a cause of undue anxiety about a cough or another respiratory symptom.

The social history is always important, if for no other reason than because it provides a better understanding of the patient's circumstances, potentially yielding information helpful in both making a diagnosis and planning therapy (e.g., assessing the likelihood of adherence problems). Specific items to be elicited include the makeup (number, age) of the household unit and the family's living arrangements (house, trailer, apartment). School or day-care attendance or child care arrangements should be reviewed, with attention paid to the environment there as well (see later section). Hobbies may also be important, especially those involving exposure to dusts, paints, and other fumes. Even hairspray use can be clinically relevant. In a setting that preserves confidentiality, the clinician should discretely ask older children and adolescents about inhaled substances of abuse, such as tobacco, marijuana, and solvents (e.g., paint, glue, correction fluid). Of course, contact with ill individuals and a travel history are also pertinent.

A careful environmental history is important. The type of heating and cooling system in place should be noted. Other information such as the age of the dwelling, the presence of a basement, and recent renovations may also be useful. The number and type of animals present should be established. Many families do not consider animals kept outside, such as farm animals or birds, to be pets, so it may be better to ask about "animals" rather than "pets." It is important to inquire about exposure to potential irritants. The most common of these is smoke, either from tobacco use or use of wood for heating, cooking, or both. New composite furniture (manufactured from particle board and veneers), waterbeds, carpets, and ceiling tiles may contain volatile aldehydes that can incite asthma.

Often neglected in the pediatric patient, a review of systems can provide important information. Headache may be a sign of sinus disease or, especially if occurring in the early morning, a result of obstructive sleep apnea. Ocular symptoms such as conjunctivitis and blepharitis, as well as nasal symptoms, may indicate an atopic predisposition or in the young infant a chlamydial infection. Recurrent mouth ulcers or thrush can be associated with immunodeficiency, as may chronic or recurrent ear drainage. Poor feeding, edema, shortness of breath, and exercise tolerance can be clues to the presence of congestive heart failure. Stool characteristics, abdominal bloating, and fatty food intolerance are important features of cystic fibrosis. Neurologic symptoms such as seizures or developmental delay are important in evaluating the child with apparent life-threatening events or suspected chronic or recurrent aspiration.

PHYSICAL EXAMINATION

This section focuses on the chest and respiratory system, with pertinent findings in other systems included as appropriate. For examination of other systems, the reader is referred to one of the general physical examination texts listed in the references.[1,2] It is best to establish a consistent pattern for the physical examination so that part of it is not omitted. The order in which the components of the examination are presented here is arbitrary. At all times, the privacy of the patient should be respected, the examination being conducted out of view and out of hearing of other patients. In the case of adolescents, the use of another staff member, the same gender as the patient, as a chaperon may be appropriate.

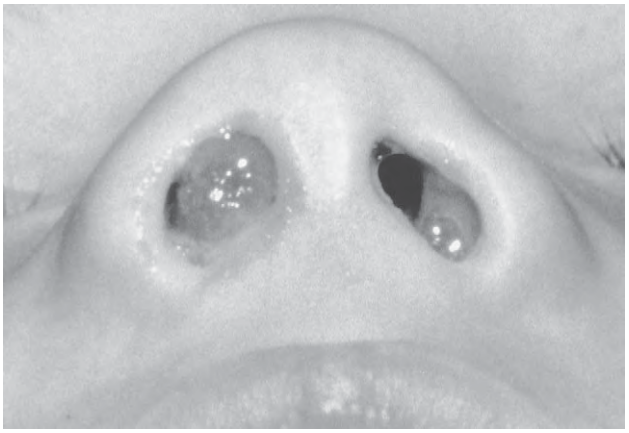
Upper Airway

Although not truly an airway or gas-exchanging tissue, the ear is considered part of the respiratory tract for several reasons. The middle ear and eustachian tube develop embryologically from the first pharyngeal pouch and share a contiguous mucosal surface with the respiratory tract.[6] The lining of the eustachian tube consists of ciliated pseudostratified columnar epithelium identical to the remainder of the respiratory tract.[7] Although the middle ear is lined predominantly with simple squamous or cuboidal epithelium, patches of ciliated pseudostratified columnar epithelium have been described there as well.[7] There are also cough receptors located in the external auditory canal. Thus, it is important to examine the ears for foreign bodies and for signs of middle ear infection or another abnormality as a source of chronic cough.

The nasal passages are uniquely configured to perform their role as the portal for inspired air. The turbinates and, to some degree, the paranasal sinuses warm and humidify inspired air from ambient temperature and humidity to roughly body temperature and 100% relative humidity. Careful inspection of the nose can identify subtle changes indicative of local and sometimes systemic disorders. Children with inhalant allergies frequently develop a transverse nasal crease, the result of repetitive up-and-down rubbing to relieve itching and discomfort. This may be accompanied by other signs associated with allergic disease, such as dark circles under the eyes ("allergic shiners") and Dennie sign,

skin creases radiating from the inner canthus of the eye to approximately two-thirds the length of the lower lid margin. The nasal bridge is normally straight. A deviation of the bridge may indicate a congenital abnormality or previous trauma and should prompt careful inspection of the septum for deviation and obstruction. Widening of the nasal bridge can be seen in individuals with extensive nasal polyps (Fig. 10-1). The relative patency of the passages can be assessed by asking the child to sniff (or simply listening in the younger child) while manually occluding one naris. A question of complete obstruction can be clarified by passage of a feeding tube or red rubber catheter. With congenital or acquired absence of the alar cartilage, the nares may collapse with each inspiration.

The nasal passages themselves can often be visualized through the use of an otoscope and a large (4- to 5-mm) ear speculum by placing the free hand on the top of the patient's head and, with the thumb, gently lifting the tip of the patient's nose. Alternatively, a nasal speculum can be used.



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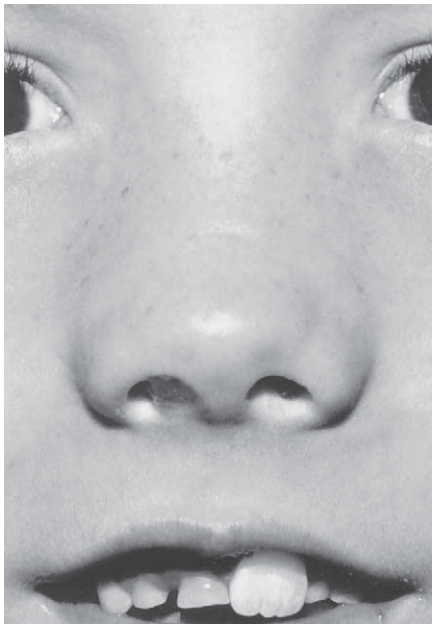

B

Figure 10-1 **A,** Child with cystic fibrosis and large nasal polyp. **B,** Note the widening of the nasal bridge and the polyp projecting from the right naris.

The nasal mucosa, normally pink and glistening, should be inspected for edema and changes in color (inflamed or pale, boggy or gray), and the color, consistency, and odor of any secretions are noted. Inflamed mucosa suggests infection, whereas pale, boggy mucosa is frequently seen in allergic rhinitis. With chronic rhinitis, the mucosa may take on a grayish appearance. Foul-smelling and sometimes bloody secretions suggest a foreign body or chronic sinus disease, whereas clear secretions may occur in allergic rhinitis or early in the course of an uncomplicated upper respiratory infection. A smear of nasal secretions, stained with Hansel's stain, may be helpful, a predominance of eosinophils suggesting allergic disease and a predominance of polymorphonuclear leukocytes (especially when accompanied by a single bacterial morphology) suggesting bacterial sinus disease. No conclusions regarding the causative organism should be drawn from these results, however. The septum should be inspected for deviations, perforations, and sites of bleeding. (Bleeding in the nasopharynx is a common source of perceived hemoptysis.) Foreign bodies, polyps (see Fig. 10-1), and masses within the nares should be carefully sought out and inspected.

Examination of the paranasal sinuses is difficult in children younger than 10 years. Techniques such as transillumination and percussion not only are impeded by lack of cooperation but also may be difficult to interpret because of the relative thickness and density of the overlying soft tissues. However, it may be possible to localize the source of purulent secretions in the nose by direct inspection. Most commonly, this is the middle meatus, which is located between the middle and inferior turbinates; the middle meatus drains the frontal, maxillary, and anterior ethmoid sinuses. The confluence of these three meatuses is called the *osteomeatal complex*. Obstruction from edema, a foreign body, or a polyp in this region is a frequent cause of chronic sinus disease. However, this may not be readily identified on examination; computed tomography (CT) is a more reliable means of diagnosis.

The profile of the mandible should be inspected carefully for the presence of retrognathia or micrognathia, either of which may lead to airway obstruction, especially during sleep. The state of oral hygiene, including not only of the teeth but also of the oral mucosa, should be noted. The integrity of the palate should be ensured either by visualization or preferably by gentle palpation because a submucous cleft palate can easily be missed on simple inspection. The size and shape of the uvula are noted. A long uvula may cause chronic cough, whereas a bifid uvula may be a clue to an occult submucous cleft palate. The motion of the uvula and soft palate during phonation and gagging is important to note, especially in children with known neurologic abnormalities. Poor or abnormal motion may suggest palatal insufficiency or cranial nerve palsy that may be associated with dysfunctional swallowing and an increased risk of aspiration. The clinician should also note the presence and size of the tonsils as well as any other masses, especially unilateral enlargement, which can be seen in retropharyngeal or tonsillar abscess or lymphoma. Adenoidal tissue visible on the posterior pharyngeal wall ("cobblestoning") is abnormal and implies hypertrophy in association with allergic disease.

The presence or absence of foul breath should be noted. Fetid breath may indicate poor dental hygiene, a nasal foreign body, anaerobic infection, or even pneumonia.

The position of the trachea is important to note during examination of the neck. Deviation to one side may be associated with pneumothorax, neck mass, unilateral pulmonary agenesis or hypoplasia, or unilateral hyperinflation such as with foreign body or congenital cystic lung disorders. With the exception of unilateral pulmonary agenesis or hypoplasia and large areas of atelectasis, which cause deviation toward the involved side, the trachea is deviated away from the abnormality. The neck should be palpated for masses, thyromegaly, and adenopathy.

The character of the voice often provides important information as well. Hoarseness with or without stridor suggests an abnormality of the vocal cords such as edema, dysfunction (e.g., paresis, paralysis), or injury. A weak voice accompanied by high-pitched inspiratory stridor but no hoarseness can result from a subglottic obstruction, whereas a muffled voice associated with a low-pitched stridor but no hoarseness suggests a supraglottic obstruction. Narrowing of the glottis itself results in hoarseness with high-pitched stridor only on inspiration. Hoarseness or a muffled cry in a newborn is very suggestive of a congenital glottic or subglottic abnormality and should prompt further investigation, especially in infants at risk for laryngeal papillomatosis because of maternal genital papillomatosis.

Chest

INSPECTION

Examination of the chest, as with other areas, should begin with inspection. The general shape of the chest and the presence of any deformities are noted. The circumference of the chest, as measured at the nipple line, should be roughly equal to the head circumference in infants and is larger in older children. Barrel chest deformity, an increase in the anteroposterior dimension of the chest, is associated with obstructive lung disease. There is a good correlation between the degree of severity of this deformity and both increased lung volumes (functional residual capacity, residual volume, total lung capacity, functional residual capacity/total lung capacity ratio, and residual volume/total lung capacity ratio) and radiographic findings of hyperinflation in children with poorly controlled asthma.[8]

Asymmetry of the chest can be seen in children with cardiomegaly (especially with right-sided ventricular hypertrophy), pneumothorax, and scoliosis. Pectus carinatum ("pigeon breast") or pectus excavatum ("funnel chest") can be present to a variable degree. The latter may falsely accentuate the severity or even mimic the presence of sternal retractions. Harrison's groove or sulcus, a horizontal depression in the lower thoracic cage at the site of anterior diaphragmatic attachment, may be seen in patients who have chronically increased work of breathing, as in pulmonary fibrosis, cystic fibrosis, or poorly controlled asthma.

Work of breathing is assessed mainly through inspection. The respiratory rate, preferably noted with the child at rest or asleep, is a fairly sensitive clinical indicator of pulmonary health (Table 10-1). However, fever and metabolic acidosis can lead to an increased respiratory rate in the absence of pulmonary disease. Nasal flaring, an attempt to reduce nasal resistance to airflow, is a manifestation of increased work of breathing, as is the use of accessory muscles of respiration such as the sternocleidomastoid muscles. Retractions or indrawing of the skin of the neck and chest is a sign of increased work of breathing as well. Areas of retraction include the suprasternal notch (suprasternal retractions), the subxiphoid region (infrasternal retractions), and the costal interspaces (intercostal retractions). In infants and toddlers, the sternum itself draws in during inspiration, a manifestation of the increased chest wall compliance in this age group. Because of this, other sites of retraction may be absent in this age group, whereas in the older child, suprasternal and intercostal retractions predominate.

Table 10-1
Respiratory Rates of Normal Children

	Sleeping		Awake	
Age	**Mean**	**Range**	**Mean**	**Range**
Waring				
6-12 mo	27	22-31	64	58-75
1-2 yr	19	17-23	35	30-40
2-4 yr	19	16-25	31	23-42
4-6 yr	18	14-23	26	19-36
6-8 yr	17	13-23	23	15-30
Age	**Boys**	**Girls**		
Iliff and Lee				
0-1 yr	31	30		
1-2 yr	26	27		
2-3 yr	25	25		
3-4 yr	24	24		
4-5 yr	23	22		
5-6 yr	22	21		
6-7 yr	21	21		
7-9 yr	20	20		
9-13 yr	19	19		
13-14 yr	19	18		
14-15 yr	18	18		
15-16 yr	17	18		
16-17 yr	17	17		
17-18 yr	16	17		

Adapted from Waring WW: The history and physical examination. In Kendig EL (ed): Disorders of the Respiratory Tract in Children. Philadelphia, WB Saunders, 1972, pp 71-97; and Iliff A, Lee VA: Child Dev 23:237-245, 1952.

Children with evidence of increased work of breathing are said to have dyspnea, although complaints of shortness of breath are subjective and may not be related to a true respiratory pathologic condition. Children with neuromuscular disease, quadriplegia, paralyzed hemidiaphragm, and other such conditions may complain of dyspnea associated with metabolic acidosis or fever because of their inability to effectively increase their minute ventilation, the normal response in such a setting. The degree of dyspnea may be estimated by noting the number of words a child is able to speak before having to take a breath or by asking the child to count and noting the highest number reached. Both the use of accessory muscles and dyspnea correlate closely with lung function as measured by the 1-second forced expiratory volume and oxyhemoglobin saturation in children with acute exacerbations of asthma.[9]

The respiratory pattern may also provide valuable information. It is important to remember that the respiratory pattern is set by the respiratory centers in the brain stem.

Changes in the pattern can reflect responses to oxygenation state, acidosis, or alkalosis or can indicate a primary abnormality of the respiratory centers themselves. The depth of respiration should also be noted. One author has suggested that each physician establish informal "norms" for depth of respiration in children of various ages by noting the distance from the nose at which the breath can be felt on the hand.[10]

Individuals with restrictive lung disease may have shallow, rapid respirations. Hyperpnea, rapid and deep respiration, can be associated with a number of underlying problems, including hypoxia and metabolic acidosis. Alkalosis may result in slow, shallow breaths. Biot respiration, a pattern of very irregular respirations with alternating periods of hyperpnea and apnea, can be seen in meningitis, encephalitis, and other central nervous lesions involving the respiratory centers. Cheyne-Stokes respirations are a repetitive pattern of gradually increasing and decreasing respirations over 30 seconds to 1 minute and are generally associated with coma. The relative length of the respiratory phases (the inspiratory/expiratory ratio) is significant, with the inspiratory and expiratory phases normally being approximately equal. Prolonged expiration is seen in obstructive diseases such as bronchiolitis, acute exacerbations of asthma, and cystic fibrosis. Some degree of paradoxical respiration, or abdominal ("belly") breathing, may be normal, especially in children up to 6 or 7 years of age. Prominent respirations of this type in any child, however, generally reflect a pulmonary abnormality such as pneumonia, upper airway obstruction, obstructive lung disease, or respiratory muscle weakness.

PALPATION

Although more generally thought of in terms of the abdominal examination, palpation is important in the respiratory examination as well. It is used to confirm the visual observations of chest wall shape and excursion. Palpation is performed by placing the entire hand on the chest and feeling with the palm and fingertips. Friction rubs may be felt as high-frequency vibrations in synchrony with the respiratory pattern. Tactile fremitus, the transmission of vibrations associated with vocalization, is at times difficult to assess in children because of a lack of cooperation and a higher-pitched voice; lower-pitched vocalization is more effectively transmitted. It is best felt with the palmar aspects of the metacarpal and phalangeal joints on the costal interspaces. Decreased fremitus suggests airway obstruction, pleural fluid, or pleural thickening, whereas increased fremitus is associated with parenchymal consolidation. Occasionally a "thud" can be felt high in the chest or in the neck, a finding suggestive of a free tracheal foreign body. One can also assess chest excursion by placing the hands with the fingertips anterior and thumbs posterior and noting the degree of chest wall movement, comparing excursion of one side with the other by noting the movement of the thumbs away from the midline (the spinous processes). The point of maximal impulse, frequently shifted to the left in cardiac disease, may be shifted inferiorly and to the right in severe asthma, a large left-sided pleural effusion, or a tension pneumothorax. With massive left-sided atelectasis, it may be shifted to the left.

PERCUSSION

Much like its counterpart in the musical world, percussion of the chest relies on differences in vibratory characteristics, in this case using various tissues, to produce characteristic sounds. First described by Leopold Auenbrugger in Vienna in 1761, the technique was largely ignored by the medical community until around the turn of the next century, when it was revived by Napoleon's personal physician, Corvisant. It is widely thought that Auenbrugger adapted the technique from that used by his innkeeper father to determine the level of wine in barrels, though it is not known for certain how Auenbrugger developed the idea. There are two different methods of performing percussion: direct (or immediate), in which the chest is struck directly with the finger, and indirect (or mediate), in which sound is generated by striking a finger laid on the chest. This discussion involves the indirect method only. A discussion of direct percussion can be found elsewhere.[11]

Correct technique is critical in both performing and interpreting percussion of the chest, especially in small children. Percussion is best performed with the child upright with the head in a neutral position. A single finger from one hand (the pleximeter) is placed on an interspace; care is taken to avoid contact of the other fingers and palm with the chest because contact between the chest and any other part of the nonstriking hand dampens the sound generated and leads to erroneous interpretation. The finger is then struck with a single finger from the other hand (the plexor) by holding the hand fixed and pivoting at the wrist, quickly removing the striking finger, again to avoid dampening the sound. Many examiners find it comfortable to use the long fingers of each hand for this technique. Generally, the clinician strikes two or three times in each position. The force used should be consistent with each strike and should not be too strong. Excessive force may lead to an erroneous impression of hyperresonance, especially in a small child. Some have suggested the use of a reflex hammer as the plexor; this should not be done in children because it may lead to the false impression of increased resonance. Sounds commonly elicited by percussion of the chest are listed in Table 10-2.

The clinician can delineate the level of the diaphragmatic leaves anteriorly and posteriorly by carefully percussing along the lower thoracic cage (Table 10-3). This can be helpful in guiding auscultation. The clinician may even be able to assess diaphragmatic excursion in older children and adults with suspected diaphragmatic dysfunction by percussing during inspiration and expiration; in adults this is normally 5 to 6 cm. The extent of the mediastinal structures can also be delineated by percussion.

AUSCULTATION

With the development of the stethoscope by René Laënnec in 1816 and its improvement by Piorry, Williams, Cammann, and others, physicians had the capability to recognize changes in sound characteristics in the chest and to correlate these changes with specific pathophysiologic events in health and disease. (An excellent review of the history and physics of the stethoscope is available.[12]) Although the standard stethoscope does not amplify sound, by excluding extraneous environmental sounds and to some degree localizing sounds, it allows the clinician to assess gas movement within the lungs

Table 10-2
Sounds Elicited by Percussion of the Chest

Term	Definition
Tympany	A low- to medium-pitched sound with a musical quality, this sound is usually heard only with percussion of the abdomen; massive pneumothorax is suggested if it is heard in the chest.
Hyperresonance	Somewhat similar to tympany, this is an accentuation of the sound heard when percussing the chest of a normal individual. This sound is associated with hyperinflation as with emphysema, asthma, or free intrapleural air.
Bell-metal resonance	Also called the *coin test,* this is a clearly transmitted metallic sound heard with a stethoscope when tapping a coin that is held flat against the chest with another coin; it indicates a pneumothorax.
Skodiac resonance	This peculiar, high-pitched sound is obtained by percussion just above the level of a pleural effusion.
Resonance	This is the normal state in the chest; it is sometimes called *vesicular resonance.*
Dullness	A flat, thud-like sound, this sound is associated with pleural fluid or parenchymal consolidation.
Flatness	This sound can be mimicked by percussing over muscle; its presence in the chest suggests massive pleural effusion.

and relate changes to known associations with specific abnormalities. Thus, developing expertise in interpreting auscultatory findings is very much an experiential process, and as such, there is no substitute for having listened to a large number of patients, both with and without lung disease. Audio programs, such as one available from the American College of Chest Physicians,[13] can be helpful in establishing a base on which to build this skill.

For most physicians, the standard binaural stethoscope is adequate as long as it is in good repair. The earpieces should fit well to exclude environmental sounds. The tubing should not be cracked or kinked and ideally should be no longer than 30 cm (12 inches), although many physicians accept longer lengths for ease and comfort in examining patients. The bell should be fitted with a rubber ring, and the diaphragm should be intact. Pulmonologists may find it more convenient to use a differential stethoscope, a stethoscope with two chest pieces, one connected to each earpiece, allowing simultaneous auscultation and direct comparison of sounds in different locations. However, use of the differential stethoscope requires even more practice than the standard binaural stethoscope for effective use, so it is probably not practical for the general pediatrician or family physician.

The diaphragm, which filters out low-pitched sounds, thereby isolating high-pitched sound, should be pressed tightly against the skin. In contrast, the bell should be placed lightly on the skin to preferentially isolate low-pitched sounds.

Table 10-3
Usual Level of Diaphragm as Assessed by Percussion

Term	Left	Right
Anterior	Ribs 8-10	Rib 6 (midaxillary line)
Posterior	Ribs 8-10	Ribs 8-10

If excessive pressure is applied when using the bell, the skin below the bell may be stretched taut, thereby functioning as a diaphragm and filtering out the low-pitched sounds being sought. A loud, roaring sound generally indicates inadequate contact between the chest piece and skin, especially when the bell is used. This can be especially problematic when examining an infant or small child unless a stethoscope with appropriate-sized chest pieces is used. Instruments with chest pieces appropriate for premature infants, infants, children, and adolescents and adults are available. The clinician should avoid listening through clothing or bedclothes and should listen (if possible) with the patient breathing slowly and deeply through the mouth in a neutral position, either upright, prone or supine.

As always, it is best to develop a consistently used pattern of examination to avoid missing areas (Fig. 10-2). The upper lobes are best heard by listening anteriorly in the infraclavicular regions, the lower lobes by listening posteriorly below the scapulae, and the right middle lobe and lingula by listening anteriorly lateral to the lower third of the sternum. All lobes can be heard in the axillae.

When auscultating, the clinician should note the amplitude of the sounds produced. It is also important to specify the timing (continuous, early, or late), pitch (high, medium, or low), and character (fine, medium, or coarse) of sounds. These sounds can be divided into breath sounds (produced by the movement of gas through the airways), voice sounds (modifications of phonation not heard distinctly in the normal state), and adventitious sounds (neither breath or voice sounds). Table 10-4 lists the most commonly heard sounds.

Breath Sounds

Vesicular breath sounds are the sounds heard during respiration in a healthy individual. They have a low-pitched, "whishing" quality with a relatively longer inspiratory phase and a shorter expiratory phase and are louder on inspiration. These sounds emanate from the lobar and segmental airways and are then transmitted through normal parenchyma.[14]

Bronchial breath sounds are usually louder than vesicular sounds and have short inspiratory and long expiratory phases. They are higher pitched and louder during expiration. They may be the result of consolidation or compression (i.e., airlessness) of the underlying parenchyma. A similar sound can be heard by listening directly over the trachea.

Bronchovesicular breath sounds, as the name implies, are intermediate between vesicular and bronchial sounds. The respiratory phases are roughly equal in length. This sound is felt to be indicative of a lesser degree of consolidation or compression (airlessness) than bronchial sounds. Bronchovesicular (and sometimes bronchial) breath sounds can occasionally be heard in normal individuals in the auscultatory triangle (the area in the back bound by the lower border of the trapezius, the latissimus dorsi, and the rhomboideus major muscles) and the right upper lobe.

Wheezes are continuous musical sounds, more commonly expiratory in nature, and usually associated with short inspiratory and prolonged expiratory phases. They can be of single (monophonic) or multiple (polyphonic) pitches, which are higher pitched than vesicular sounds. These can often be very

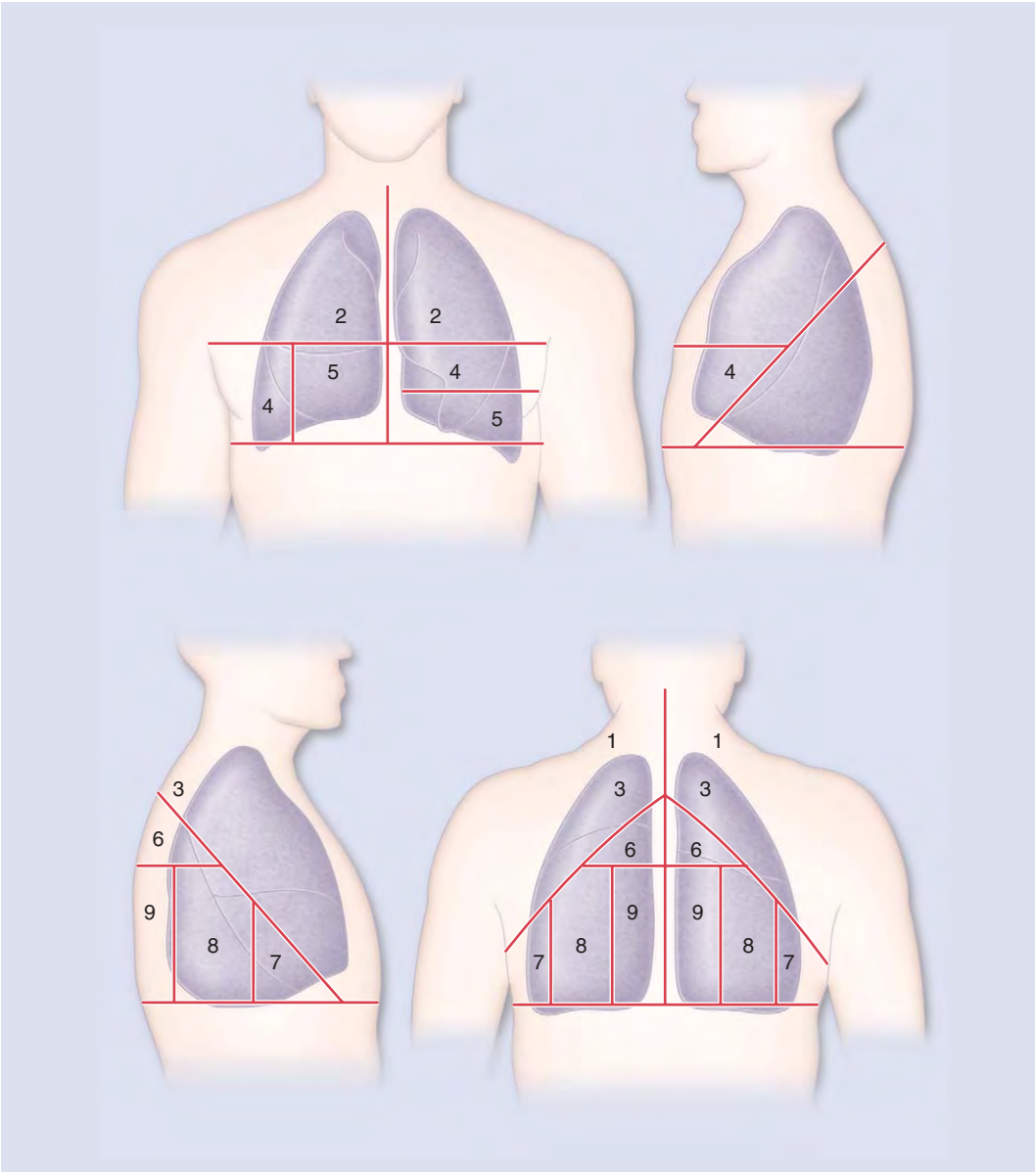

Figure 10-2 Projections of the lobar/segmental pattern on the surface of the chest. *1*, Apical segment of the upper lobes; *2*, anterior segment of the upper lobes; *3*, posterior segment of the upper lobes; *4*, superior lingular *(left)* and lateral *(right)* segments of the middle lobe; *5*, inferior lingular *(left)* and medial *(right)* segments of the middle lobe; *6*, superior segment of the lower lobes; *7*, anterior basal segment of the lower lobes; *8*, lateral basal segment of the lower lobes; *9*, posterior basal segment of the lower lobes.

difficult to distinguish from snoring and upper airway sounds such as stridor.

Stridor is a musical, monophonic, often high-pitched sound, usually thought of as inspiratory in nature; it can be expiratory as well, such as when produced by partial obstruction of a central, typically extrathoracic airway. Its presence in both inspiration and expiration suggests severe, fixed airway obstruction.

A cardiorespiratory murmur is a localized vesicular sound that appears to be synchronized with the heartbeat, mimicking a cardiac murmur or bruit. It can be heard anywhere in the chest but is frequently very dependent on body position, often disappearing with position change. It may be heard in systole, diastole, or both during quiet respiration.

Voice Sounds

The normal lung parenchyma filters vocalization so that whispered sounds are not usually heard during auscultation and normally spoken syllables are indistinct. Bronchophony is the distinct transmission of spoken syllables as the result of an underlying consolidation or compression. More severe consolidation or compression results in the transmission of whispered sounds or whispered pectoriloquy. Egophony is very similar to bronchophony but has a nasal quality as well. It may reflect an underlying effusion, consolidation or compression, or both conditions.

Adventitious Sounds

The nomenclature for adventitious sounds is perhaps the least standardized of all physical findings and therefore is prone to

Table 10-4
Pulmonary Auscultatory Sounds*

Common Terminology	American College of Chest Physicians–American Thoracic Society "Preferred" Terminology
Breath Sounds	***Breath Sounds***
Vesicular sounds	Normal
Bronchial sounds	Decreased
Bronchovesicular sounds	Absent
Wheeze	
Stridor	
Cardiorespiratory murmur	
Voice Sounds	***Voice Sounds***
Whispered pectoriloquy	Clarity increased or decreased
Bronchophony	Intensity increased or decreased
Egophony	
Adventitious Sounds	***Adventitious Sounds***
Fine (subcrepitant) crackles or rales	Crackles or rales (no subclassifications)
Coarse (crepitant) crackles or rales	Mediastinal crunch
Rhonchi	Wheezes or rhonchi (varying pitch, quality, intensity)
Pleural friction rub	Pleural rub Pleuropericardial rub
Squawk	

*See text for description of terms.

confusion. Synonymous terms such as *rales* and *crackles*, *subcrepitant* and *fine*, and *crepitant* and *coarse* are widely used in a variety of combinations. Because past attempts at standardization have met with variable success,[15] the authors have chosen to identify these sounds using several descriptors, allowing the reader to choose which to use and hopefully allowing him or her to recognize others when used by colleagues.

Fine (subcrepitant) crackles are thought to be the result of the explosive reopening of alveoli that closed during the previous exhalation or exhalations.[16] These occur exclusively during inspiration and are associated with conditions such as bronchitis, pneumonia, pulmonary infarction, and atelectasis. They can also be normal when heard in the posterior lung bases during the first few breaths on awakening. They may be imitated by rolling several strands of hair between the thumb and forefinger in front of the ear or by pulling apart Velcro. Hamman's sign, also called a *mediastinal crunch*, is the finding of crackles associated with systole and is suggestive of pneumomediastinum.

Coarse (crepitant) crackles are popping sounds likely produced by the movement of thin fluids in bronchi or bronchioles.[16] They occur early in inspiration and occasionally in expiration as well, may be audible at the mouth, and may clear or change pattern after a cough. They can sometimes be heard in the anterior lung bases during exhalation to residual volume. An example of these sounds is the crackles typically heard in patients with cystic fibrosis.

Rhonchi (sometimes more descriptively called *large airway sounds*) are gurgling or bubbling sounds usually heard during exhalation. These sounds are the result of movement of fluid within larger airways.

A squawk is a short inspiratory wheeze often heard in association with fine crackles. It is thought to result from the explosive opening and fluttering of a large airway.

In individuals with pleural inflammation, a pleural friction rub may be heard. This loud, grating sound may come and go over a short period of time. It is usually associated with a subpleural parenchymal inflammatory process.

Finally, peristalsis may sometimes be heard within the thorax, especially over the left lung base because of the proximity of the stomach and large bowel. The clinician must be alert to the possibility of acquired or congenital diaphragmatic hernia.

OTHER SIGNS AND SYMPTOMS

Occasionally, pulmonary disease is manifest by changes or signs in other organ systems. An example is digital clubbing, the broadening and thickening of the ends of the fingers and toes that occur as the result of connective tissue hypertrophy and hyperplasia[17] and increased vascularity[18] in the distal phalanges (Fig. 10-3). It may be quite subtle but can be confirmed clinically by checking for Schamroth's sign (Table 10-5). Although clubbing can be a primary finding (either idiopathic or inherited), it is usually seen in association with lung disease, heart disease, or liver or other gastrointestinal diseases as well (Box 10-1). The degree of clubbing can be quantitated by several methods as a way of following the progression of lung disease.[19,20] Clubbing may occur acutely (e.g., with a bout of severe pneumonia) but may also regress if the underlying cause is corrected. When associated with a usually painful periostosis, clubbing is one component of hypertrophic osteoarthropathy.

The pathophysiology of clubbing associated with lung disease is unclear. It may be the result of the lungs' failure to remove or inactivate a circulating fibroblast growth factor,[21] although the arachidonic acid metabolites prostaglandins $F_{2\alpha}$ and E have been implicated in patients with cystic fibrosis.[22] Still another theory proposes that clubbing is the result of peripheral impaction of megakaryocytes and platelets in the digits, with subsequent release of platelet-derived growth factor, which induces the histologic and anatomic changes associated with clubbing.[23]

BOX 10-1 Digital Clubbing

Intrapulmonary shunting and inflammation
- Bronchiectasis
- Severe pneumonia, lung abscess, or empyema
- Interstitial lung disease (autoimmune and infectious)
- Pulmonary arteriovenous malformation
- Hepatopulmonary syndrome
- Pulmonary malignancy

Cardiac and cardiovascular causes
- Cyanotic congenital heart disease
- Bacterial endocarditis

Noncardiopulmonary causes
- Inflammatory bowel disease
- Thyrotoxicosis

Familial

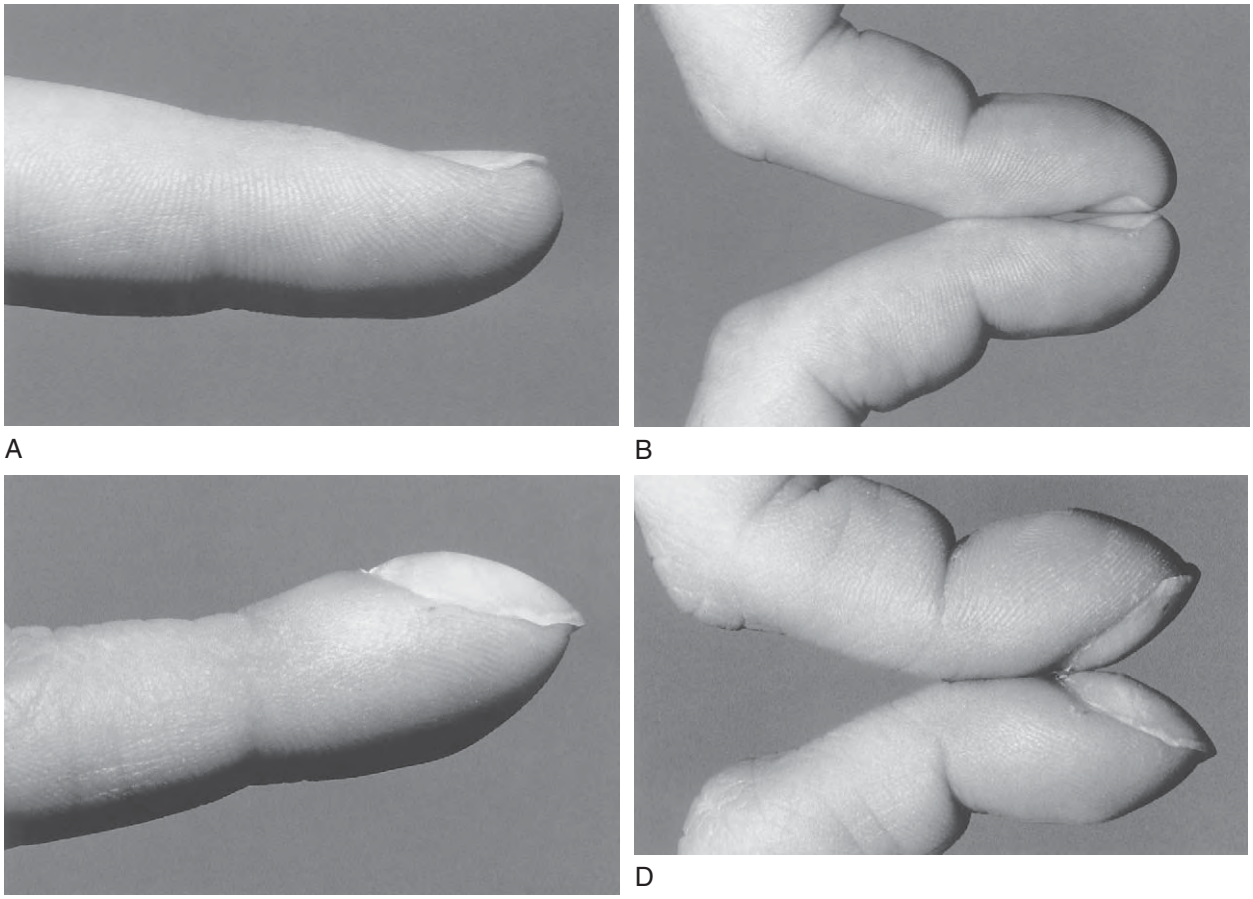

Figure 10-3 Lateral views of the index finger and Schamroth's sign in a healthy individual (**A** and **B**) and in an individual with severe clubbing (**C** and **D**).

Table 10-5
Pulmonary "Signs"

Sign	Definition
Abrahams	Rales and other adventitious sounds, changes in respiratory murmurs, and an increase in whispered sounds can be heard on auscultation over the acromial end of the clavicle for some time before they become audible at the apex.
Aufrecht	Diminished breath sounds occur in the trachea just above the jugular notch in cases of tracheal stenosis.
Baccelli	There is good conduction of a whisper in nonpurulent pleural effusions.
Bird	There is a zone of dullness on percussion with the absence of respiratory signs in the presence of a hydatid cyst of the lung.
di'Espine	In pulmonary tuberculosis, bronchophony over the spinous processes is heard at a lower level than in healthy people.
Ewart	In large pericardial effusions, an area of dullness with bronchial breathing and bronchophony is found below the angle of the left scapula.
Ewing	Dullness on percussion to the inner side of the angle of the left scapula denotes an accumulation of fluid in the pericardium behind the heart.
Fischer	In a case of tuberculosis of the bronchial glands, if one bends the child's head as far back as possible, auscultation of the manubrium sterni sometimes reveals a continuous loud murmur caused by the pressure of the enlarged glands on the vena anonyma.
Hamman	Crackles associated with systole is suggestive of pneumomediastinum; this sign is also called the *mediastinal crunch.*
Hoover	A modification in the movement of the costal margins during respiration is caused by flattening of the diaphragm; this sign suggests emphysema or another intrathoracic condition causing a change in the contour of the diaphragm.
Jackson	During quiet respiration, the movement of the paralyzed side of the chest may be greater than that of the opposite side, whereas in forced respiration, the paralyzed side moves less than the other.
Lorenz	This sign is stiffness of the thoracic spine in early pulmonary tuberculosis.
Perez	Rales are audible over the upper part of the chest when the arms are alternately raised and lowered; it is a common occurrence in cases of fibrous mediastinitis and aneurysm of the aortic arch.
Rotch	Percussion dullness occurs in the fifth intercostal space on the right side in cases of pericardial effusion.
Schamroth	In patients with clubbing, there are loss of the normal diamond-shaped aperture at the base of the nails and an increased angle at the nail tips when the dorsal surfaces of the terminal phalanges are approximated.
Skoda	High-pitched percussion sound just above a pleuritic effusion.

BOX 10-2 Cyanosis

Central Cyanosis

Arterial hypoxemia

Normal levels of arterial oxygen

- Hematologic causes
  - Methemoglobin
  - Other hemoglobinopathies
- Vascular cause
  - Superior vena caval obstruction

Peripheral Cyanosis

Vascular causes
- Peripheral cyanosis resulting from vasomotor instability or hypothermia
- Venous obstruction
- Shock or hypoperfusion with venous stasis

Hematologic cause
- Polycythemia

Cyanosis, another abnormality that may be associated with lung disease, is the bluish discoloration of tissues caused by increased concentrations of reduced (unoxygenated) hemoglobin, which is purple (Box 10-2). It occurs more readily in tissues with low blood flow or higher oxygen extraction than tissues with higher flow or lower oxygen extraction. This accounts for the traditional interpretation that peripheral cyanosis (or acrocyanosis) reflects less severe hypoxemia than central cyanosis.

The use of cyanosis as a clinical indicator of hypoxemia is confounded by a number of factors. Simply identifying the cyanotic patient can be problematic because of variations in skin pigmentation, poor lighting, the presence of nail polish, or temperature extremes (especially cold). Even when cyanosis is unequivocally present or absent, inferences made regarding the oxygenation state of the patient may not be correct. Cyanosis occurs when the concentration of reduced arterial hemoglobin exceeds 3 g/dL. At this level the concentration of reduced hemoglobin in the capillary beds is generally 4 to 6 g/dL. However, the blood's oxygen-carrying capacity, and therefore blood oxygen content, depends primarily on total hemoglobin concentration. Thus, the actual oxygen content may be normal in a cyanotic patient with polycythemia, but an anemic patient may have an abnormally low oxygen content in the absence of cyanosis. Clinical impressions of oxygenation, such as cyanosis, should therefore be verified by arterial blood gas analysis or pulse oximetry.

Pulsus paradoxus is another physical sign sometimes associated with pulmonary disease, particularly obstructive lung disease. Pulsus paradoxus is the fluctuation in arterial systolic blood pressure with the respiratory cycle, the pressure falling during inspiration and rising with exhalation. It is quantified as the difference between the systolic pressures measured during inspiration and expiration. It can be measured a number of ways, most easily by using a sphygmomanometer. It can also be qualitatively identified by observing the pressure tracing of an intraarterial catheter or the pulse tracing of a pulse oximeter. It may also be detected by palpation in patients with pulsus paradoxus greater than 20 mm Hg, signifying more severe obstructive lung disease (see later section).

The pathophysiology of pulsus paradoxus is likely multifactorial.[24] With wider swings in intrathoracic pressure associated with airway obstruction, there is a wider gradient between pressure within the intrathoracic and extrathoracic arterial vessels. Thus, the left ventricle must generate increased force to keep the arterial pressure relatively constant. Because the ventricle does not do so in an instantaneous fashion, there is a drop in arterial pressure. The wider swing in intrathoracic pressure also results in greater right ventricular filling pressure, leading to increased right ventricular end-diastolic volume and displacement of the ventricular septum leftward. This reduces left ventricular filling, thereby reducing stroke volume and further decreasing arterial pressure during and immediately after inspiration.

Pulsus paradoxus is useful in evaluating children with cystic fibrosis[25] and asthma, in which pulsus paradoxus of more than 15 mm Hg has been found to correlate with a 1-second forced expiratory volume of less than 60% of the predicted value.[26] It should be noted that the levels of pulsus paradoxus commonly seen with obstructive lung disease are much higher than those seen in individuals in whom cardiac tamponade is the etiology of pulsus paradoxus.

EVALUATION OF THE CHILD WITH CHRONIC COUGH

Physiology

Cough is an extremely important component of pulmonary host defense. When functioning effectively, it clears bulk material from the airway. In patients with impaired mucociliary clearance either from acquired or congenital abnormalities of ciliary function or other mechanical factors, cough may be the only airway clearance mechanism available. The loss of effective cough in patients with advanced neuromuscular or neurologic disease is a critical factor in the morbidity and mortality of those disorders.

Although a seemingly simple action, cough is actually a very complex reflex involving afferent pathways in the vagus and efferent pathways in the somatic nervous system. Cough can be produced or suppressed volitionally, although it is not always completely suppressible. Although their existence has not yet been confirmed histologically (only inferred by physiology and suggested by electron micrographic studies), cough receptors are thought to be fairly widely distributed in the respiratory tract. They are found predominantly in the extrapulmonary airways (larynx, trachea, mainstem bronchi) but are also present in the external auditory canals, tympanic membranes, upper airway, pleura, pericardium, and diaphragm. Few, if any, are found in the lung parenchyma itself.

The sequence of events associated with a cough are well described. The initial phase consists of opening of the glottis and a short inspiration, which increases lung volume for the next phases. The glottis then closes, and the chest wall, abdominal, and perineal muscles contract, generating high

intrathoracic and transpulmonary pressures. With the sudden opening of the glottis, there is rapid decompression of the airway with a high-velocity expulsion of gas and movement of airway contents (e.g., secretions and other solid material) proximally. In smaller airways the intrathoracic pressure generated may lead to airway closure, trapping some material distally. Thus, cough primarily clears the larger, more central airways. Recognition of this phenomenon has led to alternative methods of airway clearance, such as autogenic drainage[27] and the use of positive expiratory pressure and flutter valve devices,[27,28] which are thought to be more effective at clearing the smaller, more distal airways.

Movement of material as the result of coughing occurs by three mechanisms. First, the high-velocity airflow results in a wavelike gas or liquid pumping of the mucous blanket and movement of loose mucus and other material. The increase in intrathoracic pressure causes airway compression, which squeezes some material proximally into larger airways. This is especially important peripherally, where gas velocities are insufficient to propel mucus. Finally, the vibration of the airway walls and the shearing force of the high-velocity gas flow dislodge mucus from the walls. The sounds produced by coughing are the result of the vibration of secretions and nonrigid respiratory structures.

In contrast to the beneficial airway clearing effects of cough, there are a number of potential deleterious effects as well. Extremely forceful coughing may induce bronchospasm in some individuals. With extremely forceful coughing, there may be injury to the larynx or development of an air leak such as a pneumothorax, a pneumomediastinum, or interstitial emphysema. The high intrathoracic pressures generated during coughing impede venous return to the heart, may result in transient systemic hypertension, or may induce arrhythmias. Syncope can occur because of strenuous coughing. With very forceful coughing, rib fractures may occur. Other complications include rupture of the rectus abdominis muscles, urinary incontinence, pulmonary emboli, and kinking and knotting of venous catheters. An excellent in-depth review of cough is available.[29]

Evaluation

There are many etiologies of chronic cough in childhood (Box 10-3). Without some guidance in tailoring it to the individual, evaluation of this complaint could consume a tremendous amount of time and medical resources. The guidance needed can usually be provided by a careful history.

Onset of cough in the neonatal period is suggestive of a congenital airway malformation. In the perinatal period, abnormalities such as tracheal stenosis, laryngeal web, and tracheosophageal fistula may present with cough, whereas tracheomalacia typically results in cough later in the neonatal period. There may be an association with infectious symptoms such as TORCH (toxoplasmosis, other agents, rubella, cytomegalovirus, herpes simplex) syndrome, chlamydial infection, or pertussis; in older children, there may be an association with tuberculosis or sinusitis. The character of the cough can also provide important clues to the etiology. A continual cough, perhaps worse at night, may be found in asthma, cystic fibrosis, or other forms of bronchiectasis (especially if the cough is productive). Features suggestive of asthma (such as prolonged cough after upper respiratory tract infections, exercise, or exposure to environmental irritants) or the presence of risk factors for asthma (family history, history of prematurity) should prompt a careful evaluation for asthma or cough-variant asthma as a cause. A loud, honking cough absent during sleep is highly suggestive of a psychogenic cough, habit cough, or cough tic. History of a choking or gagging spell followed by chronic cough may promote concern over a possible aspirated foreign body, although there may be no such history, even in cases of documented foreign body aspiration. Chronic aspiration or gastroesophageal reflux as the cause of cough may be elicited by a careful neurologic and feeding history. Obviously, signs or symptoms of chronic illness, such as poor growth, recurrent fevers, and purulent sputum, should prompt a search for more severe pulmonary or systemic disease. Finally, the social history often provides information vital to elucidation of the cause. Factors such as exposure to environmental tobacco smoke, wood stoves, solvents, and dusts can explain chronic respiratory symptoms. The presence of family or school conflicts may support a suspicion of psychogenic cough.

The physical examination must be complete and carefully performed, with emphasis placed on the head and neck (transverse nasal crease, allergic shiners, boggy nasal mucosa, polyps, ear disease, foreign body in ear or nose, postnasal drip, long uvula, cobblestoning of posterior pharynx), chest (hyperinflation, wheezes, crackle, stridor), and heart (murmurs, gallops, signs of heart failure). The laboratory evaluation, which could easily be exhaustive, should be directed by findings elicited in the history and examination. Common tests include pulmonary function testing, including bronchoprovocation (pharmacologic, exercise, cold air); chest radiograph (two views, occasionally inspiratory and expiratory or lateral decubitus) and other imaging studies (CT, magnetic resonance imaging [MRI], sinus series and CT); barium esophagogram; esophageal pH monitoring; and bronchoscopy. The use of flexible versus rigid bronchoscopy in evaluating pediatric patients has been reviewed[30] and bronchoscopy may be appropriate in selected patients. Unless foreign body aspiration is considered likely, flexible fiberoptic bronchoscopy is generally the procedure of choice. Laboratory studies that may be helpful include a complete blood count with differential (evaluating for leukocytosis, eosinophilia), total immunoglobulin E assay, purified protein derivative and control skin tests, sweat test, sputum culture (including culture for acid-fast bacillus and fungus), ciliary biopsy, and limited allergy skin testing (limited to locally common aeroallergens and animals and foods known to be in the child's environment). It may also be reasonable to perform an empiric trial of bronchodilators or a short course of systemic corticosteroids.

EVALUATION OF THE CHILD WITH AIRWAY OBSTRUCTION

Regardless of the etiology of the obstruction, wheezing and stridor with increased work of breathing are the cardinal manifestations of clinically significant airway obstruction. Usually the term *stridor* refers to a vibratory sound that is loudest on inspiration and is predominantly due to dynamic extrathoracic airway obstruction. In contrast, wheezing is

BOX 10-3 Persistent Cough*

Congenital Anomalies

Connection of the airway to the esophagus
- Laryngeal cleft
- Tracheoesophageal fistula

Laryngotracheomalacia
- Primary laryngotracheomalacia
- Laryngotracheomalacia secondary to gastroesophageal reflux disease, vascular or other compression

Bronchopulmonary foregut malformation

Congenital mediastinal tumors
- Congenital heart disease with pulmonary congestion or vascular airway compression

Infection

Recurrent viral infection (infants and toddlers)

Chlamydial infection (infants)

Whooping coughlike syndrome
- *Bordetella pertussis* infection
- Chlamydial infection
- *Mycoplasma* infection
- Cystic fibrosis (infants and toddlers)

Granulomatous infection
- Mycobacterial infection
- Fungal infection

Suppurative Lung Disease (Bronchiectasis and Lung Abscess)

Cystic fibrosis

Foreign body aspiration with secondary suppuration

Cilia dyskinesia

Immunodeficiency
- Primary immunodeficiency
- Secondary immunodeficiency (especially human immunodeficiency virus and acquired immunodeficiency syndrome)

Paranasal sinus infection

Allergy and Asthma

Asthma and cough-variant asthma

Allergic or vasomotor rhinitis and postnasal drip

Aspiration (Fluid Material)

Dyskinetic swallowing with aspiration
- General neurodevelopmental problems
- Möbius syndrome

Bottle-propping and bottle in bed (infants and toddlers)

Gastroesophageal reflux

Foreign body aspiration (solid material)
- Upper airway aspiration (tonsillar, pharyngeal, laryngeal)
- Tracheobronchial aspiration
- Esophageal aspiration with an obstruction or aspiration resulting from dysphagia

Physical and Chemical Irritation

Smoke from tobacco products (active and passive)

Wood smoke from stoves and fireplaces

Dry, dusty environment (hobbies and employment)

Volatile chemicals (hobbies and employment)

Psychogenic or habit cough

Iatrogenic

Angiotensin-converting enzyme inhibitors

*Longer than 3 weeks.

usually produced by intrathoracic obstruction that worsens on expiration. At times, it can be difficult to distinguish between wheezing and stridor, and it should be remembered that critical airway obstruction can lead to stridor or wheeze in both phases of respiration (Box 10-4). A monophonic wheeze suggests obstruction of a large central airway, whereas a polyphonic wheeze reflects peripheral airway obstruction.

Although asthma is certainly the most common disorder associated with wheezing, not every child with wheezing has asthma, nor does every child with asthma wheeze. The differential diagnosis of wheezing varies significantly with the age of the child. Congenital anatomic abnormalities that produce wheezing, like those associated with cough, are generally more likely to present in early infancy rather than later. Laryngotracheomalacia is an exception, usually presenting at several weeks of age or later. Laryngomalacia and extrathoracic tracheomalacia typically present as inspiratory stridor, whereas intrathoracic tracheomalacia and bronchomalacia are associated with low-pitched expiratory wheezing. Asthma, bronchiolitis, and bronchopulmonary dysplasia all may be associated with wheezing in infancy but can generally be distinguished on historical grounds. Along with asthma, cystic fibrosis and chronic aspiration (secondary to gastroesophageal reflux or a neurologic abnormality with dysfunctional swallowing) may present as wheezing at any age. Foreign body aspiration, most commonly pulmonary but also esophageal, classically presents as a monophonic, unilateral wheeze and is unusual before 6 months of age. This diagnosis, however, should be considered regardless of history (or lack thereof). Congestive heart failure may lead to wheezing secondary to lymphatic engorgement and resultant compression of the airway within the peribronchovascular sheath. Finally, wheezing may be produced by vocal cord opposition, either volitionally (often subconsciously) or because of vocal cord dysfunction.[31]

BOX 10-4 Airway Obstruction: Wheeze and Stridor

Inspiratory Obstruction = Extrathoracic

The vibratory sound produced by inspiratory obstruction is heard during inspiration, is usually monophonic, and may be high pitched as in croup or low to medium pitched as in snoring resulting from adenotonsillar hypertrophy.

- Congenital malformations
  - Nasal, nasopharyngeal, and oropharyngeal malformations
    - Retrognathia (Pierre Robin syndrome)
    - Nasal, choanal, or nasopharyngeal stenosis; tumor; mass
    - Anterior encephalocele
    - Teratoma
  - Adenotonsillar hypertrophy
  - Obesity or redundant pharyngeal tissue
  - Hypotonia (e.g., Down syndrome)
  - Oral cavity or pharyngeal tumor
  - Lingual tumor
    - Lingual thyroid tumor
      - Hemangioma
    - Neck masses
      - Bronchial cleft cyst
      - Cystic hygroma
- Laryngeal or subglottic airway malformations
  - Laryngomalacia
  - Paralyzed vocal cords
  - Laryngeal or subglottic cysts
  - Laryngocele
  - Subglottic stenosis
  - Subglottic hemangioma
- Infection
  - Nasal, nasopharyngeal, and oropharyngeal infection
    - Tonsillitis and peritonsillar abscess
    - Sublingual abscess (Ludwig's angina)
    - Retropharyngeal abscess
  - Laryngeal and subglottic infection
    - Epiglottitis
    - Croup (spasmodic)
    - Bacterial tracheitis (usually some expiratory wheeze)
    - Juvenile respiratory papillomatosis (early)
    - Tetanus with laryngospasm
- Foreign body or aspiration
  - Gastroesophageal reflux with edema, laryngospasm
  - Foreign body aspiration in pharynx, larynx, or subglottis
- Trauma
  - Laryngeal hematoma
  - Laryngeal burns or scalds
  - Stenosis secondary to instrumentation
  - Vocal cord paralysis after surgery
- Allergy and asthma
  - Anaphylactoid reaction to food or inhalant
- Psychogenic
  - Vocal cord dysfunction
- Metabolic problem
  - Hypocalcemia or hypomagnesemia
- Acquired tumor (rare)

Expiratory Obstruction = Intrathoracic

The vibratory sound produced by this obstruction is best heard on expiration and may be focal or monophonic and of low to medium pitch or may be diffuse or polyphonic and of medium to high pitch

- Congenital malformations
  - Tracheobronchial tree malformations
    - Tracheobronchomalacia
    - Primary (focal or diffuse) tracheobronchomalacia
    - Tracheobronchomalacia secondary to compression by tumor (focal)
    - Tracheostenosis
      - VATER (vertebral defects, imperforate anus, tracheoesophageal fistula, radial and renal dysplasia) association
      - Complete tracheal rings
  - Vascular compression (ring or sling)
    - Aberrant subclavian vein
    - Pulmonary artery sling (aberrant left pulmonary artery)
    - Right-sided thoracic aorta with left ductus arteriosus
    - Left-sided thoracic aorta with right ductus arteriosus
    - Double aortic arch
  - Dilated cardiac chamber or dilated pulmonary artery with compression
- Infection
  - Intrinsic airway narrowing
    - Bronchitis
    - Bronchiolitis
    - Laryngotracheobronchitis
    - Bacterial tracheitis
    - Bronchiectasis
    - Cystic fibrosis
    - Juvenile respiratory papillomatosis (late)
  - Extrinsic airway compression
    - Mycobacterial or fungal infection with lymph node enlargement
    - Infection of congenital foregut malformations, cysts
    - Lung abscess
- Foreign body or aspiration
  - Gastroesophageal reflux with bronchitis
  - Foreign body in airway
  - Foreign body in esophagus
- Trauma
  - Tracheobronchial burns or scalds
  - Tracheobronchial injury (blunt or penetrating)
- Allergy and asthma
  - Anaphylactoid reaction to food or inhalant
  - Asthma with inflammation or bronchospasm
- Autoimmune disease
  - Bronchiolitis obliterans after lung or bone marrow transplant
  - Idiopathic bronchiolitis obliterans

Continued

BOX 10-4 Airway Obstruction: Wheeze and Stridor—cont'd

- Tumor
  - Primary airway narrowing
    - Hamartoma
    - Benign tumors (e.g., lipoma, chondroma, myoblastoma)
    - Malignant tumor
      - Bronchial adenoma
      - Bronchogenic carcinoma
      - Sarcoma
  - Extrinsic airway compression
    - Hodgkin's lymphoma
    - T cell lymphoproliferative disease with mediastinal mass
    - Sarcoma
- Pulmonary edema

Inspiratory and Expiratory Obstruction

When obstruction is evident in both phases of breathing, the obstruction may be variable and may simultaneously occur in both the intrathoracic and extrathoracic airways (e.g., croup with laryngotracheobronchitis). If this has not occurred, the obstruction may have become critical in nature. This is particularly the case in extrathoracic airway obstruction in which the development of obstruction during expiration is particularly worrisome. In contrast, with severe intrathoracic airway obstruction resulting from asthma or bronchitis, wheezing may occur in both phases of respiration but can usually be localized to the chest as opposed to the upper airway.

Evaluation of the child with wheezing starts with a careful history followed by thorough examination. When present, signs and symptoms of increased work of breathing or distress may dictate swift intervention before etiologic evaluation can take place. Depending on the age of the patient and the suspected etiology, ancillary tests may be helpful. These could include imaging studies (chest radiograph, CT, MRI, esophagogram, swallowing study), pulmonary function testing with bronchoprovocation or bronchodilator response, microbiologic studies (especially for respiratory syncytial virus in infants), and an empiric trial of bronchodilators. Bronchoscopic evaluation may also be helpful.

EVALUATION OF THE CHILD WITH EXERCISE INTOLERANCE

The majority of patients with chronic lung or cardiac disease and exercise intolerance usually have a clear reason for the inability to exercise; this may include deconditioning secondary to the primary illness. Instead of deconditioning, this section addresses the apparently normal child who has a difficult time exercising and develops dyspnea with a normal workload. These patients are commonly brought to their physician because they are unable to complete physical education at school or have a difficult time on sports teams. The approach to the apparently normal child with exercise intolerance involves delineating whether the child has a cardiorespiratory problem or is simply deconditioned (Box 10-5). The history is critical in this assessment. Data regarding symptoms compatible with asthma, cystic fibrosis, or another lung condition such as preexisting bronchopulmonary dysplasia need to be obtained. Similarly, a history of congenital or acquired cardiac disease needs to be reviewed.

Other than deconditioning, the leading cause of exercise intolerance is a variant of asthma, exercise-induced bronchospasm (EIB).[32] Children with EIB usually complain of a tightening or pain in the chest or submental triangle after vigorous exercise. This pain may be associated with frank wheezing or cough. Usually, patients complain of difficulty breathing that does not improve on stopping the exercise, but instead worsens after they sit down to rest. The symptoms then usually subside spontaneously. On cold or dry days, the tightness and cough are worse with exercise involving free running, such as soccer, football, and hockey. Swimming and cycling seem less prone to inducing bronchospasm. Some athletes notice that they can "run through" their bronchospasm or even prevent it by doing brief sprints before competing to obtain the protective effect of exercise on further EIB. Children with EIB may also have a history of spontaneous or prolonged wheezing and cough with colds. Collateral allergic symptoms should also be sought. The physical examination may be normal, but signs of allergy and asthma should be sought. Occasionally, wheezing or hyperinflation may be found; however, in children with these signs, usually asthma has already been diagnosed. Laboratory studies such as an exercise or cold-air challenge test, or eucapnic voluntary

BOX 10-5 Exercise Intolerance

- Chronic lung disease
  - Asthma
    - Exercise-induced bronchospasm
    - Vocal cord dysfunction
    - Deconditioning resulting from exercise-induced bronchospasm
  - Other pulmonary conditions
    - Bronchopulmonary dysplasia
    - Cystic fibrosis
    - Pulmonary fibrosis/interstitial lung disease
    - Other
- Congenital or acquired cardiac disease
- Deconditioning with or without obesity
- Myopathy or muscular dystrophy
- Endocrine abnormalities
  - Thyroid dysfunction
  - Cortisol insufficiency
  - Diabetes mellitus
- Other chronic illnesses

hyperventilation may be conducted both to demonstrate airway hyperreactivity and to reproduce the symptoms so that the child can confirm their nature (see Chapter 58). In contrast, a trial of a β-agonist such as albuterol before exercise may be effective in diagnosing EIB, as well as assessing a treatment modality.

Cardiovascular disease leading to exercise intolerance in an apparently normal child is uncommon and is usually diagnosed based on a history of diaphoresis and dyspnea with initiation of exercise. Furthermore, dyspnea resolves with resting compared to the persistence or worsening of EIB. A history of ankle edema, palpitations, fainting, chest pain, and nocturnal symptoms such as orthopnea or paroxysmal nocturnal dyspnea should be obtained but is positive only in children with relatively severe disease. Physical examination may reveal weight loss and fatigue, a hyperactive precordium, pathologic murmurs, and evidence of hypervolemia such as hepatomegaly and peripheral edema. Electrocardiography, chest radiography and echocardography are central to the laboratory assessment; however, a child with dyspnea and signs of cardiac disease should be referred to a pediatric cardiologist for clinical assessment and management.

It is relatively common for the pulmonary specialist to be asked to assess a child for exercise intolerance who has neither EIB nor heart disease. These children are commonly mildly to moderately obese, have a sedentary lifestyle, and do not readily engage in sports. They are commonly assessed because of an inability to keep up with school exercise programs. Their dyspnea and fatigue usually occur during exercise such as running laps. They usually do not have chest pain or cough and do not complain of any dysphoria or tightness in the submental region. They may complain of headache, leg pain, and cramping with exercise. Lacking the symptom complexes and findings previously noted, this group may most benefit from exercise testing. The clinician can use the test to reproduce the symptoms and demonstrate that the child does not have bronchospasm. Furthermore, the child may be unable to exercise vigorously enough to successfully complete an exercise challenge test. These clinical and laboratory findings combined can be useful to reassure the family that cardiorespiratory disease is not present and that deconditioning is the main problem. An exercise program and weight-control program can then be prescribed to help the child return to an active lifestyle.

EVALUATION OF THE CHILD WITH CHEST PAIN

The child with chest pain can present a challenge for the practitioner; parental anxiety is usually high because of the concern that the child may have heart disease (Box 10-6). In fact, the majority of children with chest pain have either EIB or a musculoskeletal cause that will respond to anti-inflammatory medication or nonspecific therapies.[33,34] Chest pain resulting from cardiac disease is uncommon in an apparently healthy child without other cardiac symptoms. However, chest pain associated with syncope should prompt urgent cardiac evaluation. The history should be focused after the clinician determines that the child is generally well. The pain should be characterized using the PQRST approach (see History). The pain is described as sharp, burning, or dull and aching. It is localized, and any radiation such as from the spine through an intercostal space should be noted. Radiation to the shoulder suggests diaphragmatic irritation. Worsening of the pain with breathing or movement should be noted, as should other provocative factors. The history should include a survey of activities compatible with muscular strain such as recent trauma, contact sports, and sports such as weight training. Surprisingly, many children do not associate anterior parasternal chest pain with the fact that they just began weight training to increase their pectoral muscle bulk. Also, many children carry schoolbooks in a pack or bag slung over one shoulder, leading to shoulder girdle strain. Patients with asthma, pertussis, and cystic fibrosis may develop chest pain associated with chronic cough and repetitive trauma to the ribs and muscles of the chest wall. The history should also review recent symptoms of lung infection, allergies, asthma, and EIB. Symptoms of arthritis or joint disease should be assessed, as should any recent skin changes or weight loss. Gastroesophageal reflux with esophagitis can also present as chest pain. A history of reflux after meals or on lying down with heartburn, a bitter taste in the mouth, water brash, and

BOX 10-6 Chest Pain

Musculoskeletal or soft tissue problems (most common)
- Chronic cough (asthma, cystic fibrosis, pertussis) with muscle injury
- Sports or weight training that caused muscle or joint strain
- Blunt trauma to the ribs or joints
- Costochondritis
- Tietze's syndrome
- Rheumatoid arthritis
- Breath development, inflammation
- Diaphragmatic pain
- Slipping rib syndrome

Asthma
- Acute bronchospasm, especially with exercise
- Pneumomediastinum
- Pneumothorax

Pleural inflammation
- Viral inflammation: Bornholm disease or pleurodynia
- Bacterial, mycobacterial, or fungal infection with pleurisy

Gastrointestinal or abdominal problems
- Gastroesophageal reflux
- Gastric or duodenal ulcer
- Diaphragmatic irritation caused by an intra-abdominal process

Cardiac problems (uncommon)
- Aberrant coronary problems
- Pericarditis, myocarditis, or myopathy
- Palpitations or arrhythmias that are confused with pain

Pulmonary vasculature
- Pulmonary embolus
- Sickle cell pulmonary crisis

Psychogenic or psychophysiologic problems

sensitivity to acid, high-fat foods, or coffee can be helpful. The physical examination should be relatively complete and include an assessment of general well-being and the respiratory, cardiovascular, gastrointestinal, and musculoskeletal systems. Changes on the chest wall with swelling or any mass, particularly over the costochondral and clavicular joints, should be specifically noted. Tenderness over the site of chest pain strongly implicates a musculoskeletal process. Although acute infection such as pneumococcal pneumonia with pleurisy is usually a clear diagnosis, other infections such as histoplasmosis, coccidioidomycosis, and tuberculosis may have a slow course and present with pleuritic pain. Thus, a careful chest examination for reduced air entry, crackles, or a friction rub is important. The results of chest radiography are usually normal in musculoskeletal chest pain but may be reassuring to both the parent and practitioner. Electrocardiography or stress testing is only occasionally useful in cases without additional cardiac symptoms or signs.

EVALUATION OF THE CHILD WITH HEMOPTYSIS

The approach to diagnosing hemoptysis in a child depends on whether there is a known preexisting disease such as cystic fibrosis.[35,36] In the previously well child with hemoptysis, the history is critical (Box 10-7). Care should be taken to ensure that the red or purple material expectorated was actually blood and not coloring from food. Afterward, the most important point is to try to determine that the bleeding truly represents respiratory bleeding from the lower respiratory tract and is not due to nasal, pharyngeal, or gastrointestinal bleeding (Table 10-6). A history of recent epistaxis, acute or recurrent tonsillitis, or throat trauma focuses attention on the upper respiratory tract. Indeed, examination of the nasopharynx by a specialist is sometimes important in ruling out a bleeding site in the upper respiratory tract. A history of gastroesophageal reflux, vomiting, liver disease, or portal hypertension focuses concern on the gastrointestinal tract as the source of the bleeding.

Although some streaking of the sputum in bacterial bronchitis or pneumonia is relatively common, true hemoptysis in the previously well child is rare. The hemoptysis should be characterized by the volume of blood (i.e., streaking versus submassive [<240 mL] versus massive [≥240 mL]). Whether the blood was a bright red liquid that clotted or simply old purple-brown clots should be noted. In the case of submassive and massive hemoptysis the patient may have a warm, bubbling feeling over the affected segment. The history

BOX 10-7 Hemoptysis

Pulmonary Origin of Bleeding

- Infection
  - Acute tracheobronchitis or severe pneumonia
  - Bronchiectasis
  - Erosion by an infected lymph node (mycobacteria, fungi)
  - Lung abscess
  - Fungal infection, including secondary mycetoma
  - Parasitic infection
  - Pulmonary hemorrhage in severe viral pneumonia
- Foreign body aspiration
- Bronchial tumor
  - Primary tumor
  - Secondary tumor
- Autoimmune lung disease
  - Idiopathic pulmonary hemosiderosis
  - Goodpasture syndrome
  - Milk allergy (Heiner syndrome)
  - Wegener's granulomatosis
  - Other vasculitis (e.g., Churg-Strauss)
- Pulmonary vascular conditions
  - Pulmonary embolism
  - Primary pulmonary hypertension
  - Obstructed pulmonary veins
  - Raised left atrial pressure
    - Congestive heart failure or pulmonary edema
    - Mitral valve stenosis
    - Aortic valvular stenosis or obstruction
  - Arteriovenous malformations
  - Osler-Weber-Rendu disease
  - Sickle cell pulmonary crisis
  - Pulmonary hemorrhage in acute respiratory distress syndrome
- Bronchopulmonary foregut malformations
- Trauma
  - Blunt trauma with pulmonary contusion or airway disruption
  - Penetrating trauma

Nonpulmonary Origin of Bleeding

- Upper airway conditions
  - Epistaxis
  - Sinusitis
  - Adenoidal or tonsillar bleeding
  - Severe pharyngitis or pharyngeal trauma
  - Coagulopathy with trauma to the mouth or pharynx
- Gastrointestinal conditions
  - Esophagitis with gastroesophageal reflux
  - Esophageal varices secondary to portal hypertension
  - Gastric or duodenal ulcer
  - Mallory-Weiss syndrome or esophageal erosion with severe vomiting or bulimia
  - Munchausen or Munchausen by proxy syndrome

Fictitious Bleeding

- Natural and artificial coloring in food
- Dyes in medicines
- Nasal foreign body with dye (e.g., crayon)

Table 10-6
Differential Features of Hemoptysis and Hematemesis

Hemoptysis	*Hematemesis*
Blood is coughed up, not vomited. Retching and nausea may come from pharyngeal irritation from blood.	Blood is vomited.
A portion of the blood should be frothy.	Blood is never frothy.
Blood is usually, but not always, bright red in color.	Blood is dark red in color.
Blood is alkaline in reaction.	Blood is acid in reaction.
Hemoptysis is preceded by a gurgling noise or a sensation stimulating a cough reflex. This may be absent in massive hemoptysis.	Hematemesis is preceded by nausea and vomiting.
There is sometimes a history of past cough.	There may be history of alcoholism and/or gastric disturbances, plus clinical findings of liver disease.
There is continued blood-tinged sputum, which lasts for several days.	Blood-tinged sputum is usually absent.
Blood is mixed with pus, organisms, or macrophages; some of the macrophages may contain hemosiderin particles.	Vomited blood may contain food particles.
Anemia may or may not be present.	There are often clinical and laboratory findings of blood loss before the actual hematemesis.

From Lyons HA: Basics of RD. ATS news, New York, American Lung Association, 1976.

BOX 10-8 Tissue Hypoxia

- Hypoxemic hypoxia: low arterial partial pressure of oxygen
  - Low inspired oxygen concentration (low inspired oxygen partial pressure)
    - Low barometric pressure (high altitude)
    - Low inspired oxygen concentration (low fraction of inspired oxygen)
  - Cardiorespiratory disease
  - Hypoventilation
  - Diffusion block
  - Ventilation-perfusion imbalance
  - Shunting
    - Intrapulmonary shunting
    - Extrapulmonary shunting
- Anemic hypoxia
  - Anemia
  - Carbon monoxide poisoning
  - Hemoglobinopathy
- Circulatory hypoxia
  - Shock or hypoperfusion
    - Hypovolemic shock
    - Obstructive shock
    - Cardiogenic shock
    - Distributive shock
  - Local vascular obstruction
- Histotoxic hypoxia
  - Sepsis with poor oxygen use
  - Cyanide poisoning

should rigorously assess the possibility of foreign body aspiration. This may not have been a recent event because foreign bodies leading to bleeding must usually be in the respiratory tree long enough to cause chronic infection or irritation with mucosal erosion. Past respiratory illness such as remote foreign body aspiration, pertussis, and severe pneumonia can also be associated with hemoptysis related to bronchiectasis formation. A history of heart disease should be obtained because increased left atrial pressures or obstructed pulmonary veins can lead to bleeding. Usually, however, the cardiovascular history is negative. Physical examination is usually negative in the absence of acute lung infection or chronic lung problems such as cystic fibrosis. Focal lung changes such as reduced or lagged air entry and focal hyperinflation may suggest foreign body aspiration. Coarse crackles and reduced air entry may lead to the consideration of infection and, if accompanied by clubbing, bronchiectasis. Chest radiography is used to rule out pneumonia, gross bronchiectasis, and cavitary disease. Evidence of focal hyperaeration or atelectasis may suggest focal airway obstruction resulting from a foreign body, infected lymph node, or tumor. If the diagnosis of bronchiectasis is considered, a thin-section, high-resolution CT scan rapidly identifies the presence of these lesions. Bronchoscopy can also be used, but the site may be obscured in the presence of moderate bleeding. Bronchoscopy may be most useful after the bleeding has quieted, when lesions such as bronchial adenomas, lymph nodes eroding the mucosa, and foreign bodies can be better seen. Angiography may be used and echocardiography and cardiac catheterization may have a role in diagnosing recurrent hemoptysis with no apparent lesion. In this case the hemoptysis may result from an obstructed pulmonary vein. Studies to evaluate possible vasculitis are particularly relevant when there is significant air space involvement on chest roentgenogram or associated hematuria.

EVALUATION OF THE CHILD WITH HYPOXIA

The approach to evaluating the child with evidence of tissue hypoxia requires the determination of whether the hypoxia is due to a failure of oxygen delivery or an inability of the tissues to use oxygen (Box 10-8). Failure of oxygen delivery or use may be evidenced by an alteration in global metabolism, resulting in anaerobic glycolysis with the production of a lactic acidosis, or an end-organ dysfunction (e.g., confusion secondary to cerebral hypoperfusion). A common approach has been to classify tissue hypoxia as occurring in one of four manners. The first two abnormalities lead to reduced oxygen content in the blood. The most common cause in patients with lung disease, hypoxemic hypoxia, is due to a reduced arterial partial pressure of oxygen, leading to an inadequate saturation of hemoglobin (see later section). The second is anemic hypoxia. Even with a normal arterial partial pressure of oxygen and hemoglobin saturation, anemia (reduced functional hemoglobin) leads to reduced oxygen delivery resulting from reduced oxygen capacity in the blood. This occurs in carbon monoxide poisoning, in which the hemoglobin is bound with the carbon monoxide, reducing the amount available to carry oxygen. In addition, carbon monoxide poisoning increases the affinity of hemoglobin for oxygen, further

reducing oxygen delivery to the tissues. If oxygen content is adequate but signs of tissue hypoxia are present, there are two possibilities. Either the oxygen is not being delivered to the tissues, or the tissues are unable to use oxygen in aerobic metabolism. The former is called *circulatory hypoxia* and may occur globally as in shock or locally as in vascular obstruction with ischemia. The latter, *histotoxic hypoxia*, occurs in sepsis and cyanide poisoning of aerobic metabolism when the cells are unable to conduct aerobic glycolysis.

The approach to hypoxemic hypoxia (see Box 10-8) is to divide potential causes into five categories. As in assessing tissue hypoxia, the clinician simply needs to work through the steps of the oxygenation of blood in the lung to delineate potential problems. First, a reduced inspired oxygen partial pressure leads to hypoxemia in the absence of compensatory hyperventilation. This may result from a reduced fractional concentration of oxygen secondary to oxygen consumption by combustion or of other gases in the environment. It may also occur with a reduced barometric pressure caused by increases in altitude. Hypoventilation with an increase in the level of alveolar carbon dioxide and decrease in the level of alveolar oxygen causes hypoxemia as a result of a failure to ventilate adequate oxygen into the lungs to meet the body's metabolic demands. These first two causes of hypoxemia are associated with a normal alveolar-arterial oxygen difference. Thickening of the alveolar-capillary membrane may cause the normal perfusion limitation of oxygen transfer to become diffusion limited and lead to hypoxemia. Increased cardiac output and reduced alveolar oxygen levels exacerbate this diffusion block. Areas of local hypoventilation in the lung resulting from either airway or airspace disease lead to hypoxemia secondary to a ventilation-perfusion imbalance, with incomplete saturation of blood passing through these regions of the lung. Finally, blood from the systemic venous system may bypass the ventilation entirely, either because of intrapulmonary shunting with lung disease or arteriovenous fistulae or because of extrapulmonary shunting with congenital heart or great vessel malformation (cyanotic congenital heart disease). The arterial carbon dioxide level may be normal in all of these conditions except hypoventilation. This is because the healthy, well-ventilated lung can compensate for the dysfunctional lung by clearing excess carbon dioxide. Unfortunately, blood that is normally ventilated is already nearly completely saturated with oxygen, and thus healthy units cannot return arterial oxygen to normal by overcompensating for units with diffusion block, ventilation-perfusion imbalance, or shunt. Finally, shunt is commonly separated from the other causes of hypoxia because it does not respond to the administration of supplemental oxygen with a significant increase in arterial oxygen levels.

EVALUATION OF THE CHILD WITH HYPOVENTILATION

The definition of *hypoventilation* is an increase in the arterial carbon dioxide level above 45 mm Hg; it is, by definition, a respiratory acidosis. It may differ with the apparent minute ventilation, tidal volume, or respiratory rate. *Hyperpnea* and *hypopnea* refer to an apparent increase or decrease in overall breathing; however, *hyperventilation* and *hypoventilation* refer specifically to the level of arterial carbon dioxide achieved. The first step in assessing the child with hypoventilation is to try to determine whether the respiratory pump is functioning as well as expected in response to substantive lung disease or whether it is a primary or adjunctive cause of the increased arterial carbon dioxide (Box 10-9). Second, the pump may be functioning properly and delivering adequate minute ventilation; however, there may be an increased ventilation of physiologic dead space with reduced alveolar ventilation. This may result either from a reduction in tidal volume with a fixed physiologic dead space or from an increase in physiologic dead space that is not matched by an increase in tidal volume. In either case, the dead space/tidal volume ratio increases, and alveolar ventilation is compromised, leading to carbon dioxide retention.

The differential diagnosis of airspace or airway disease that can lead to carbon dioxide retention is broad and is not addressed further here. The differential diagnosis of a failure of the respiratory pump is considered here because it may apply even in patients in whom lung disease is paramount. A useful approach is to work through the steps necessary for the maintenance of minute ventilation, starting centrally with respiratory control and ending with the respiratory muscles and chest wall (see Box 10-9). Failure may result from central controller failure or disruption of upper motor neuron function, such as in sedation or cervical cord damage. Lower motor neuron disease may occur at a cellular level, such as in poliomyelitis, or may be more peripheral resulting from damage to the phrenic nerves caused by trauma or demyelinating diseases. The neuromuscular junction may inadequately conduct the neural impulse, such as in botulism, or the muscle may be unable to respond, such as in profound hypokalemia. Finally, even if the controller/feedback system is functioning and the respiratory muscles are able to respond, the chest wall itself must be able to function as a pump without reduced motion or inappropriate paradoxical motion.

EVALUATION OF THE CHILD WITH BRONCHITIS

Bronchitis is a clinical respiratory problem that is common in childhood. It occurs as an acute illness generally secondary to a viral upper respiratory tract infection, as well as a chronic component of underlying asthma, cystic fibrosis, foreign body aspiration, immunodeficiency, immotile cilia syndrome, and other conditions. Low-grade airway inflammation occurs secondary to inhalable noxious agents such as passive smoke or various environmental pollutants. In children, unlike in adults, chronic bronchitis per se is not considered a final diagnosis.

Because of its frequent occurrence, it would seem that bronchitis should be easily characterized and defined. However, the primary and at times exclusive manifestation of the disease is cough, a symptom of little diagnostic specificity. Other than viral studies, no noninvasive laboratory tests are available to specifically diagnose bronchitis in young children. The self-limited course of acute bronchitis as well as the lack of a consistent definition of *chronic bronchitis* in childhood have limited pathologic investigation and characterization of the disease in childhood. In adults, *chronic bronchitis* is defined as a condition of chronic or recurrent productive cough that is present on most days for 3 months in a year for 2 years.[37] Whether this definition can be applied

BOX 10-9 Hypoventilation

Reduced Minute Ventilation

- Respiratory pump failure as a primary cause
  - Central controller failures
    - Encephalopathy or brain stem dysfunction
      - Infection
      - Intoxication
      - Metabolic dysfunction or seizure
      - Tumor
      - Trauma, concussion, or hemorrhage
      - Malformation (Arnold-Chiari malformation)
    - Central hypoventilation syndrome
    - Metabolic alkalosis
  - Cervical spinal cord disruption (upper motor neuron)
    - Infection
    - Tumor
    - Trauma, concussion, or hemorrhage
    - Inflammation (transverse myelitis)
    - Compression (achondroplasia, Down syndrome)
    - Multiple sclerosis
  - Cervical spinal cord (lower motor neuron: cell)
    - Infection (poliomyelitis)
    - Inflammation or degeneration (transverse myelitis)
    - Vasculitis or vascular accident
    - Werdnig-Hoffman disease
  - Phrenic or intercostal nerves (lower motor neuron: axon)
    - Trauma (thoracic surgery or penetrating injury)
    - Demyelinating neuropathies (Guillain-Barré syndrome)
    - Tumor
  - Neuromuscular junction failure
    - Myasthenia gravis
    - Botulism
    - Aminoglycosides
    - Pseudocholinesterase deficiency
  - Respiratory muscle failure
    - Muscular dystrophies
    - Extreme electrolyte abnormalities
    - Extreme starvation or metabolic imbalance
    - Familial paralysis syndromes (e.g., hypokalemia)
  - Chest wall disease or disruption
    - Flail chest
    - Restrictive chest wall disease
      - Kyphoscoliosis
      - Congenital chest wall malformation or dystrophy
      - Ankylosing spondylitis
    - Prune-belly syndrome (infancy)
- Increased elastic and resistive work with muscle fatigue
  - Increased elastic work
    - Pulmonary fibrosis
    - Pulmonary edema
      - Cardiogenic edema
      - Noncardiogenic edema (adult respiratory distress syndrome)
    - Diffuse pneumonia
  - Increased resistive work
    - Upper airway obstruction
    - Lower airway obstruction
  - Mixed increase in elastic and resistive work

Increased Physiologic Dead Space

- Increased physiologic dead space
  - Increased anatomic dead space
    - Severe bronchiectasis
  - Increased alveolar dead space
    - Alveolar distention or overexpansion
      - Intrathoracic airway obstructive airway disease
      - Mechanical ventilation with inadvertent positive end-expiratory pressure
    - Shock with reduced pulmonary perfusion pressures
    - Pulmonary embolus
- Reduced tidal volume with normal physiologic dead space

to childhood bronchitis remains unclear. Thus, no generally agreed-on definition of *acute*, *chronic*, *recurrent*, or *wheezy bronchitis* in childhood exists.[38] Furthermore, the clinical presentation of children with asthma, wheezy bronchitis, and recurrent and chronic bronchitis overlaps considerably. A diagnosis of bronchitis should therefore cautiously be considered.[39] It has the potential to divert the pediatrician from detecting a more specific respiratory condition.

Several studies have demonstrated the importance of childhood respiratory problems in the development of chronic pulmonary disease in adulthood.[40-43] Despite these limitations, it seems important to understand bronchitis in its various forms.

ACUTE BRONCHITIS

Acute Viral Bronchitis

Viruses produce most attacks of acute bronchitis.[44] Rhinovirus, respiratory syncytial virus, influenza virus, parainfluenza virus, adenovirus, rubeola virus, and the paramyxoviruses all have been identified as etiologic agents.[45,46] Attacks of acute bronchitis can occur at any time during the year but are most common in the winter, when the respiratory virus season peaks.[47] A knowledge of which pathogens are currently endemic is helpful but not conclusive etiologic evidence.

Because acute bronchitis is usually a mild and self-limited condition, the pathology is ill defined because of the lack of tissue to study. Mucous gland activity increases, and desquamation of the ciliated epithelium occurs. Infiltration of polymorphonuclear leukocytes into the airway walls and lumen contributes to a purulent appearance of the secretions. Because this leukocytic migration is a nonspecific response to airway damage, purulent sputum does not necessarily imply bacterial superinfection.[48]

Acute bronchitis usually follows symptoms of upper respiratory tract infection such as serous rhinitis and pharyngitis. The cough usually appears 3 to 4 days after the rhinitis. The

cough is initially harsh and dry but frequently evolves into a loose cough with significant sputum production. Because young children do not expectorate but generally swallow the mucus, vomiting associated with cough paroxysms can occur. Chest pain secondary to a progressive severity and production of sputum with cough may be a prominent complaint in older children.

Auscultation of the chest is usually unremarkable in the early stages. As the cough progresses, variable rhonchi, harsh breath sounds, wheezes, or a combination thereof may be heard. Crackles are infrequent. Chest radiographs are normal or may have increased bronchial markings. Generally, the symptoms resolve within 10 to 14 days. If the clinical signs persist beyond 2 to 3 weeks, a chronic condition should be suspected. Occasionally, a secondary bacterial infection occurs.

Acute Bacterial Bronchitis

Mycoplasma pneumoniae has occasionally been identified as an organism producing acute bronchitis in school-age children and adolescents.[46,49] There are no characteristic clinical findings. Positive cold hemagglutination titers associated with a concomitant rise in specific *Mycoplasma* titers confirm the diagnosis. Treatment with a macrolide antibiotic or tetracycline in children over 9 years of age can be effective.

In unimmunized children, infections with *Bordetella pertussis* and *Corynebacterium diphtheriae* are associated with a characteristic tracheobronchitis. During the catarrhal stage of pertussis, symptoms of upper respiratory tract infection, such as rhinitis, conjunctivitis, low-grade fever, and cough, predominate. As the paroxysmal stage develops, episodes of coughing increase in number and severity. Characteristically, repetitive series of forceful coughs during a single expiration are followed by a sudden massive inspiratory effort, which produces the whoop. This cough eventually dislodges thick, tenacious mucus. Posttussive emesis associated with the paroxysms is a characteristic symptom even in the child without whoop. The pathologic findings of pertussis bronchitis include infiltration of the mucosa with lymphocytes and polymorphonuclear leukocytes. Furthermore, necrosis of the midzonal and basilar layers of the mucosa has been observed. Leukocytosis with an absolute lymphocytosis occurs characteristically at the end of the catarrhal stage and the beginning of the paroxysmal stage. Culture and fluorescent antibody tests of secretions can confirm the diagnosis. Treatment of pertussis is largely supportive. Erythromycin may eliminate pertussis organisms from the nasopharynx within 3 to 4 days, thereby decreasing spread of the disease. Given within 14 days of the onset of illness, erythromycin may abort pertussis. However, once paroxysms of cough develop, this medication has little effect on the course of the illness.[50]

Progressive cough and lung disease starting at a few weeks of age in conjunction with conjunctivitis or blepharitis is highly suggestive of chlamydial infection. Diagnosis can be made by culture, fluorescent antibody, or serology studies, and therapy with erythromycin is usually effective. Infection with *Ureaplasma* organisms may closely mimic chlamydial disease.[51] Although difficult to diagnose, these infections may respond to a therapeutic trial with erythromycin.

CHRONIC, RECURRENT, AND WHEEZY BRONCHITIS

The persistence of signs and symptoms of acute bronchitis or frequent recurrences should initiate an attempt to identify an underlying illness. Clinicians do not generally agree on a definition of chronic or recurrent bronchitis in childhood. Factors that must be defined are where the isolated, recurrent episodes end and the chronic state begins and how many episodes are "too many." For the purpose of this discussion, *chronic bronchitis* is defined as the symptom complex of chronic (greater than 1 month) or recurrent (at least four) episodes of productive cough per year that may be associated with wheezing or crackles on auscultation.

The chronicity and recurrence of the condition suggests either that an endogenous susceptibility or increased response to acute airway injury exists or that continuing exposure to noxious environmental agents produces the symptoms. Host factors include a variety of underlying illnesses, whereas exogenous factors affect susceptible and normal airways as well. An airway that suffers an insult responds in a limited number of ways.[39] Inflammation, edema, increased sputum production, and disordered mucus clearance occur in varying degrees and produce cough. Depending on the severity of the airway damage and the resulting increase in airflow resistance, wheezing may also be present. In subjects with bronchial hyperresponsiveness, acute airway injury may furthermore trigger bronchial obstruction, also leading to cough and wheeze. Thus, cough and wheezing are nonspecific symptoms that reflect airway damage and narrowing without regard to mechanism and etiology.

This overlap of syndromes has created considerable confusion in clinical as well as in epidemiologic studies of chronic bronchitis in childhood and has limited assessment of its prevalence. When restricting the definition of *chronic bronchitis* to a productive cough that received medical therapy and lasted more than 2 weeks, Peat and associates[52] found an overall prevalence of 14% to 24% in Australian children. Other definitions of *chronic* or *recurrent bronchitis* have led to widely different estimates of its prevalence (Table 10-7). The overlap of syndromes and the lack of tissue studied have furthermore hampered pathologic investigation of chronic bronchitis in childhood.

Table 10-7
Prevalence of Childhood Bronchitis

Reference	Study	Prevalence	Asthma/ Bronchitis Ratio
Burrows et al[41]	1977: Arizona children (chronic)	46.4%	1 : 1.6
Peat et al[52]	1980: Sydney children (acute and chronic)	20%	1 : 3
Dockery et al[112]	1980/1981: children living in six U.S. cities	3.6-10.0%	1 : 0.7 to 1:2.4
von Mutius et al[119]	1989/1990: East German children (recurrent)	33.7%	1:1.7
von Mutius et al[120]	1989/1990: West German children (recurrent)	15.9%	1:4.7

CLINICAL ASSESSMENT AND DIFFERENTIAL DIAGNOSIS

The diagnosis of chronic bronchitis should occur in two phases (Box 10-10). The first is consideration and identification of several well-defined respiratory disorders according to a staged management protocol (Box 10-11). The second but simultaneous phase is elimination or modification of exogenous factors that produce or maintain the child's illness. Diagnostic tests selected on the bases of the child's history, the incidence of the suspected disease, the morbidity to the patient, and the costs are performed. At the same time, the parents are encouraged to avoid exposing the child to irritants such as cigarette smoke or recurrent viral respiratory tract infections in daycare centers.

Phase I: Differential Diagnosis

ASTHMA

Asthma is the most likely diagnosis in a child with recurrent or chronic bronchitis. Burrows and Lebowitz[53] showed in an epidemiologic survey in the United States that 74% of children with a diagnosis of chronic bronchitis were wheezing. Moreover, skin test reactivity was associated with symptoms of bronchitis. When subjects in whom asthma was first diagnosed between the ages of 10 and 20 years were prospec-

BOX 10-10 Differential Diagnosis of Chronic and Recurrent Bronchitis

Phase I: Specific Etiologies

- Asthma
- Preexisting lung disease
  - Respiratory distress syndrome and bronchopulmonary dysplasia
  - Postinfectious bronchiectasis
- Cystic fibrosis
- Foreign body aspiration
  - Intrathoracic or extrathoracic airway
  - Esophagus
- Aspiration syndromes
  - Abnormal enteropulmonary communications (e.g., laryngeal cleft)
  - Dysfunction of swallowing
  - Gastroesophageal reflux
- Airway compression
  - Weakened wall (e.g., tracheomalacia)
  - Extrinsic compression (e.g., vascular ring)
- Congenital heart disease
- Immunodeficiency
- Primary cilia abnormalities

Phase II: Nonspecific Airway Irritation

- Exposure to recurrent respiratory tract infections in daycare centers
- Cigarette smoke
  - Passive smoke exposure
  - Active smoking
- Air pollution
  - Outdoor secondary to particulate matter, automobile exhaust, and other pollutants
  - Indoor secondary to wood burning, irritants, and chemicals

BOX 10-11 Diagnostic Evaluation of Bronchitis

Initial Assessment

History
- Assessment of the presence of cough, wheezing, and lower respiratory tract infections
- Identification of specific symptoms of possibly underlying respiratory conditions

Physical examination
- Assessment of general well-being, height, weight, chest circumference, and signs of chronic airway disease
- Notice of worrisome signs such as clubbing

Laboratory
- No tests in acute bronchitis
- Complete blood count and differential, immunoglobulin E level, sweat chloride test, and chest radiograph
- Skin prick tests to assess atopy and specific allergens
- Skin tests for tuberculosis and fungal infection
- Baseline pulmonary function testing and response to bronchodilators or bronchial challenge
- Chlamydial culture, serology, or both tests in infants younger than 6 months of age

Therapy
- Bronchodilators
- Chest physiotherapy and management of gastroesophageal reflux
- Trial of erythromycin in infants and school-age children

Follow-up

Interim history
- Response to therapeutic trial
- Repeat of questions about specific symptoms of possible underlying respiratory conditions

Interim physical examination
- Improvement of findings after therapeutic trial
- Unexpected changes in pulmonary status

Laboratory
- Barium swallow, high-kilovolt airway films
- Measurement of levels of immunoglobulin G and its subclasses
- Assessment of cilia

Therapy
- If patient is doing well, continuation of bronchodilators and physiotherapy for 1 month and then consideration of trial off medication
- If patient is not doing well, consideration of parental compliance by starting theophylline and measuring the medication level
- If patient is not doing well, consideration of a trial of antibiotics

tively investigated, a prior diagnosis of chronic bronchitis was found to be an independent risk factor for asthma, more reflecting the natural history of the disease than estimating the risk for developing it.[54] Boule et al[55] found decreased dynamic compliance with evidence of air trapping and increased airway reactivity in 29 children with recurrent bronchitis. Conversely, chronic cough in children without any clinical evidence of asthma or another respiratory disease has been associated with exercise-induced airway hyperreactivity.[56] Both the cough and airway hyperreactivity were relieved by oral theophylline therapy. This overlap of the clinical presentations of asthma and chronic bronchitis has made the distinction between these conditions very difficult.

Wheeze in relation to viral infections has commonly been labeled *wheezy bronchitis* or *wheezing associated respiratory illness* (WARI) to differentiate it from asthma because of additional precipitating factors and different age distributions of the disease.[57] Evidence suggests that in many children with recurrent wheeze, WARI is simply the first presentation of what will later become diagnosed as asthma. In an Australian study, both children with wheezy bronchitis (wheeze with viral infections only) and children with asthma differed from a control population in several atopic markers.[58] Furthermore, no difference in the genetic backgrounds of either condition could be found.[59] Finally, the clear demonstration that asthma was both underdiagnosed and undertreated[60,61] was in part held to be attributable to the use of terms such as *wheezy* or *asthmatoid bronchitis*. The prognosis and pathophysiologic features of each condition may differ, however. The outcome of childhood wheeze after 25 years was significantly worse for adults with a diagnosis of childhood asthma compared with those with a diagnosis of wheezy bronchitis.[62] Lower levels of lung function in the first months of life precede and predict the development of wheezing respiratory illnesses during the first 3 years of life.[63-65] Thus, in some infants, wheezing respiratory illnesses may be driven by anatomic abnormalities such as initial lower airway diameters and lengths or alterations of the lung parenchyma and may disappear with lung maturation. The challenge for the clinician is to assess the likelihood that recurrent wheeze in an infant or toddler actually represents a nascent asthma phenotype and not either non-atopic wheeze or other pathologic condition.

The recognition of the variability in obstructive airway disease presentation and course in children led to the description by Martinez and associates[66] of distinct wheezing phenotypes in childhood, namely, transient early wheeze (present in the first year of life, resolving by early school years), late-onset ("non-atopic") wheeze (onset in the first 3 years of life, resolving in early adolescence), and persistent ("atopic") wheeze (onset in mid-preschool years with persistence into adolescence) (Fig. 10-4). Presented a slightly different way, Figure 10-5 combines the phenotypes to allow estimation of the proportion of each phenotype at any given age. Early in life transient wheeze predominates, whereas in the early school years, the non-atopic wheeze group makes up about two thirds of children with wheeze. However, after ages 9 to 12, atopic wheeze and persistent asthma account for most of the wheezing children, highlighting the role of atopy in preventing remission of wheezing illness.

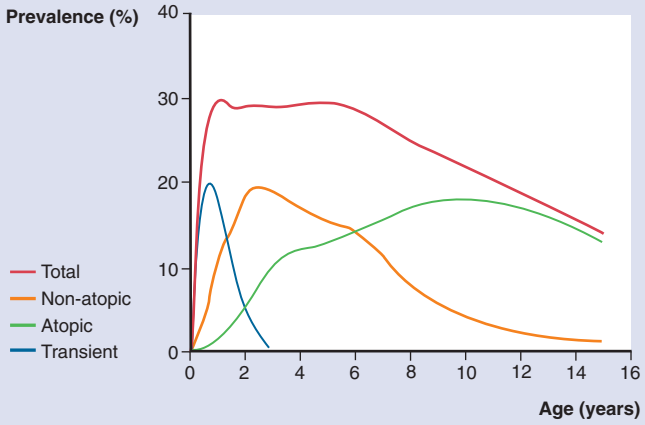

Figure 10-4 Schematic representation of the incidence of asthma phenotypes in childhood. (Redrawn with permission from Martinez FD, Godfrey S: Wheezing Disorders in the Preschool Child. New York, Martin Dunitz, Taylor & Francis Group, 2003, p 15.)

Wheezing illnesses continuing beyond infancy and the development of asthma may be determined by a child's susceptibility to become atopic.[67] For clinical practice, infants with recurrent wheezing illnesses and atopic stigmata such as eczema, elevated immunoglobulin E (IgE) levels, or a family history of atopy may be more likely to develop asthma in later years, whereas non-atopic wheezing infants who have been exposed to environmental noxious agents such as maternal smoking may have a better prognosis. However, a diagnosis of wheezy bronchitis should not prevent the pediatrician from initiating a therapeutic trial of bronchodilators.

A history of wheezing in children with recurrent or chronic bronchitis that responds to bronchodilator therapy or occurs with exercise, cold air, laughter, or exposure to allergens should be considered evidence of asthma. Nocturnal cough apart from colds or cough with exercise is suggestive of airway hyperreactivity. A family history of asthma or allergy may further add to the diagnosis of asthma. Evidence of

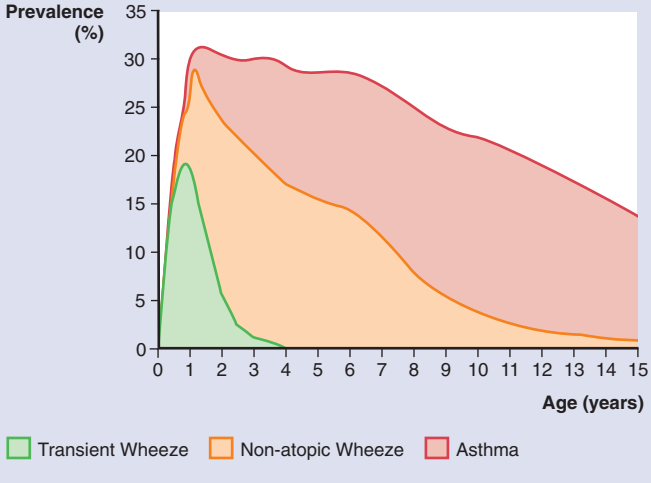

Figure 10-5 Relative proportion of childhood wheezing attributable to various phenotypes.

BOX 10-12 Asthma Predictive Index

Child with ≥3 Episodes of Wheeze by 3 Years of Age

Major Criteria	Minor Criteria
Parental asthma (physician diagnosed)	Allergic rhinitis (physician diagnosed)
Eczema (physician diagnosed)	Wheezing apart from colds
	Peripheral eosinophilia (≥4%)

Adapted from Castro-Rodriguez JA, Holberg CJ, Wright AL, et al: A clinical index to define risk of asthma in young children with recurrent wheeze. Am J Respir Crit Care Med 162:1403-1406, 2000.

allergy such as positive skin prick tests, elevated serum IgE levels, blood eosinophilia, or more than 20% eosinophils in sputum examined with Hansell stain can support the diagnosis of asthma. However, airway hyperreactivity can exist without concomitant allergy. Thus, the absence of atopy should not obviate a therapeutic trial of bronchodilators.

Castro-Rodriguez and associates[68] found an index composed of some of these characteristics to be helpful in predicting continued wheezing in young children with recurrent wheezing (Box 10-12). In a child with three or more episodes of wheezing by 3 years of age, the index is considered to be "positive" if a child has one major criterion or two minor criteria. A positive index is associated with an increased risk of continued frequent wheezing at ages 6, 8, 11, and 13 years. Thus, it may be more reasonable to institute anti-inflammatory therapy earlier in children with a positive asthma predictive index than in those whose index is negative. While doing so may result in better symptom control, early anti-inflammatory therapy has recently been shown to not influence subsequent outcome in terms of development of asthma in later childhood.[69]

Pulmonary function tests can be reliably performed in children as young as 5 years. Measurement with spirometry allows the baseline assessment of airway obstruction. A significant bronchodilator response aids in the diagnosis. Furthermore, airway reactivity to different physical stimuli such as exercise or cold air or to pharmacologic agents such as methacholine or histamine can be determined. The availability of relatively inexpensive spirometers should make the measurement of pulmonary function an integral part of the assessment of every child with chronic airway disease.

A trial of bronchodilator therapy is useful in both the diagnosis and management of children with asthma. However, long-term therapy should be aimed at reducing airway inflammation by administering medications such as cromolyn, nedocromil, and inhaled steroids.

PREEXISTING PULMONARY DISEASE

Congenital abnormalities and airway injury acquired early in life can predispose children to subsequent pulmonary disease. Considering and identifying such early pulmonary insults may be crucial in understanding the clinical course of some chronic airway diseases. Infants who survive neonatal respiratory distress syndrome are at higher risk for developing respiratory illnesses in the first year of life and beyond.[70-73] The risk is highest for children who require mechanical ventilation and subsequently develop bronchopulmonary dysplasia, but it is also increased in children who have a history of respiratory distress syndrome but no bronchopulmonary dysplasia. In a significant number of these children, airway hyperreactivity, exercise-associated desaturation, cough, and wheezing can be demonstrated.[71,72,74,75]

Early lung injury by chlamydial, viral, or *B. pertussis* infection is associated with long-term pulmonary sequelae[76,77] and may leave a child vulnerable to repeated lower respiratory tract infections. This increased susceptibility may be attributable to the induction of airway hyperreactivity, preexisting small airways, or a fixed small airway obstruction. In some cases, pneumonia caused by adenovirus, respiratory syncytial virus, measles virus, or *B. pertussis* may lead to the development of bronchiectasis. This condition should be suspected in a child who has a history of sustained productive cough exacerbated by a postural change or who has digital clubbing.

CYSTIC FIBROSIS

Cough is the most constant symptom of pulmonary involvement in cystic fibrosis. At first, the cough may be dry and hacking, but eventually, it becomes loose and productive. Sometimes the disease remains asymptomatic for long periods, or the infant seems to have prolonged acute respiratory infections. Accompanying symptoms of gastrointestinal malabsorption, such as bulky, greasy stools, and failure to gain weight despite a large food intake, should alert the pediatrician to the diagnosis of cystic fibrosis. Thus, serial documentation of weight and height measurements should be part of every follow-up of children with chronic respiratory conditions. Furthermore, a diagnosis of cystic fibrosis should be considered in children with increased anteroposterior diameters of the chest, generalized hyperresonance, digital clubbing, and bronchiectasis. Cystic fibrosis is the diagnosis most tragic to miss in children with chronic or recurrent bronchitis because early initiation of therapy may alter the course of the illness and early diagnosis can alert the parents to the risk of having other children with the same disease. Thus, a sweat chloride determination should be obtained in every child with chronic or recurrent bronchitis.

The sweat test should be performed using quantitative pilocarpine iontophoresis to collect sweat and to analyze its chloride content. Because this method requires care and accuracy, it should be performed by a center that frequently performs these tests.[78] The amount of sweat collected should be measured and reported. For reliable results, at least 75 mg, preferably 100 mg, of sweat should be collected. Because of low sweat rates, accurate testing may be difficult in the first weeks of life. More than 60 mEq/L chloride in sweat is diagnostic of cystic fibrosis.

FOREIGN BODY ASPIRATION

Foreign bodies aspirated into and retained in the tracheobronchial tree should always be considered in the differential diagnosis of chronic bronchitis.[79] A careful history and a high index of suspicion are important for the identification of this

condition. Sudden violent cough, wheezing, and gagging may occur, but after the aspiration of small foreign bodies, the onset may be insidious or overlooked, and a persistent cough and wheezing may be the only presenting signs. Occasionally, persistent or recurrent pneumonia that does not completely clear with adequate antibiotic therapy may lead to the diagnosis. Unsuspected foreign bodies have been identified as the cause of chronic respiratory illness in a significant number of children. They may produce chronic airway inflammation, distal atelectasis, bronchiectasis, and severe lung damage and may thus distract from an accurate diagnosis. Physical examination, especially differential auscultation with a binaural stethoscope, can be helpful.[39] Decreased breath sounds are found over the affected side; delayed air entry into the involved lobe, regional prolongation of exhalation, and a louder wheezing can be heard. Inspiratory-expiratory and decubitus chest radiographs confirm the physical findings and may show unilateral obstructive emphysema or atelectasis. Bronchoscopy should always be performed if the possibility of a foreign body aspiration exists.

ASPIRATION SYNDROMES

A history of cough with feeding is suggestive of conditions associated with recurrent aspiration of feedings or gastric contents after reflux. "Bottle propping" (i.e., propping the bottle up in the crib so that the infant can drink while falling asleep) can cause chronic cough and wheezing in infants and toddlers and is associated with later persistence of asthma or recurrent wheezing into the school years.[80] Furthermore, chronic irritation of the airway subsequent to feeding can occur in conditions such as an H-type tracheoesophageal fistula, a laryngeal cleft, and dysfunctional swallowing mechanisms such as familial dysautonomia, submucous cleft palate, cerebral palsy, and muscular dystrophy.[81] If very small amounts of material are aspirated or aspiration occurs primarily during sleep, chronic cough, wheezing, and rattling breathing may be the only presenting signs. The extent of pulmonary injury after aspiration is in part determined by the pH, the amount, and the particulate content (milk or other foods) of the aspirate.[82] Wolfe and colleagues[83] have proposed that chronic aspiration produces airway erythema with disruption of the normal tracheal clearance. Increased mucus production and a subsequent "wet" cough could then mimic the clinical appearance of chronic bronchitis.

Nocturnal cough may indicate the presence of gastroesophageal reflux. The pathophysiologic changes in chronic pulmonary disease subsequent to reflux may be attributable to microaspirations of refluxed material into the lungs or to reflex bronchoconstriction when acid is present in the lower esophagus. Chronic respiratory illness may also be seen in patients who have undergone repair of esophageal atresia. The prevalence of annual bouts of bronchitis was 74% in children under 15 years of age in an Australian center.[84] Multiple factors, including recurrent inhalation of gastric or esophageal contents, structural instability of the major airways, and abnormal airway epithelium, may contribute to these problems.

Swallowing as well as esophageal anatomy and function can be assessed with a barium swallow and esophagram. The documentation of gastroesophageal reflux may require prolonged pH monitoring.

AIRWAY COMPRESSION

Chronic airway compression can lead to a chronic, dry, irritative cough. Extrathoracic lesions such as laryngomalacia and subglottic hemangioma lead to collapse during inspiration, with a resulting characteristic inspiratory stridor. These conditions are rarely mistaken for chronic bronchitis. Tracheomalacia and intrathoracic airway compression, however, result in collapse on expiration with wheezing. Functional or structural abnormalities of the tracheal cartilages have been reported in primary tracheomalacia, whereas vascular rings or slings as well as perihilar adenopathy and mediastinal tumors account for intrathoracic airway compression. Irrespective of the underlying condition, the wheezing is most obvious with forced exhalation during cough and laughing. In addition, lower respiratory tract infections worsen both the cough and the wheezing because of increased airway resistance upstream of the obstruction, resulting in a more dynamic collapse.

Physical examination may demonstrate a wheeze and prolonged expiration. Differential auscultation with a binaural stethoscope can be helpful in further localizing the abnormality, and the findings on auscultation are similar to those of a foreign body aspiration. Airway compression by an abnormal vessel may be seen on an esophagram, and echocardiography may confirm the diagnosis of an aberrant vessel such as a double aortic arch. Chest CT scanning, particularly spiral CT, can be useful in delineating vascular and other compressions of the central airways. The ease with which flexible fiberoptic bronchoscopy can now be conducted by skilled and experienced bronchoscopists makes this a most useful study in assessing children with suspected extrinsic airway compression.[85] Before surgical correction, MRI can be used to definitely outline the vascular anatomic structures without requiring intravascular contrast medium or x-ray exposure.[86]

CONGENITAL HEART DISEASE

Wheezing and chronic airway obstruction can be major manifestations of pulmonary edema. Narrowing of both large and small airways may underlie this condition. Although peribronchiolar cuffs of fluid would be expected to lead to increases in airway closure and resistance, morphometric studies provide no support for the notion that interstitial lung edema compresses airways.[87] They suggest that alveolar or airway luminal edema may be responsible for the increase in resistance with edema. Small airways contribute a relatively greater proportion of the total airway resistance in infants. This becomes important in the assessment of young children with known "mild" heart disease such as ventricular septal defect or patent ductus arteriosus and left-to-right-shunts. A trial of diuretics and more aggressive management of the pulmonary congestion may relieve symptoms. However, Hordof and associates[88] found no improvement until repair of the lesion was carried out despite vigorous cardiotonic therapy. In addition, some children with interstitial edema as a result of left-sided heart failure with a variety of underlying diseases, such as cor triatriatum, mitral stenosis, and congenital hypoplastic left heart syndrome, have also had recurrent wheezy attacks. The differentiation between primary and secondary lung disease in this situation requires effective communication among the cardiologist, pulmonologist, and child's pediatrician.

INFECTIONS

An additional factor important for the recurrence or maintenance of airway inflammation is the frequency of lower respiratory tract infections. A prospective study of 108 children found protracted bacterial bronchitis to be the most common cause of chronic cough.[89] The average number of infections in the infant and preschool child varies but can be as high as 8 to 10 per year. Children with frequent infections of the upper and lower respiratory tract are prone to subsequent respiratory viral infections, predominantly of the lower respiratory tract.[90] Whether this increased susceptibility is attributable to minor abnormalities in immune response mechanisms, small airway size, or altered airway reactivity remains to be elucidated. Repeated and prolonged episodes of lower respiratory tract infections should always alert the pediatrician to consider an underlying cause, most frequently airway hyperreactivity.

Other infectious agents may cause chronic bronchitis. Infections with *Chlamydia* or *Ureaplasma* organisms can lead to progressive cough and lung disease in infants. *B. pertussis* can cause airway damage and an unremitting chronic cough in infants and preschool children. *M. pneumoniae* should be considered a possible causative agent in school-age children. Furthermore, mycobacterial or fungal infection must be ruled out as a cause of chronic cough and wheezing. Delayed hypersensitivity skin testing and fungal serologies can aid in the diagnosis. The chest radiographs may reveal enlarged hilar nodes or parenchymal infiltrates.

IMMUNODEFICIENCY

Recurrent respiratory disease represents the main clinical expression in children with humoral immunodeficiency syndromes such as common variable hypogammaglobulinemia, common variable immunodeficiency, or X-linked infantile (Bruton's) agammaglobulinemia.[91] Bronchitis is often not the sole manifestation of these conditions, but there are also associated recurrent episodes of pneumonia, sinusitis, and otitis media. Therefore a thorough evaluation of the child's history and a careful physical examination provide important clues for the diagnosis.

In addition, minor abnormalities in humoral defense mechanisms such as isolated and combined IgG subclass deficiencies, in particular IgG_2 subclass deficiency, have been described in children with recurrent bronchitis.[92-94] Antibodies against polysaccharide antigens, the main determinants of encapsulated bacteria, are found mainly in the IgG_2 subclass. It has been reported that children with recurrent bronchitis and recurrent infections show a decreased humoral immune response to *Haemophilus influenzae* type b and to pneumococcal type 3 polysaccharide antigen.[95,96] The significance of selective IgA deficiency remains unknown.

PRIMARY ABNORMALITIES OF CILIA

Chronic airway disease may be produced by cilia defects. Cilia and their supporting structures contain several proteins. A great variety of genetic abnormalities can therefore lead to some form of ciliary dyskinesis. Abnormal mucociliary clearance results in chronic bronchitis and eventually in bronchiectasis as a late complication. In addition, the absence of ciliary clearance from the middle ears, eustachian tubes, and sinus cavities results in an increased incidence and greater severity of chronic otitis media and sinusitis.[97] A positive family history and situs inversus (Kartagener syndrome) may add to the diagnosis. Electron microscopy of cilia obtained from nasal or bronchial biopsy can detect structural abnormalities of the cilia. Functional abnormalities can be observed by examining the beating of cilia with a phase-contrast microscope in fresh specimens of mucosa.[98]

Phase II: Exogenous Factors Contributing to the Development of Chronic or Recurrent Bronchitis

Having ruled out the diagnoses previously discussed, it is important to identify other factors that may produce chronic or recurrent bronchitis. Moreover, these factors not only contribute to the development of bronchitis but may also maintain symptoms of bronchitis in other, better-defined conditions such as asthma. Exogenous factors such as increased exposure to infectious diseases in daycare centers, passive smoke, or air pollution may need other endogenous predisposing factors to produce bronchitis in certain affected children. Most of these factors are theoretically amenable to therapy by avoiding the exposure.

CHILD CARE SETTING

The frequency of infection in a particular child relates to his or her susceptibility regarding the degree of exposure to viral infections. The risk of developing lower respiratory tract infections has been reported to increase up to twofold or more for children between 4 months and 3 years of age who are in child care situations involving the presence of three or more unrelated children.[99] In the same study, the presence of siblings was also associated with risks of lower respiratory tract infections of a magnitude similar to the risks of exposure to unrelated children, but only in the first 6 months of life. Another case-control study has furthermore shown a similar risk for the development of lower respiratory tract infections requiring hospitalization in children younger than 2 years of age whose care situations involved the presence of more than six children.[100] These findings underline the importance of including epidemiologic aspects in the evaluation of a child with chronic or recurrent bronchitis. Also, they suggest that children with a known susceptibility to chronic airway disease such as chronic or recurrent bronchitis, asthma, bronchopulmonary dysplasia, or cystic fibrosis should avoid exposure to repeated respiratory infections in large daycare settings.

CIGARETTE SMOKE

Cigarette smoking has been identified as the major cause of obstructive lung disease among adults in the United States. In children and in young adults who have recently taken up smoking, increases in the prevalence of respiratory symptoms such as cough, phlegm production, and shortness of breath have been reported.[101,102] Among young teenagers, functional impairment attributable to smoking may be found after as little as 1 year of smoking 10 or more cigarettes a week.[103]

Passive smoke exposure may produce effects similar to those elicited by active smoking. However, several differences both between active and passive forms of exposure and among the individuals exposed need to be considered.

Approximately half of the smoke produced by a cigarette is sidestream smoke. Compared with the concentration of mainstream smoke inhaled, the concentration of smoke components inhaled by a passively exposed subject is small. However, the mean diameter of particles from sidestream smoke is smaller than that of mainstream smoke. Furthermore, the level of respirable particulate substance in an "average" indoor smoking environment is greater than the levels of total particulates considered safe in outdoor pollution monitoring.[104]

Individual susceptibility may be an important determinant of the possible adverse effects of passive smoke exposure on respiratory morbidity. Among adults a self-selection process occurs, whereby those more susceptible to the irritant effects of tobacco smoke either never start or quit smoking. Passively exposed infants and children may include a disproportionate number of subjects prone to developing chronic airway disease subsequent to exposure.

Several studies have noted that children exposed to environmental tobacco smoke are at considerably higher risk of having acute lower respiratory tract illnesses and chronic respiratory symptoms, such as cough, phlegm, and wheezing, than unexposed children.[105-110] The majority of studies found that the effect was stronger among children whose mothers smoked than among those whose fathers smoked.[105-109] In addition, several studies also reported a dose-response relationship between degree of exposure (number of cigarettes smoked) and the risk of acute and chronic respiratory illness.[109] These findings support the existence of a causal explanation for the association. There is also convincing evidence that the risk inversely correlates with age; infants no older than 3 months of age are reported to be 3.3 times more likely to have lower respiratory illnesses if their mothers smoke 20 or more cigarettes per day than infants of nonsmoking mothers.[109] A relative risk of 1.5 to 2.0 has been reported in older infants and young children. This decrease in risk may be attributed to a decrease in illness frequency, maturation of the respiratory tract and immune system, or decreased contact between mother and child with age.

Smoking caregivers in a child-care setting can add to the risk of developing lower respiratory tract infections regardless of maternal smoking status. An increased risk for wheezing lower respiratory tract infections of up to threefold or more has been demonstrated in young children who were in a child-care setting with a smoking caregiver after controlling for maternal smoking and other risk factors.[99] These findings illustrate the potential interaction of environmental factors in eliciting airway irritation and acute and chronic respiratory disease.

In the adolescent, active smoking becomes a significant problem. A study of Irish teens found that bronchitis symptoms were more common among active smokers than nonsmokers (odds ratio, 3.02, 95% confidence interval, 2.34 to 3.88; $p < 0.0001$) and in passive smokers than in nonexposed teens (odds ratio, 1.82, 95% confidence interval, 1.32 to 2.52; $p < 0.0001$).[111] Determinants of the initiation of smoking seem to be related to parental smoking, peer and sibling smoking, and personality. Every child and young adult with symptoms of chronic and recurrent bronchitis should be asked about personal smoking habits in a confidential setting; the clinician should realize that the history is of questionable validity if parents or siblings are present. The impact of passive smoke exposure on the development of the presenting symptoms can thus be assessed. In addition, preventing initiation of smoking in children at risk for chronic lung disease may be possible. The clinician should vigorously discourage any smoking in the child's environment.

AIR POLLUTION

Air pollution with high levels of sulfur dioxide and particulate matter has long been associated with respiratory morbidity in children and adults.[112-115] Studies of school children in England and Germany found increased rates of respiratory illness among children living in areas with high pollution levels, including sulfur dioxide and particulate matters.[113,116,117] Follow-up studies of these children 3 to 4 years later, after the introduction of clean-air programs, demonstrated major reductions in air concentrations of particulate matter and a decline in respiratory morbidity among the school children.[110,118] The American Six Cities Study reported a positive correlation of the prevalence of bronchitis and chronic cough with exposure to particulate matter in relatively small concentrations.[112] A twofold increased prevalence of recurrent bronchitis was furthermore demonstrated in an area with high air pollution from sulfur dioxide and particulate matter in East Germany compared with a less polluted region in West Germany.[119,120] Increased prevalence of respiratory symptoms has also been reported in children exposed to heavy automobile traffic.[121] The reasons for such an increase are unknown. Findings of an association among high concentrations of sulfur dioxide, particulate matter, and nitrogen dioxide with upper respiratory tract infections suggest that air pollutants may not only produce irritative symptoms but also enhance susceptibility to common infections and subsequent lower respiratory tract infections.[122]

In addition to outdoor pollutants, the indoor environment should be assessed for every child with symptoms of chronic and recurrent bronchitis. In particular, wood-burning stoves have been associated with acute respiratory illnesses.[123] Chronic airway irritation by noxious agents may furthermore be found with formaldehyde emissions from chipboards[124] and with activities such as house cleaning, artistic pursuits, and hobbies.

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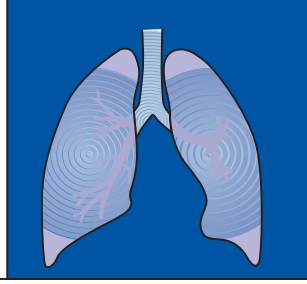


CHAPTER 11 Imaging of the Respiratory System

Eric Crotty and Alan S. Brody

TEACHING POINTS

- Multiple modalities are available for imaging the respiratory system.
- Spiral and high-resolution computed tomography have different applications.
- Controlled ventilation technique improves the quality of high-resolution computed tomography scanning.
- Use computed tomography for airways and lungs; consider magnetic resonance imaging for mediastinal masses and vascular structives.
- Nasal and paranasal structures are best imaged with computed tomography and magnetic resonance imaging.
- Complex pleural effusions are best evaluated with ultrasonography.
- Be conscious of the ALARA (As Low As Reasonably Achievable) principle.

Diagnostic imaging is an often-used discipline in the evaluation of the respiratory system in the pediatric population. It is a continuously changing area of medicine, highlighted by rapid developments of new imaging technology. However, the judicious use of this technology remains of the utmost importance, especially in the pediatric population in whom there is ongoing concern regarding the long-term effects of even low-dose radiation exposure.

This chapter discusses the various modalities available in modern imaging and their use in investigating disorders of the respiratory tract, with some advice on the appropriate use of diagnostic imaging.

PHYSICAL PRINCIPLES OF IMAGING MODALITIES

Radiography

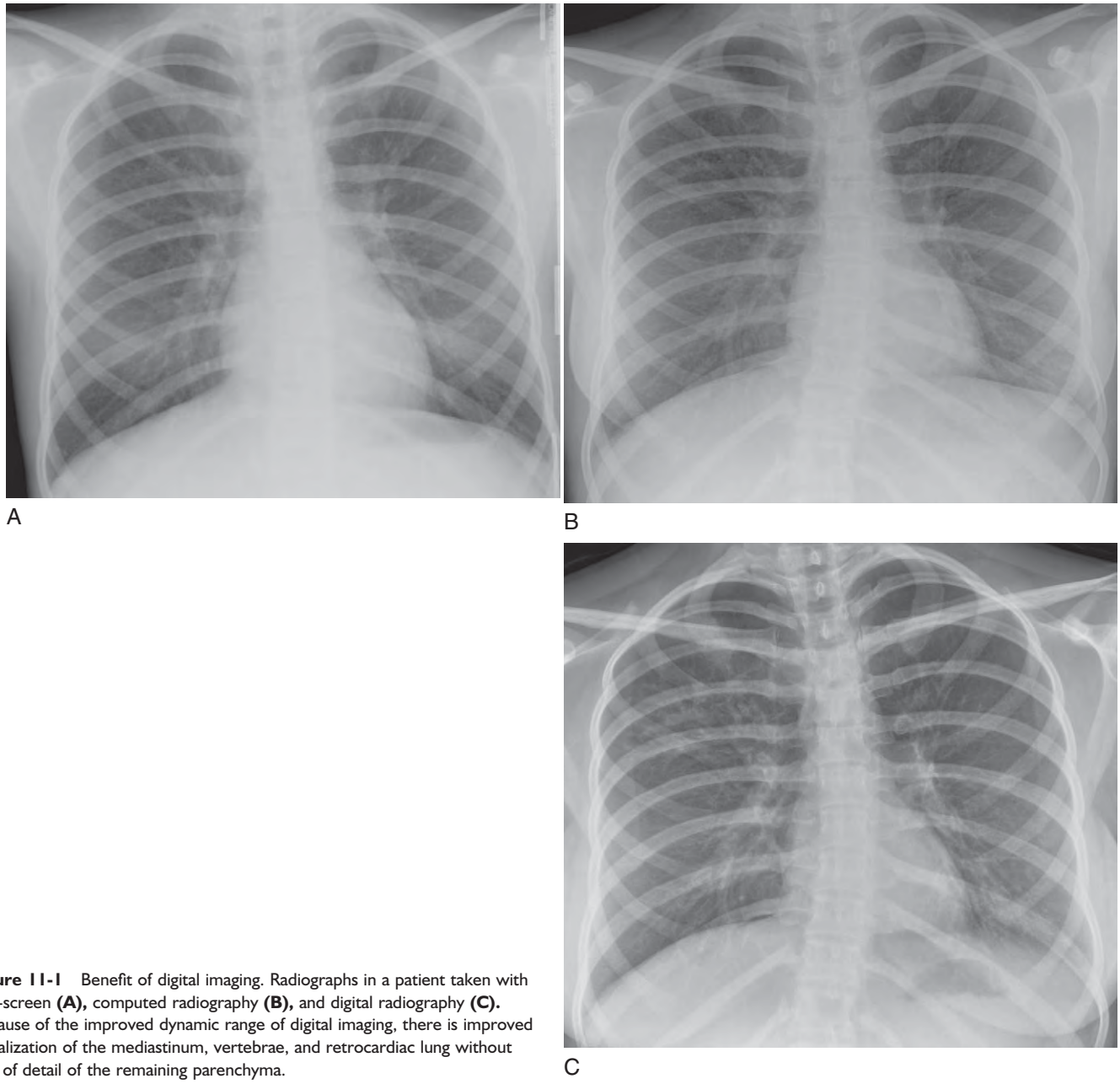
The most commonly used imaging modality is radiography, which utilizes x-rays, a form of electromagnetic radiation. A spectrum of x-rays of varying energies is produced when an electron beam emitted from a cathode strikes a target anode. The characteristics of this x-ray beam can be varied by altering the maximum voltage across the x-ray tube (kvP), the tube current in milliamperes (mA), and filtration. The characteristics of the beam are altered so that a sufficient number of x-ray photons traverse the body and interact with the film or detector such that an image is produced after processing. The photons in the beam that do not pass through the patient are generally deposited in the patient as absorbed radiation.

Current concern regarding the long-term effects of low-dose radiation exposure comes from extrapolation of data obtained from patients with a history of high-dose radiation exposure such as in atomic bomb survivors.[1] These effects include an increased risk of leukemia and other malignancies, and consequently every effort should be made to limit radiation exposure. This can be achieved if the ALARA (As Low As Reasonably Achievable) principle is implemented. The most effective method of achieving this reduction is to limit radiation exposure to those children who truly need the study and, if possible, performing imaging with modalities that do not use radiation. In addition, using low-dose techniques such as coning of the primary radiation beam, shielding of gonads, and using high-speed rare earth radiography systems will help in dose reduction in patients that do need to be exposed to radiation for diagnosis.[2,3] The introduction of digital (DR) and computed radiography (CR) has decreased the need for radiographs to be repeated, thus saving the patient from further exposure. CR and DR allow the image to be manipulated so that an adequate image is obtained rather than an image that is underexposed or overexposed (Fig. 11-1).

Both a frontal and a lateral radiograph are obtained in most patients, as additional information may be gleaned from a lateral radiograph that is not evident on the frontal radiograph alone[4] (Fig. 11-2). A frontal radiograph only is usually obtained in patients who are immobile, such as in intensive care. Occasionally, decubitus views are also obtained, usually to assess for air trapping (abnormal side down) (Fig. 11-3) or to evaluate for an effusion (abnormal side down) (Fig. 11-4).

Fluoroscopy

Fluoroscopy, which also uses x-rays, enables dynamic visualization by the radiologist of air- or contrast-filled structures and can be used to detect dynamic airway caliber changes, evidence of external compression on the trachea, and signs of air trapping from a foreign body. It is also used in esophagrams, video swallowing studies, and other positive contrast studies. This technique uses an image intensifier to convert the x-rays exiting from the patient into an image that can be viewed live and then can be recorded for review and storage. As with radiography, the use of digital fluoroscopy allows for postprocessing of the image without increasing the patient's exposure to radiation.



A

B

C

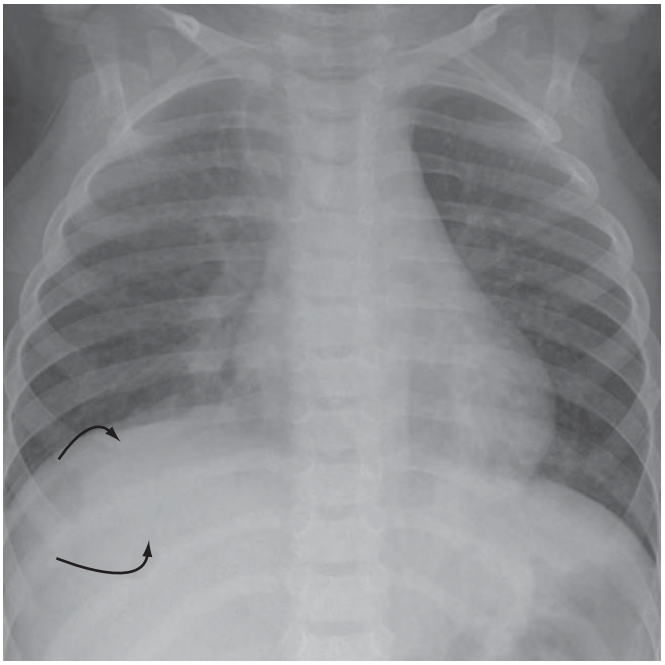
Figure 11-1 Benefit of digital imaging. Radiographs in a patient taken with film-screen **(A),** computed radiography **(B),** and digital radiography **(C).** Because of the improved dynamic range of digital imaging, there is improved visualization of the mediastinum, vertebrae, and retrocardiac lung without loss of detail of the remaining parenchyma.

Nuclear Medicine

In radiography, fluoroscopy, and other forms of imaging that use x-rays, the radiation used to make the image originates from a source external to the patient. In nuclear medicine imaging, the radiation source is the patient who has been administered the radiation-emitting substance at the start of the examination. This material can be given via various routes such as intravenously, orally, or by inhalation and is administered in such a way that its uptake is primarily in the organ of interest. The emitted energy is detected by a scintillation camera, and an image is produced.

Technetium-99m attached to macroaggregates of albumin, which are large enough to lodge in the capillary network of the lungs, are injected intravenously for lung perfusion scans, while ventilation scans are performed during the inhalation of technetium-99m–labeled diethylenetriaminepentaacetic acid (DTPA) or other radiolabeled material that is distributed in the lungs during inhalation (Fig. 11-5). Nuclear imaging is also used to demonstrate gastroesophageal reflux by mixing technetium-99m sulfur colloid with liquid or semisolid material. Patients at risk for aspiration of saliva can be investigated by performing a nuclear salivagram using sulfur colloid.[5]

Positron emission tomography (PET) is increasing in use and importance in the investigation of tumors, especially lymphoma. The degree of uptake of the most commonly used radioisotope, fluorodeoxyglucose (FDG), is related to the degree of glucose utilization. Malignant tumors are generally more metabolically active than benign tumors, with metastases being as metabolically active as the primary tumor. Infections can also accumulate FDG.



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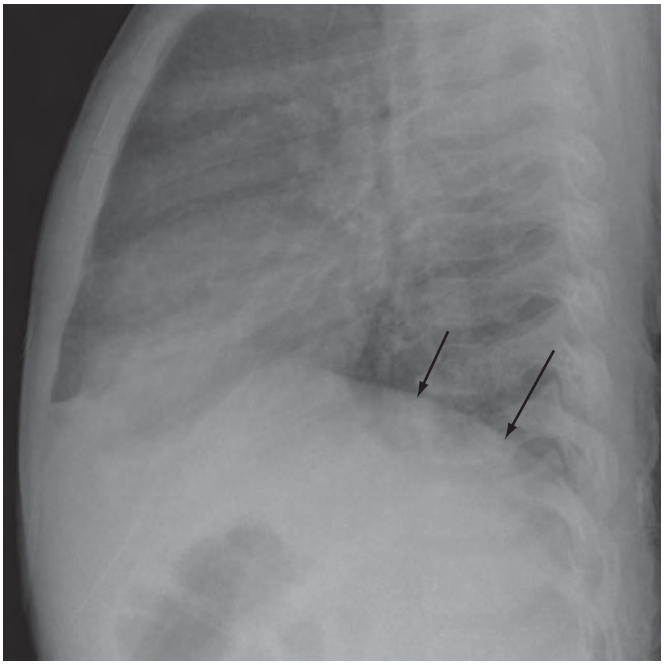
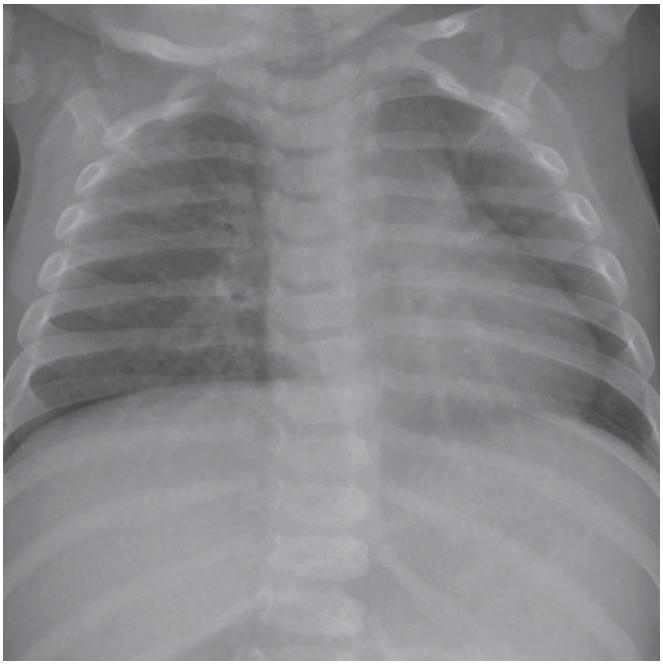


B

Figure 11-2 Usefulness of a lateral image: a 2-year-old boy with a cough and fever. The frontal radiograph **(A)** demonstrates a subtle increased density in the right lower lobe *(curved black arrows)*. However, on the lateral radiograph **(B),** the left hemidiaphragm is easily visible *(arrows)*, while the right hemidiaphragm is obscured by consolidated lung.



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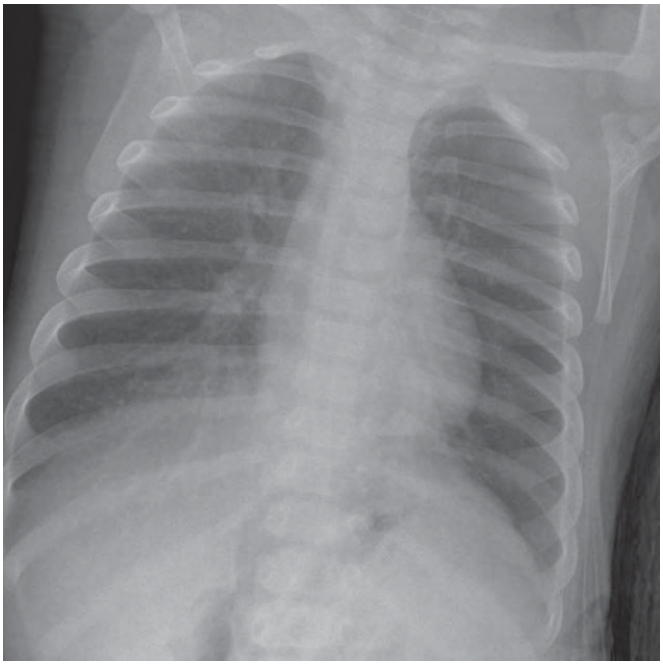
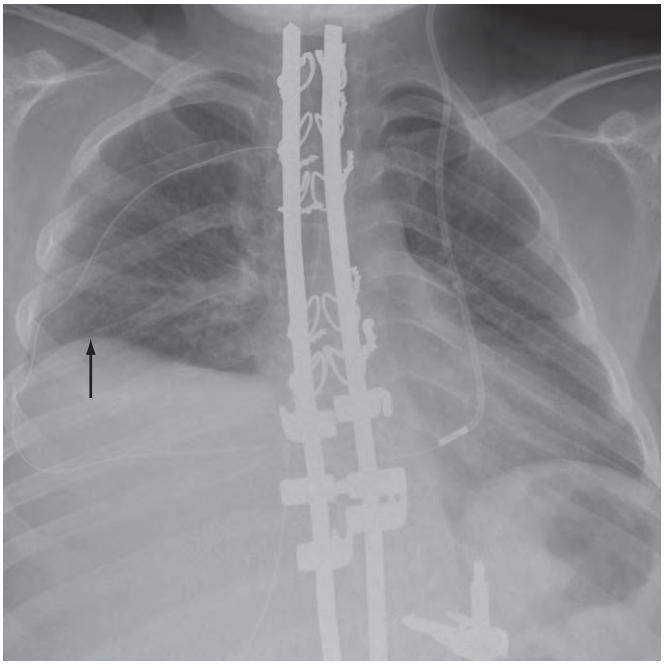


B

Figure 11-3 Usefulness of decubitus imaging: a 7-month-old girl with a cough. The frontal radiograph **(A)** demonstrates subtle increased lucency in the left lung. In the left lateral decubitus position **(B),** the left lung does not decrease in volume as expected. At bronchoscopy, a leaf was extracted from the left main bronchus.

Ultrasound

In ultrasound, high-energy sound waves are transmitted by a transducer into the area of interest. Tissues transmit and reflect these waves differently depending on their composition, and the reflected sound waves are recorded by the transducer, allowing for characterization of these tissues. As ultrasound does not use ionizing radiation, it is an imaging modality greatly favored for investigating pediatric patients. However, because air is a poor conductor of sound waves, ultrasound has limited use in the investigation of pulmonary disease as aerated lung generates an uninterpretable image. Hence, the use of ultrasound in imaging the chest is limited to the evaluation of nonaerated structures such as pleural fluid, the thymus, the diaphragm including diaphragmatic motion,[6] and soft tissue lesions of the chest wall (Fig. 11-6).



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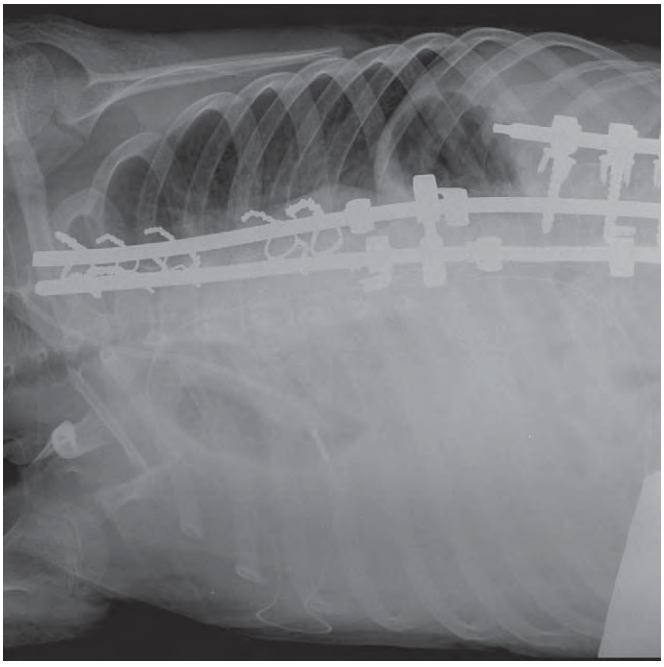


B

Figure 11-4 Usefulness of decubitus images: a 13-year-old boy status post spinal surgery. The frontal radiograph **(A)** demonstrates elevation and lateral displacement of the apex of the right hemidiaphragm *(arrow)*. Right lateral decubitus image **(B)** demonstrates layering of pleural fluid along the right chest wall, confirming the suspicion that the elevated diaphragm was due to a subpulmonic effusion.

Although the presence of a pleural effusion is usually already known from radiographs, the complexity of a parapneumonic pleural fluid collection (Fig. 11-7) and the need for intervention can be accurately assessed by ultrasound. Children with septations identified on ultrasound have been shown to benefit from intervention, whereas children with no septations do not.[7]

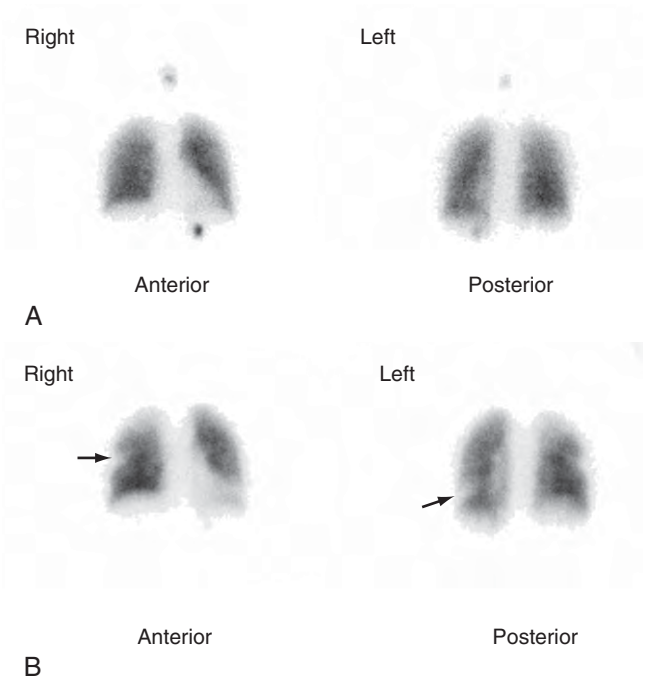


Figure 11-5 Nuclear medicine imaging: teenager with a history of a glioblastoma multiforme who presents with shortness of breath. Ventilation imaging **(A)** demonstrates even distribution of isotope throughout the lungs bilaterally. Perfusion imaging **(B)** demonstrates multiple perfusion defects *(arrows)* consistent with a high probability of pulmonary emboli.

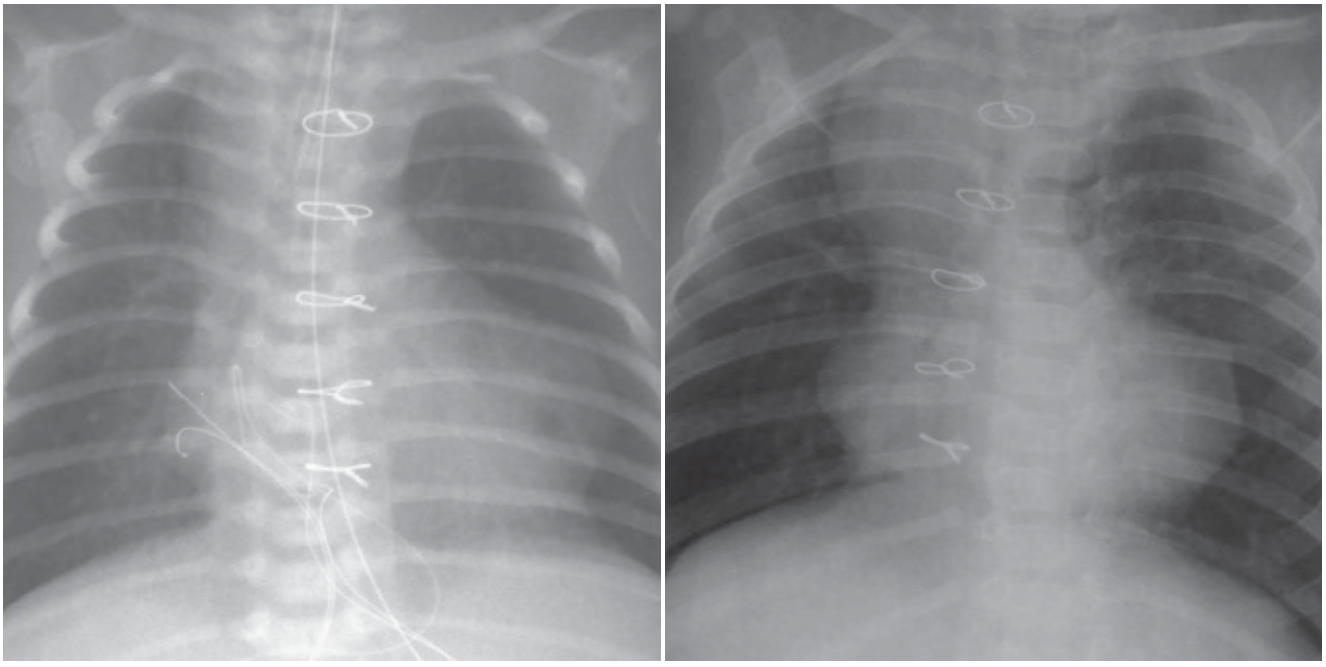
Ultrasound imaging of the fetus allows for the diagnosis of congenital lung lesions such as congenital diaphragmatic hernia, congenital cystic adenomatoid malformation, and pulmonary agenesis, allowing for anticipation of perinatal problems.

Many congenital lesions decrease in size during the third trimester, but the lesions do not completely resolve. Postnatal CT scans will demonstrate these lesions, while chest radiographs frequently will not.[8]

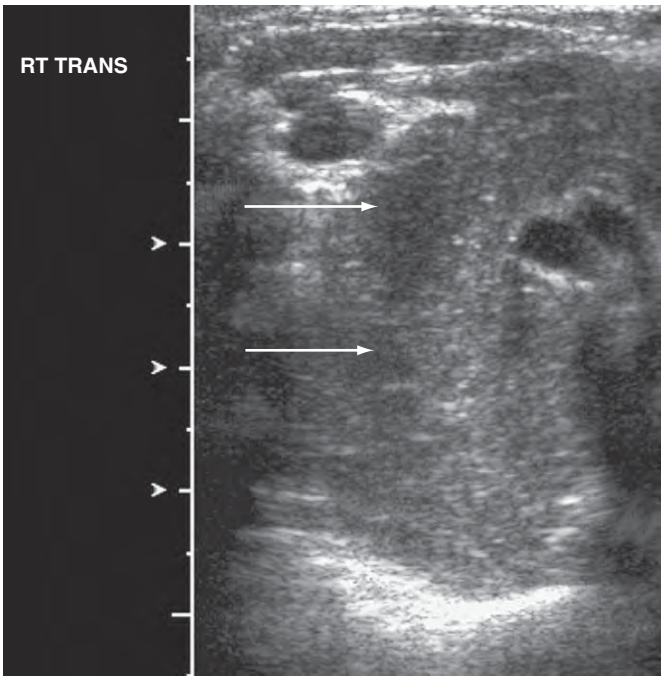
Color flow Doppler ultrasound imaging demonstrates the direction and relative velocity of flowing blood. This allows vascular structures to be accurately identified as arteries or veins and permits analysis of the vascularity of a mass. Again, because of the poor transmission of sound waves through aerated lung, color flow Doppler is useful only in evaluating chest wall or mediastinal lesions.

Computed Tomography

With CT, a group of detectors record x-rays that have been transmitted through a patient, having originated from an anode as it rotates around the body within the CT gantry. The images performed at each position during the rotation of the anode around the patient are combined during processing to form a cross-sectional image of the patient at that slice position, before the next slice position is imaged. Like radiography, the quantity of x-rays reaching the detector determines the various densities recorded; however, the range of densities that can be recorded is far greater, allowing far more accurate characterization of abnormal areas. Various algorithms are used to reconstruct the image depending on the structure that is of interest (lung, mediastinum, bone). The



A B



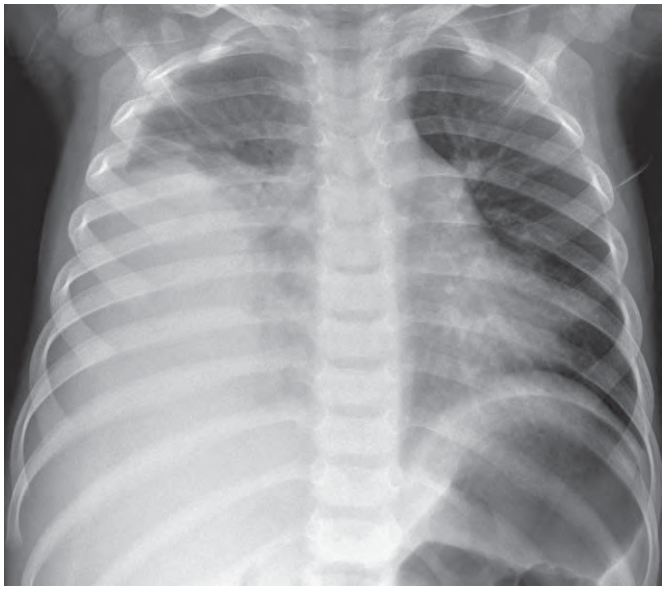
C

Figure 11-6 Utility of ultrasound imaging: infant status post surgery for congenital heart disease. Radiograph **(A)** prior to discharge demonstrates a normal mediastinum. Subsequent radiograph **(B)** 6 months later demonstrates a widened mediastinum. Ultrasound **(C)** demonstrates this to be due to rebound of normal thymic tissue *(arrows)*.

quality of CT imaging and the speed at which the imaging can be performed are continually being improved. CT scanners now use what is called spiral or helical technique, in which the patient is moved continuously through the CT scanner without stopping for each slice. In addition, a broad band of x-rays is received by a series of detectors in the longitudinal plane, producing multiple slices for each rotation of the gantry. The time taken to perform spiral CT of the chest is on the order of 2 to 5 seconds using a multidetector scanner, depending on the size of the patient. This speed allows the radiologist to obtain diagnostic quality images in uncooperative patients.

CT provides the best imaging of the anatomy of the lungs and tracheobronchial tree. Parenchymal detail, such as the secondary pulmonary lobule, can be visualized on high-resolution computed tomography (HRCT), which is used to sample the parenchyma in diffuse lung disease (Fig. 11-8).

In the spiral CT, imaging is performed contiguously from the apices of the lungs through the bases during inspiration. In traditional HRCT, there are a few important differences from spiral CT. First, imaging is performed not only during inspiration but also during expiration to assess for air trapping (Fig. 11-9). Second, very thin slices (approximately 1 mm) are taken with a gap between each slice. In inspiration, the



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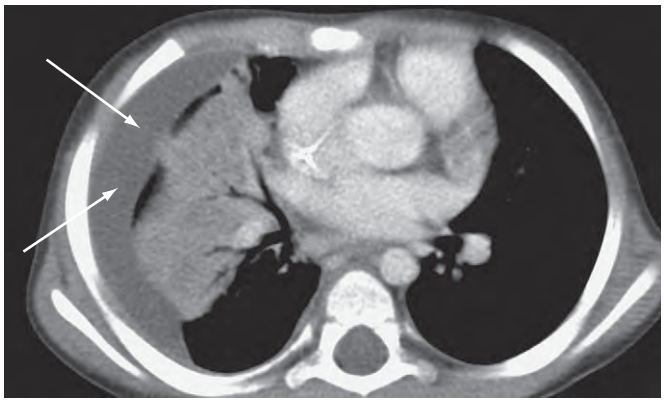

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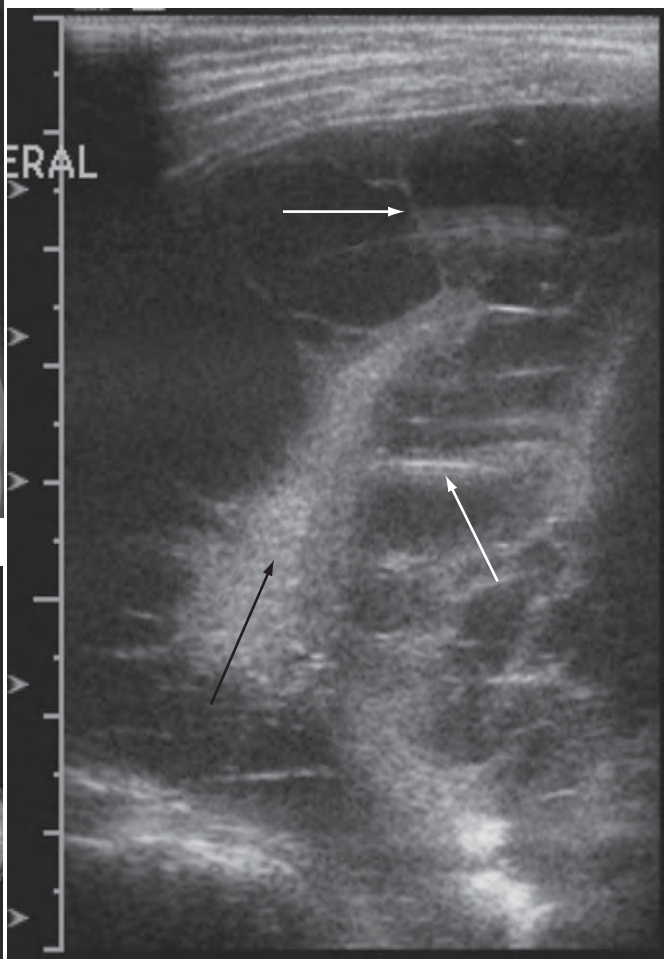


C

Figure 11-7 Utility of ultrasound: a 2-year-old boy with hypoxia and fever. Radiograph **(A)** demonstrates homogeneous opacification of the lower right chest. A CT scan **(B)** demonstrated a simple-appearing pleural effusion *(white arrows)* in the right hemithorax. Ultrasound examination **(C)** demonstrated the consolidated lung *(black arrow)* surrounded by fluid that contains many septations *(white arrows)*, indicating that this was a complex effusion.

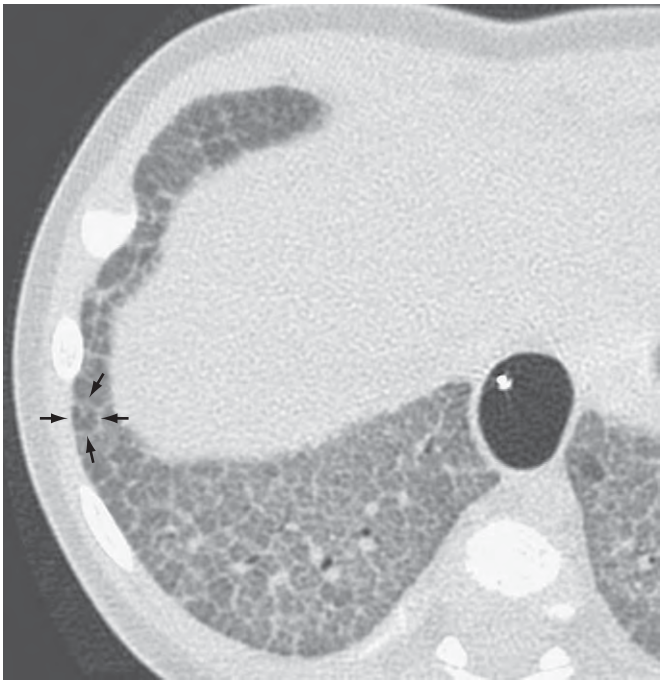


Figure 11-8 Detail seen with high-resolution computed tomography (HRCT): 3-month-old boy with chronic respiratory distress. HRCT image demonstrates interlobular septal thickening with diffuse ground-glass opacification. Note the visualization of secondary pulmonary lobules *(arrows)* in this patient with alveolar proteinosis.

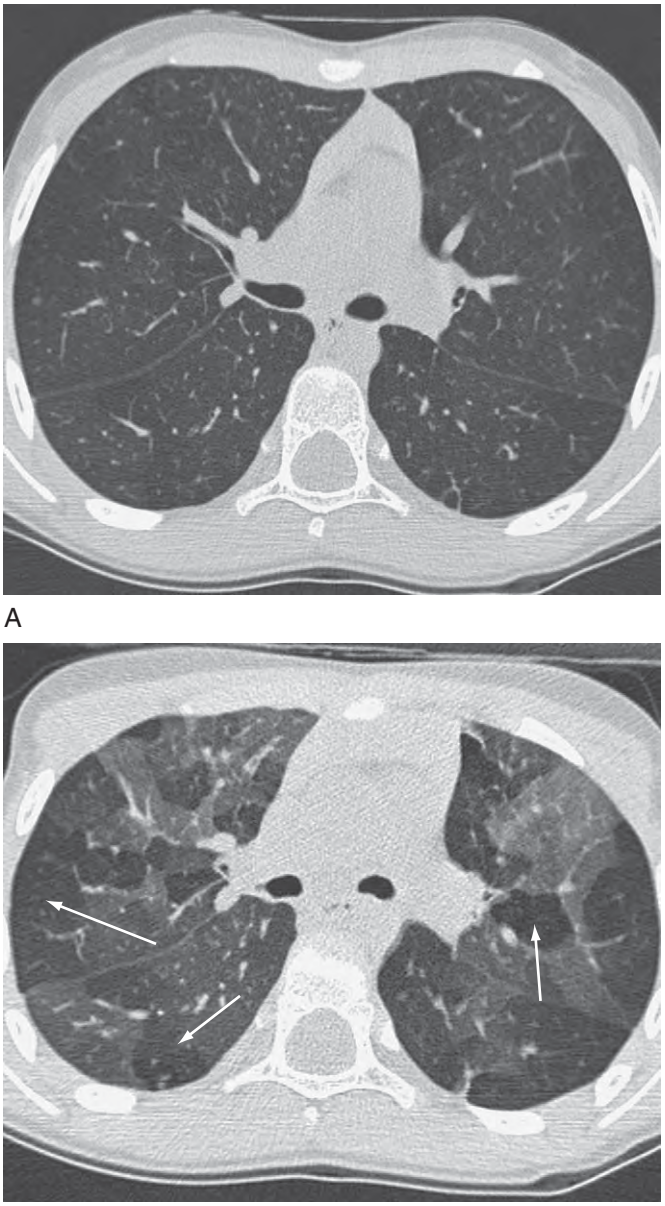


Figure 11-9 Utility of expiratory images in HRCT: 6-year-old girl with known cystic fibrosis. Image **A** was obtained during inspiration and is normal. Image **B** was obtained in expiration at the same level and demonstrates multiple regions of air trapping *(arrows)*.

gap is of the order of 10 mm, while the gap is larger, usually 20 mm, in expiration. These thin slices allow the clinician to look at fine detail, but as there is a gap between slices, some lung parenchyma is not imaged. Hence, although HRCT may help to further characterize a known diffuse parenchymal disease such as interstitial lung disease or to look for a diffuse disorder such as bronchiectasis, it is not recommended to search for small focal lesions such as metastases or small foci of atypical infection. Third, contrast is not administered in standard HRCT.

It is important that the patient does not move while CT images are being obtained in order to prevent degradation by motion artifact, and young or uncooperative children may need to be sedated. In general, children over 5 years of age can cooperate for a spiral CT scan. Children 6 to 8 years old can perform the necessary respiratory maneuvers for an inspiratory and expiratory HRCT scan.

If sedation is used to keep the patient motionless, respiratory motion alone may degrade images sufficiently to interfere with correct interpretation, especially during HRCT, when the aim of the study is to view fine structures. In addition, inspiratory and expiratory images cannot be obtained. In sedated children, respiratory artifact may be decreased and lung volume controlled using several methods. Decubitus imaging, performed by placing the patient on his or her side, provides an inspiratory image of the nondependent lung and an expiratory image of the dependent lung.[9] Motion can be eliminated and lung volume precisely controlled using a controlled ventilation technique that induces respiratory pauses with mask ventilation.[10] Finally, general anesthesia can be used.

The radiation risk from CT scanning has received a great deal of attention since 2001. Publications have suggested a risk of up to one fatal cancer for every 1000 CT scans.[11] While this level of risk can be disputed, the Biological Effects of Ionizing Radiation report in 2005 supported this level of risk and accepted the linear no-threshold model as most appropriate.[12] This model states that any radiation exposure carries some risk of causing cancer and that this risk is proportional to the amount of radiation. Authors have also pointed out that children are at greater risk than adults from the same amount of radiation.[11]

This concern must be balanced by the clear benefit provided by an indicated CT scan. There is wide agreement that this benefit is essentially always greater than the radiation risk. Several recommendations can be made to optimize this risk/benefit situation.

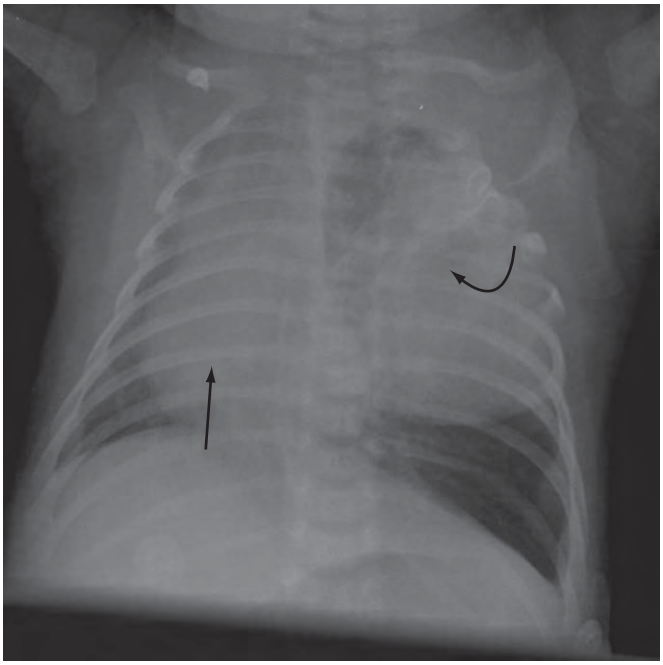
CT scanning should only be performed when necessary. When appropriate, other modalities that use less or no ionizing radiation should be performed rather than CT. The CT technique that affects the radiation dose should follow the ALARA principle. In children, this requires techniques that vary depending on the size of the patient.

Magnetic Resonance Imaging

Like ultrasound, magnetic resonance (MR) imaging does not use ionizing radiation to create an image. Instead, pulsed radiofrequency waves are sent into the patient, who is lying in a strong magnetic field. This causes hydrogen protons within the patient to realign parallel to each other, and as they relax and return to their resting state, they emit radiofrequencies that are collected and processed to form an image. MR imaging has the ability to image in any plane with excellent tissue contrast. Because of the relative paucity of protons in the lungs and the interference caused by the inhomogeneity of air and soft tissue in aerated lung, MR image quality is limited within the lung parenchyma. Another disadvantage of MR imaging relative to CT is the need for patients to remain motionless for a long time, increasing the need for sedation (Table 11-1). However, because of the excellent ability of MR imaging to characterize various tissues, the multiplanar imaging capability, and the lack of ionizing radiation, MR imaging is the method of choice for investigating mediastinal and chest wall masses and congenital aortic anomalies[13] (Fig. 11-10).

Table 11-1
Computed Tomography versus Magnetic Resonance Imaging

	Pros	Cons
Computed tomography	Rapid Decreased need for sedation versus magnetic resonance imaging Readily available Evaluates lung parenchyma Sensitive to focal calcifications	Sedation often necessary Relatively high radiation dose Iodinated contrast load worsens renal insufficiency Hypersensitivity reactions to contrast not uncommon
Magnetic resonance imaging	No radiation No need for iodinated contrast Excellent for detection of mediastinum and chest wall abnormalities	Longer imaging times Increased need for sedation versus computed tomography More difficult to perform Less readily available Relatively expensive Does not evaluate lung parenchyma Not sensitive to focal calcifications



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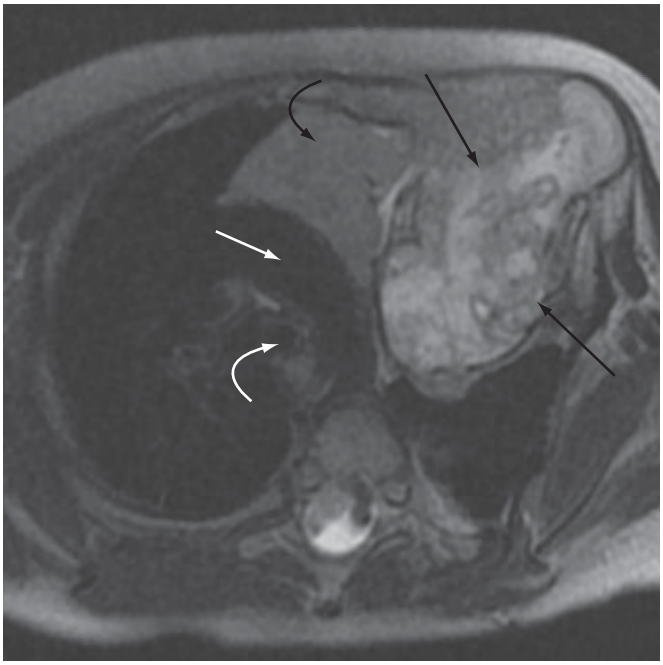

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Figure 11-10 Utility of magnetic resonance imaging: 25-day-old boy with a chest wall mass. Radiograph **(A)** demonstrates a large left chest wall mass *(curved black arrow)* deviating the heart to the right side *(black arrow)*. On an axial T2-weighted sequence **(B),** the excellent spatial resolution of MR imaging allows differentiation of the mass *(black arrows)* from the thymus *(curved black arrow)*, the trachea *(curved white arrow)*, and the aortic arch *(white arrow)*.

Angiography and Interventional Radiology

Angiography is an invasive technique traditionally used to investigate vascular lesions of the chest, such as pulmonary arteriovenous malformations or fistulas, pulmonary sequestration, pulmonary embolism, and hemoptysis secondary to cystic fibrosis or bronchiectasis (Fig. 11-11). In an angiographic procedure, fluoroscopy with the ability to capture multiple frames per second is used. These cine runs are performed in multiple projections in order that a three-dimensional appreciation of the lesion is obtained. Because this exposes the patient to a relatively large dose of radiation, and because of the invasive nature of the procedure, current imagers favor investigating vascular lesions using the excellent anatomical imaging and reformation capabilities of CT or MR imaging. Increasingly, however, treatment of these vascular lesions can be safely carried out by intravascular interventional techniques, such as embolization under fluoroscopic guidance, which are less invasive and have less morbidity than traditional surgical techniques.[14]

Interventional radiology, using ultrasound and fluoroscopic guidance, can help in the drainage of complex or loculated pleural effusions that otherwise may need surgical intervention.[15] Interventional radiology can also be of assistance in performing percutaneous biopsy or drainage of chest wall, lung parenchymal, and mediastinal masses or abscesses.[16]

ANATOMIC EVALUATION OF THE UPPER RESPIRATORY TRACT

Nasal Airway

Due to the complex anatomy of the nasal airway, plain film imaging is limited in its ability to detect abnormalities, and CT and MR imaging are both better choices. The most common congenital abnormality of the nasal cavity is choanal atresia. If clinically suspected, CT is the procedure of choice due to its ability to identify whether the abnormality is due to a bony, membranous, or mixed atresia, and it will also identify the thickness of a bony plate and whether the abnormality is unilateral, bilateral, complete, or incomplete[17] (Fig. 11-12). Other congenital nasal masses, such as dermoids, nasal gliomas, and nasal meningoceles or encephaloceles, are best investigated with MR imaging because it will better

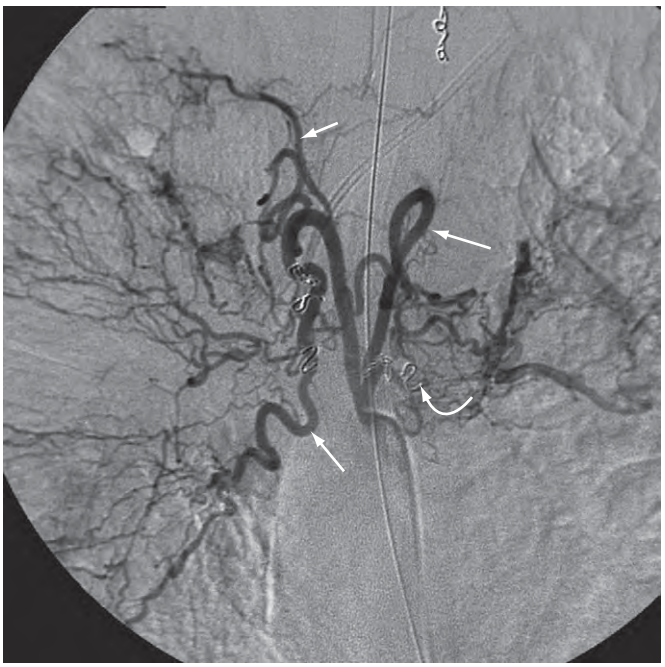


Figure 11-11 Angiography: 19-year-old woman with a history of cystic fibrosis and complicated by a history of recurrent hemoptysis. Digital subtracted angiogram of a selective injection of a vessel from the aorta demonstrates multiple irregular abnormal bronchial collateral vessels *(arrows)*. Also visible are multiple intra-arterial coils from prior embolization procedures *(curved arrow)*.

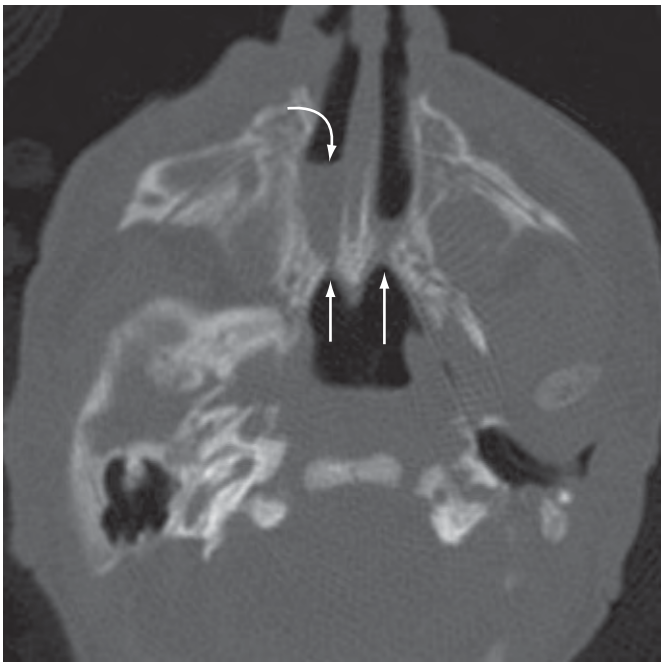


Figure 11-12 Choanal atresia: 2-day-old boy with respiratory distress. CT image demonstrates marked narrowing of the bilateral choanae *(arrows)* with air-fluid levels in the nasal cavities *(curved arrow)* consistent with mixed bony and membranous choanal atresia.

identify the extent of a soft-tissue mass and the nature of a cranial bony defect before surgical treatment. Care needs to be exercised when performing sedation for imaging neonates with nasal obstruction, as they are obligatory nasal breathers.

Box 11-1 Causes of Nasal and Paranasal Sinus Opacification

- Sinonasal polyp
- Mucocele
- Mucus retention cyst
- Antrochoanal polyp
- Sinusitis
- Juvenile nasopharyngeal angiofibroma
- Rhabdomyosarcoma

Paranasal Sinuses

Plain film imaging of the paranasal sinuses includes occipitofrontal (Caldwell), occipitomental (Water), and lateral views, each optimum for examining different sinuses. The maxillary sinuses or antra and the ethmoid air cells are present at birth. The maxillary antra are visible on radiographs from approximately 2 to 3 months of age, with the ethmoid air cell being visible between 3 and 6 months of age. The sphenoid sinuses become aerated between 7 months and 2 years of age with the frontal sinuses beginning to aerate between 6 and 12 years. The paranasal sinuses enlarge and undergo progressive pneumatization as the child ages, and generally reach adult sizes at 10 to 14 years. The maxillary antra, ethmoid air cells, and frontal sinuses are frequently involved by inflammatory disease with the sphenoid sinuses less frequently involved.

Inflammatory Sinus Disease

Mucosal thickening and opacification of the paranasal sinuses on plain films are very common in asymptomatic children (Box 11-1). Hence, commencement of therapy based solely on the presence of sinus opacification is unwarranted. The only sensitive plain film sign of acute infection is an air-fluid level (Fig. 11-13). The presence of diffuse opacification or mucosal thickening alone does not correlate with infection and may be seen with many conditions including allergic rhinitis, cystic fibrosis and asthma (Fig. 11-14). Artifactual opacification caused by rotation and normal variant underpneumatization are also commonly seen.

The role of advanced cross-sectional imaging like CT and MR imaging is to demonstrate the anatomy of the sinuses including the osteomeatal unit when surgery is being contemplated, and also to examine for suspected complications such as subperiosteal orbital abscess (Fig. 11-15) and periorbital cellulitis, as well as intracranial complications such as abscess formation, meningitis, and venous sinus thrombosis.[18]

Trauma

The bones of the nasosinus complex are among the thinnest in the body, and this makes them liable to fracture, but it also makes it difficult to detect fractures of these bones on plain film. Hence, CT has replaced plain film as the imaging method of choice for detection of fractures but should only be used when detection of a fracture will lead to alteration of

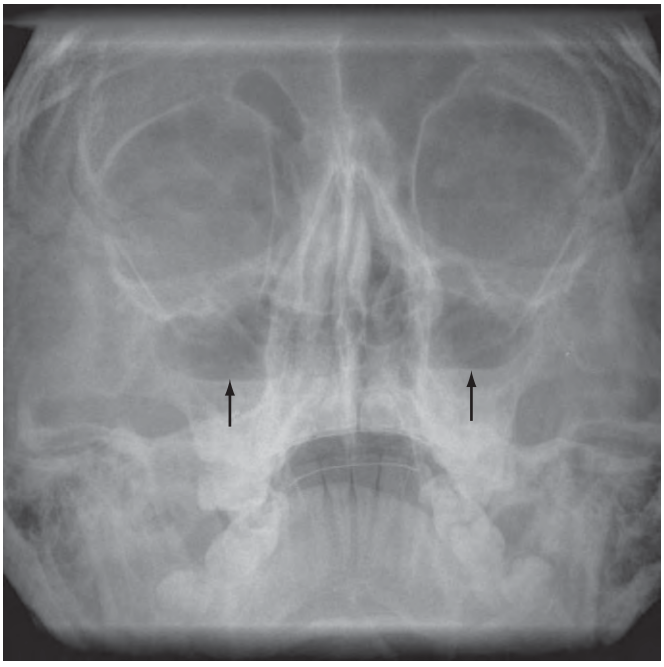
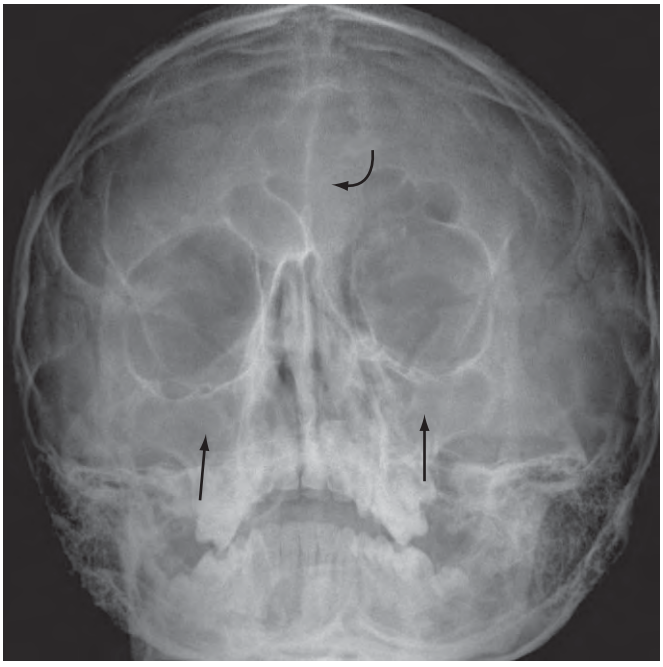


Figure 11-13 Acute sinusitis: 12-year-old boy with facial pain and congestion. Water view of the paranasal sinuses demonstrates an air-fluid level in the bilateral maxillary antra *(arrows)*, consistent with acute sinusitis.



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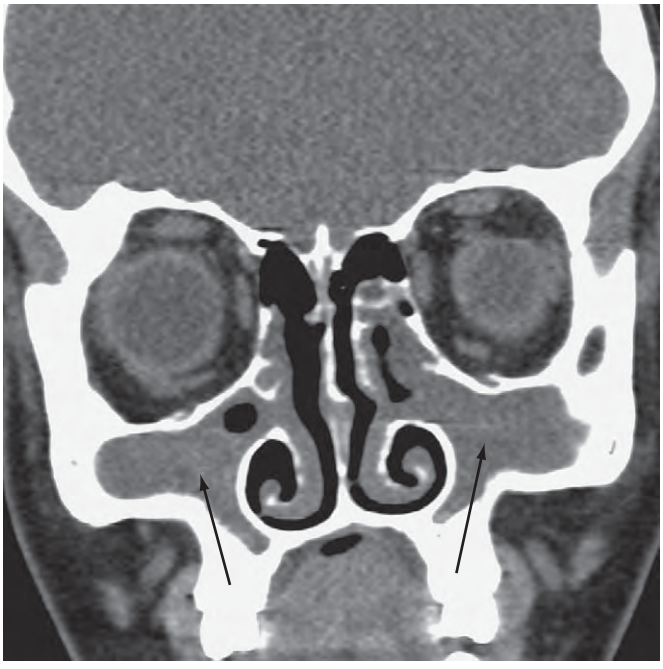


B

Figure 11-14 Sinus opacification in cystic fibrosis: 16-year-old girl with cystic fibrosis. Water view **(A)** demonstrates complete opacification of the maxillary antra *(arrows)* and also the frontal sinus *(curved black arrow)*. Coronal reformatted CT **(B)** demonstrates complete opacification of both maxillary antra *(black arrows)*.

management, such as a depressed fracture of the orbital floor with entrapment of the inferior rectus muscle and resultant diplopia[19] (Fig. 11-16).

Masses

Because tumors of the nose and paranasal sinuses are uncommon in children, they often go undetected early on as they can present with common complaints such as nasal congestion. One such tumor is a rhabdomyosarcoma, which is the most common soft tissue tumor of the head and neck region in children. Juvenile nasopharyngeal angiofibroma (JNA) is the most common benign nasopharyngeal tumor of childhood, occurring primarily in male adolescents. As well as presenting with nasal congestion, a JNA should be suspected in someone presenting with catastrophic or recurrent nosebleeds. In cases of both rhabdomyosarcoma and JNA, plain film imaging is usually nonspecific with evidence of sinus opacification (see Box 11-1). Imaging of these tumors with CT and MR imaging is needed to demonstrate the extent of the mass. In cases of rhabdomyosarcoma, imaging may also identify lymph node metastases, whereas in JNA, cross-sectional imaging will demonstrate the characteristic vascularity of this tumor and may identify large feeding arteries (Fig. 11-17). Embolization of these feeding vessels is often carried out by interventional radiology in order to decrease the size of the mass before definitive surgery or to stop an ongoing bleed.[20]

IMAGING OF THE EXTRAPULMONARY AIRWAY: PHARYNX TO THE CARINA

Upper airway symptoms of cough, stridor, wheezing, and hoarseness are common in the pediatric population. Concern for a foreign body aspiration is also a common presenting complaint. Correspondingly, imaging of the upper airway is frequently performed in pediatric radiology departments.

If radiographic investigation is needed, frontal and lateral radiographs usually suffice. These are obtained with a high-kilovoltage technique, are magnified, and have added filtration. The lateral film is taken with the neck extended during maximum inspiration so that the redundant retropharyngeal soft tissues are not falsely thickened. Failure to use this

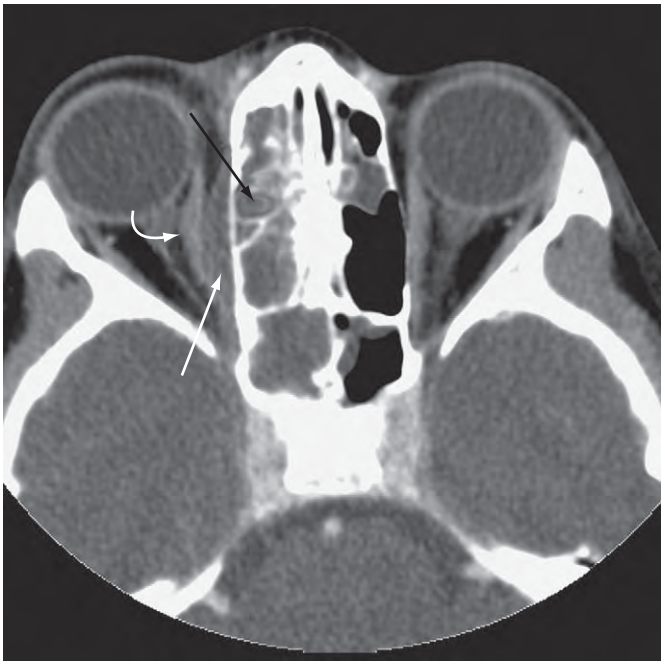


Figure 11-15 Complication of infective sinusitis: 9-year-old girl with sinusitis and periorbital swelling. Axial CT image demonstrates opacification of the ethmoid air cells *(black arrow)* with spread of infection into the adjacent right orbit *(white arrow)*, displacing the medial rectus muscle medially *(curved white arrow)*.

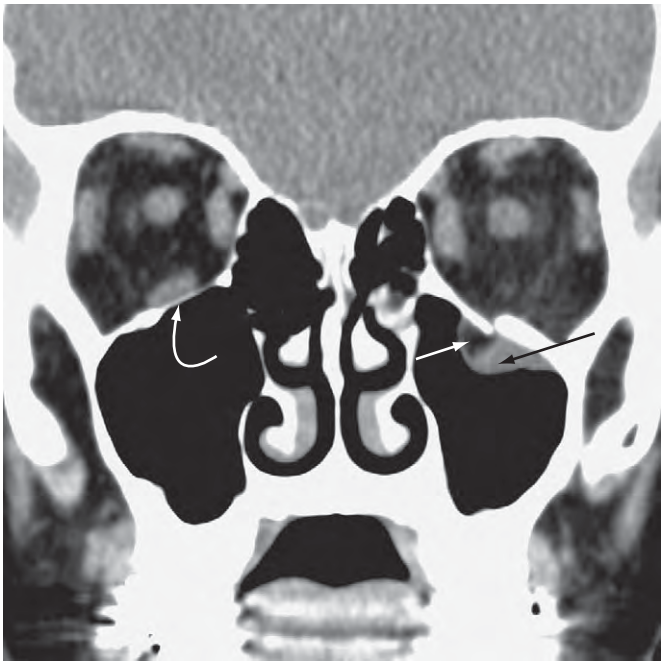
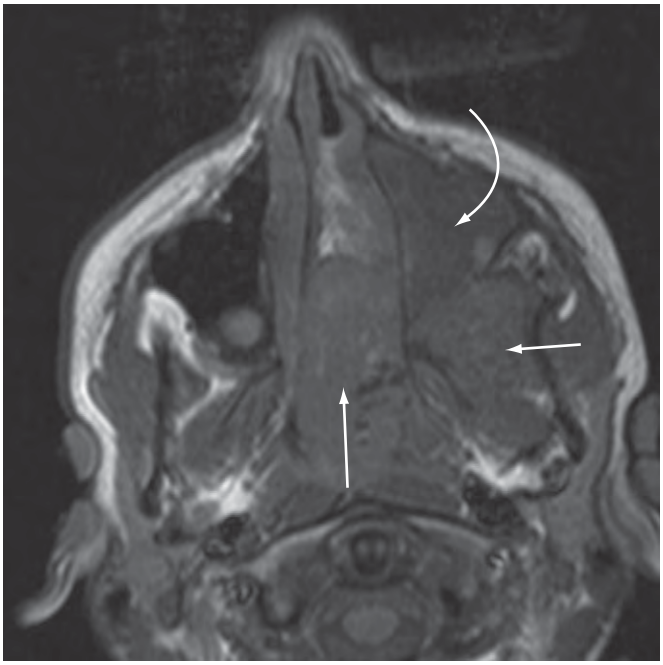


Figure 11-16 Sinus trauma: 14-year-old boy who was kicked in the face and was complaining of diplopia. Coronal reformatted CT image demonstrates fat *(white arrow)* and inferior rectus muscle *(black arrow)* trapped in the left orbit below a fracture of the orbital floor. This will prevent the inferior rectus muscle from contracting normally, resulting in diplopia. Note the normally positioned right inferior rectus muscle *(curved white arrow)*.



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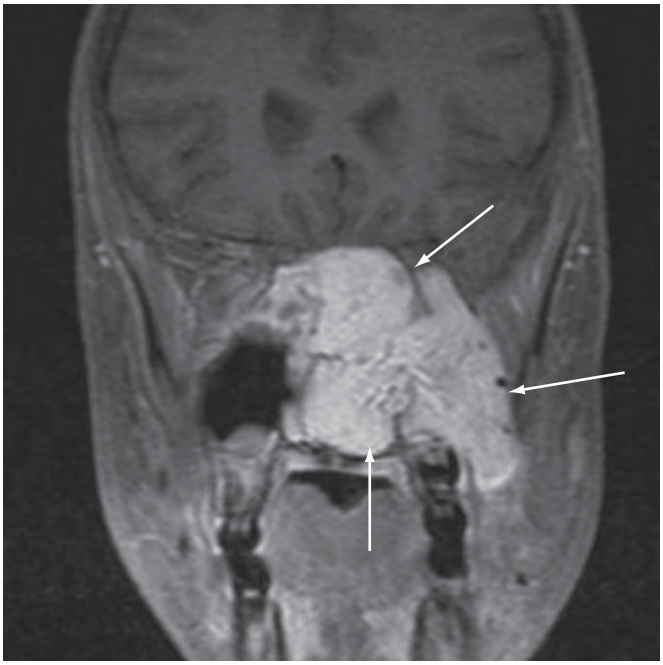

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Figure 11-17 Juvenile nasopharyngeal angiofibroma: 13-year-old boy with a history of persistent nasal congestion. Axial T1-weighed precontrast **(A)** and coronal T1-weighed postcontrast **(B)** MR images following contrast administration demonstrate a lobulated mass in the left infratemporal fossa and nasal cavity *(white arrows)*. The intense enhancement on the postcontrast images is due to the vascular nature of the tumor. Note the fluid-filled obstructed left maxillary antrum *(curved white arrow)*.

Box 11-2 Causes of an Enlarged Retropharyngeal Space

- Cellulitis
- Phlegmon or abscess
- Lymphadenopathy
- Tumor (e.g., neuroblastoma, hemangioma)
- Localized trauma such as with foreign body aspiration
- Artifactual from poor radiographic technique

technique can result in thickening of the retropharyngeal/prevertebral soft tissues (Box 11-2).

If adequate radiographic imaging cannot be obtained, then fluoroscopy can be used to determine whether the thickening of the retropharyngeal soft tissues is real. With the patient in the lateral position, the pharyngeal tissues will be seen to thin during inspiration if the thickening is a pseudo-mass but will remain thickened if there is pathology in this region (Fig. 11-18). If the retropharyngeal thickening is real and the symptoms are acute, then CT may be performed to evaluate for a drainable abscess[21] (Fig. 11-19).

Epiglottitis is rarely seen in the United States due to the widespread use of the *Haemophilus influenzae* type b vaccine, but it still is encountered in children who did not receive a vaccine, in people who were vaccinated but have a deficient immune system, and in patients with epiglottitis from other infections such as *Streptococcus pneumoniae* and *Staphylococcus aureus* or inflammatory conditions such as thermal burns (Fig. 11-20). When epiglottitis is clinically suspected but a radiograph is needed, care should be taken to have someone trained in airway management and intubation with the patient while the study is being performed. Imaging should be obtained with the patient upright, as positioning the patient supine may cause respiratory distress and apnea. Findings include thickening of the epiglottis, aryepiglottic folds, or both.

The subglottic airway is a common site of pathology in younger children. On an anteroposterior radiograph, the normal subglottic airway has a symmetrical squared-off appearance often referred to as "shouldering" (Fig. 11-21). Signs of pathology of the subglottic airway include loss of normal shouldering and symmetrical narrowing or an asymmetrical indentation on the subglottic air column. Inflammatory or diffuse abnormalities such as laryngotracheal bronchitis (viral croup) result in loss of the normal shouldering and the airway assumes the appearance of a steeple (Fig. 11-22). Focal lesions such as a subglottic hemangioma will result in a focal asymmetrical indentation (Box 11-3).

As a result of the introduction of the *H. influenzae* type b vaccine and a reduction in the incidence of epiglottitis, the most common cause of life-threatening upper airway disease in children in the United States is bacterial tracheitis.[22] In this condition, lateral radiograph findings may resemoble these of croup or may have associated mucosal irregularity and thin projections of material into the tracheal lumen (Fig. 11-23).

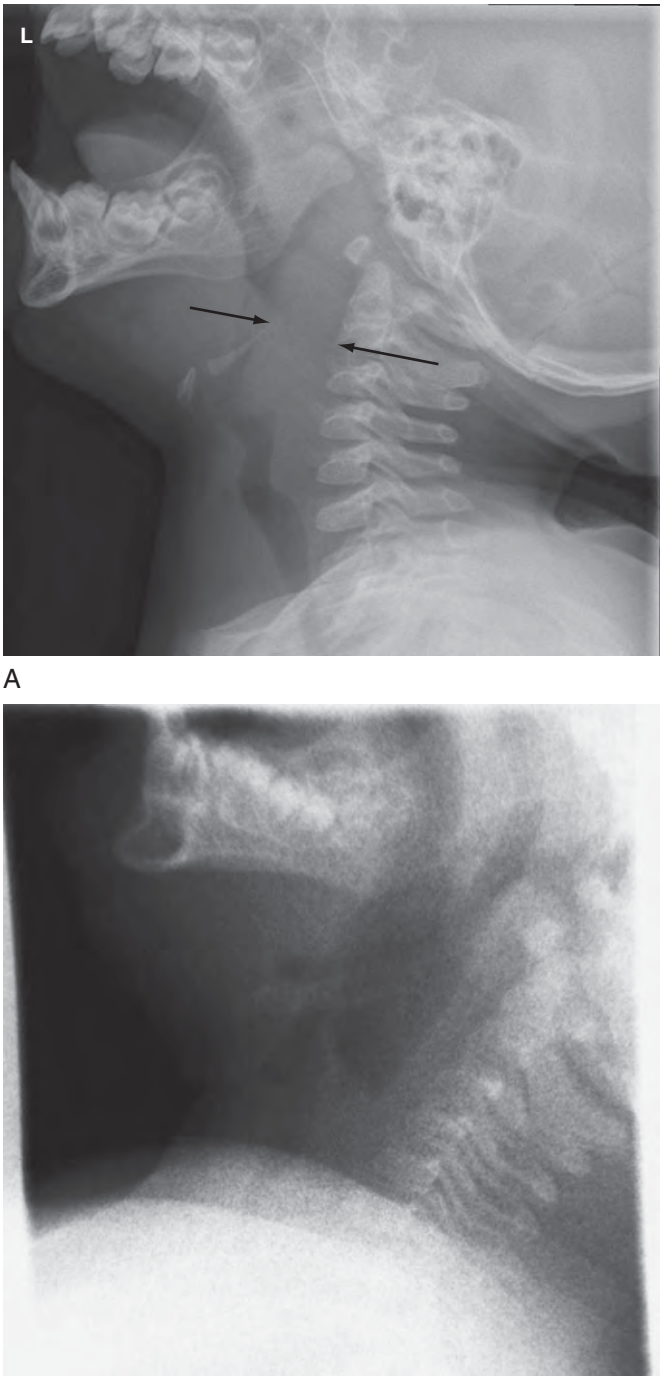
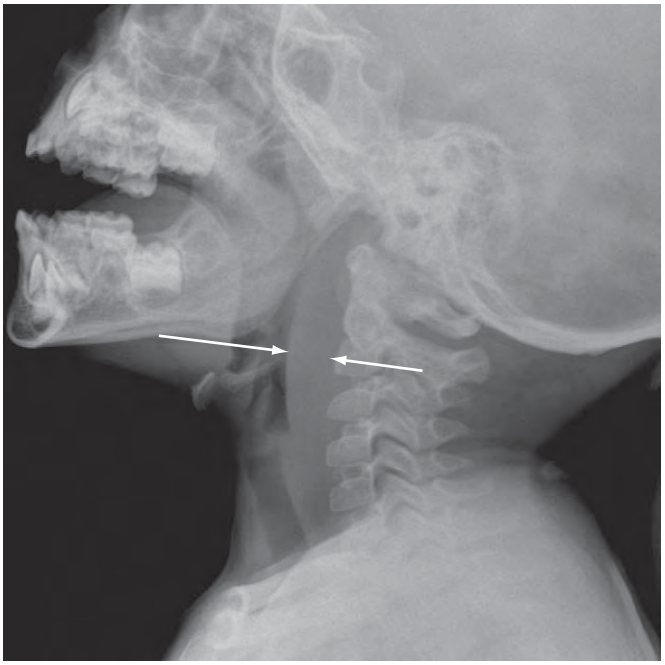


Figure 11-18 Evaluation of prevertebral soft tissues using fluoroscopy: 11-month-old boy presenting with stridor. Lateral radiograph of the airway **(A)** demonstrates apparent thickening of the prevertebral soft tissues *(arrows)*. On the lateral image obtained in inspiration during fluoroscopic evaluation **(B),** the prevertebral soft tissues are seen to be normal in thickness.

The trachea below the subglottic region has parallel walls as it descends to the carina. As it approaches the carina, it normally veers slightly to the right as it passes the aortic arch. In young infants, it is normal to have buckling of the cervical portion of the trachea to the right. If the intrathoracic trachea remains midline or deviates to the left, then a congenital vascular lesion such as a right-sided aortic arch or a double



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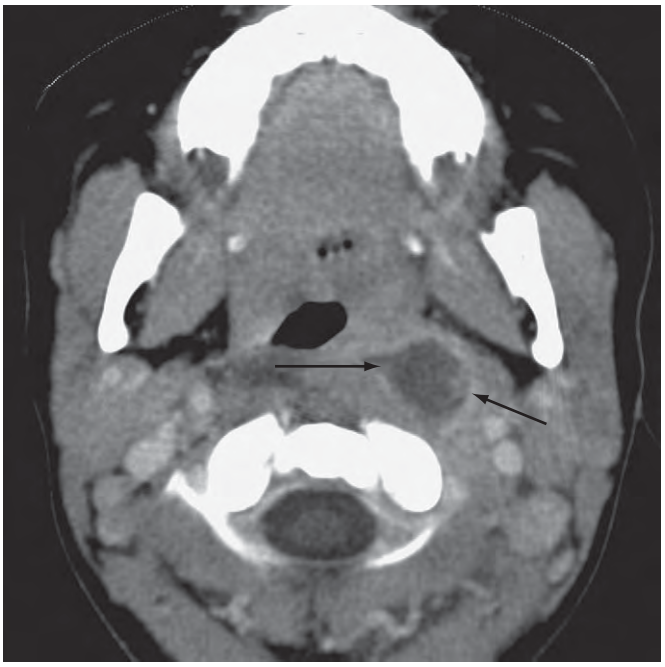

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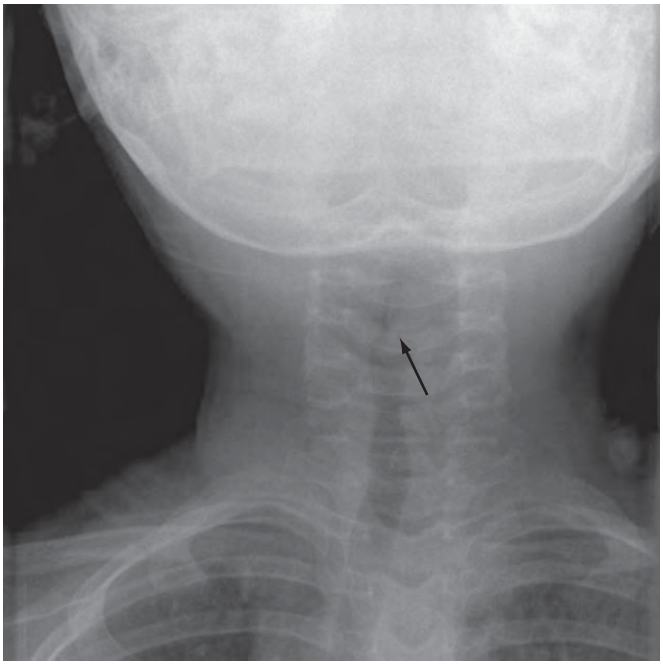
Figure 11-19 Retropharyngeal abscess: 3-year-old boy with fever and a stiff neck. Lateral radiograph **(A)** demonstrates thickening of the prevertebral soft tissues *(white arrows)*. On a contrast-enhanced CT image **(B),** there is a rim-enhancing well-circumscribed low-attenuation lesion in the left retropharyngeal space *(black arrows)* consistent with an abscess.



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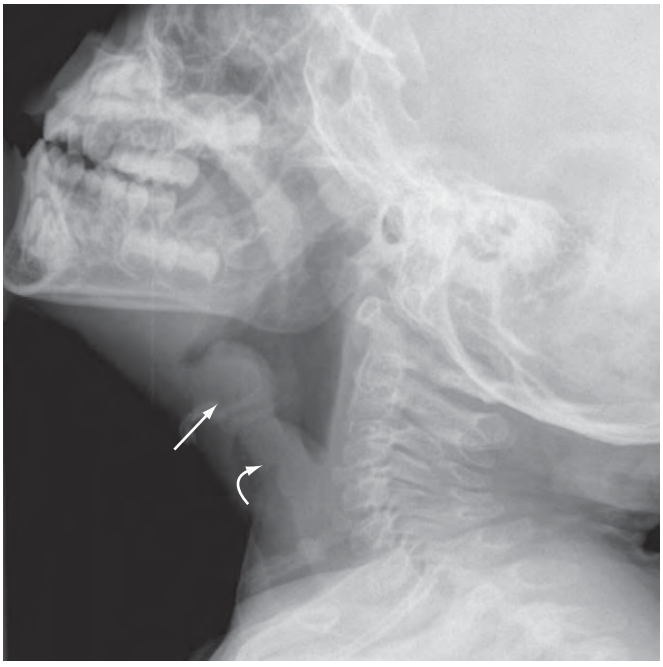
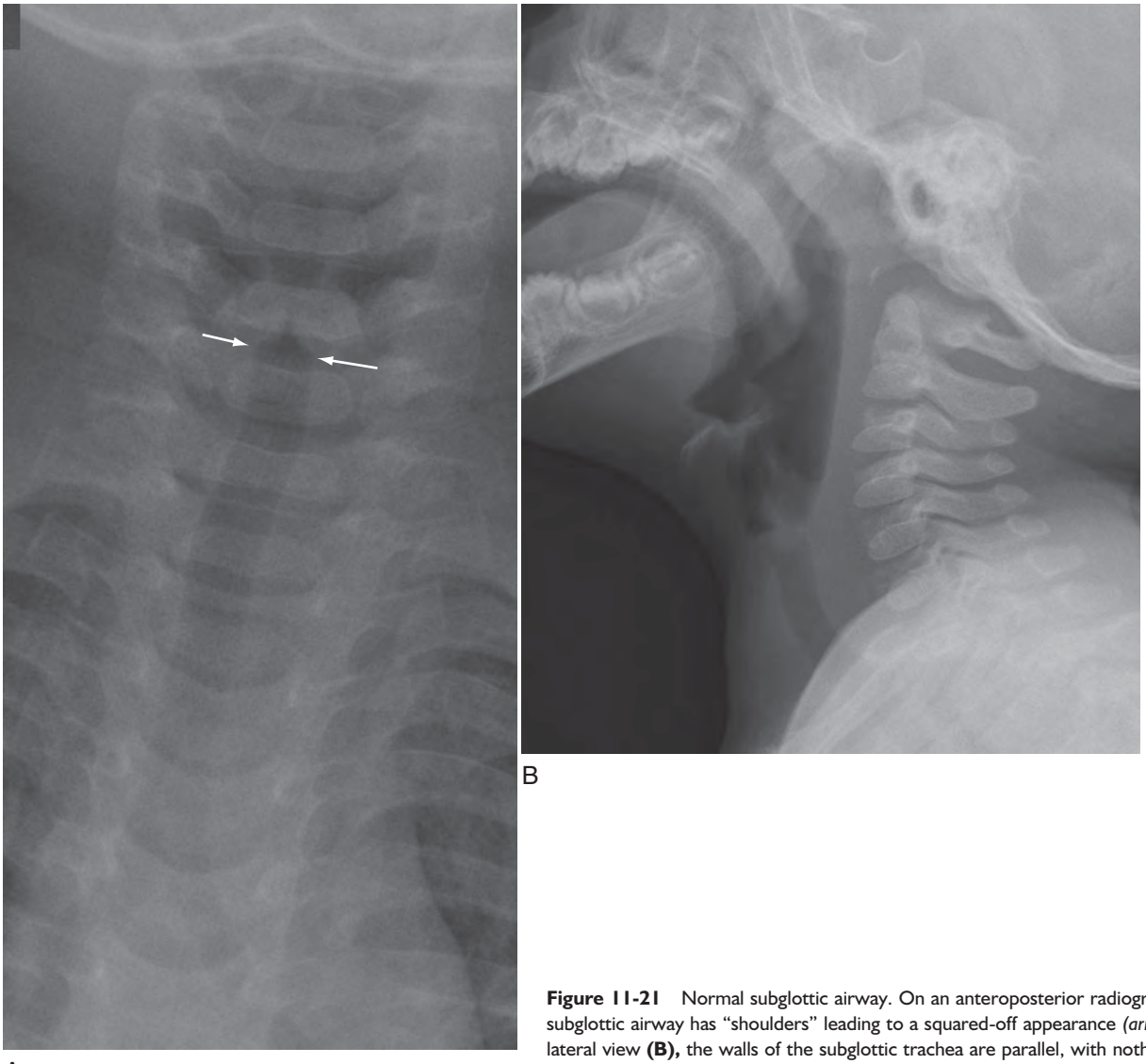


B

Figure 11-20 Epiglottitis: 2-year-old girl with respiratory distress and stridor. Anteroposterior radiograph **(A)** demonstrates an indentation on the left side of the subglottic airway *(black arrow)* with resultant asymmetrical narrowing of the subglottic airway. On the lateral radiograph **(B),** there is thickening of the aryepiglottic folds *(curved white arrow)* and epiglottis *(white arrow)*, resulting in a thumb-like configuration.

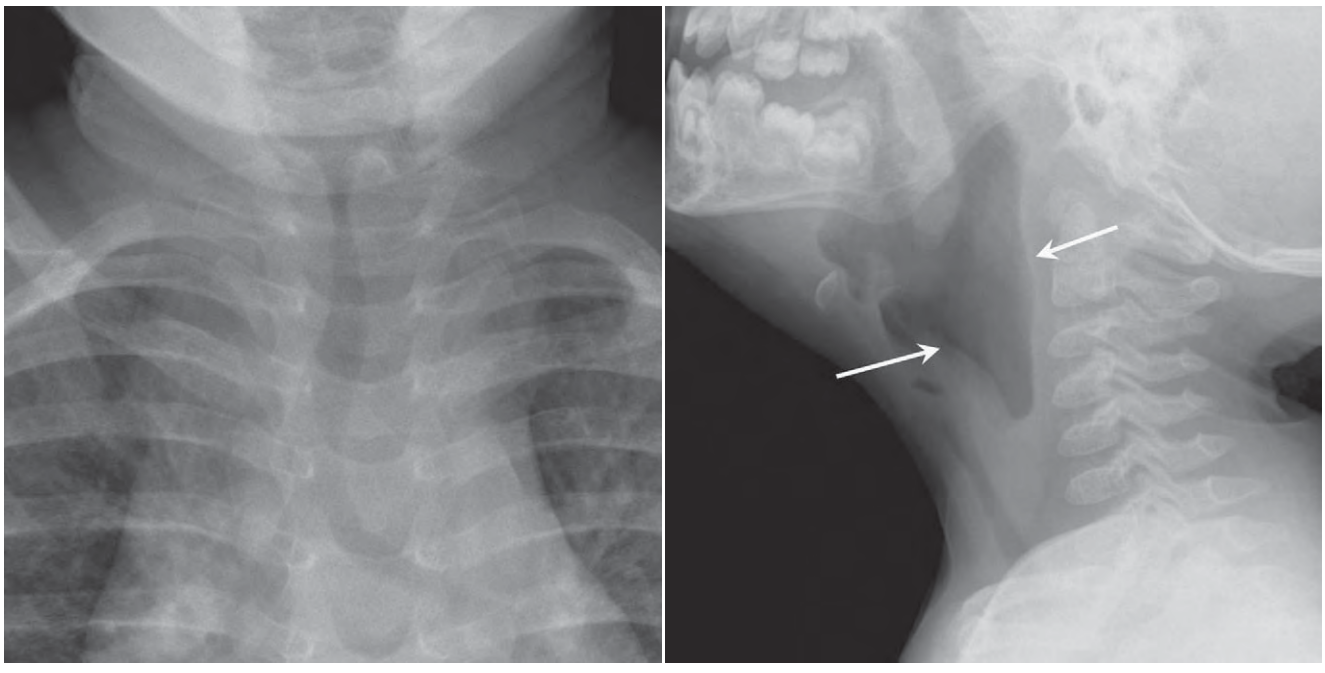
aortic arch is suspected, especially if the lateral view shows an indentation on the posterior trachea.

Cross-sectional imaging of the airway with CT and MR imaging is helpful when there is a concern for extrinsic compression of the airway.[23] Both modalities will identify the abnormal vessel, but CT is better at demonstrating the effect of the vessel on the trachea. Virtual endoscopy using CT has found favor in some centers because it nicely demonstrates the endotracheal and endobronchial lumens. However, as these patients will also receive a bronchoscopy, we believe that the extra radiation the patient receives from the CT is rarely justified in the pediatric population.



A B

Figure 11-21 Normal subglottic airway. On an anteroposterior radiograph **(A),** the subglottic airway has "shoulders" leading to a squared-off appearance *(arrows)*. On a lateral view **(B),** the walls of the subglottic trachea are parallel, with nothing projecting from the mucosa into the lumen.



A B

Figure 11-22 Croup: 16-month-old boy with stridor. Frontal radiograph **(A)** demonstrates smooth symmetrical narrowing of the subglottic airway. Lateral view **(B)** also demonstrates diffuse narrowing of the subglottic airway as well as ballooning of the hypopharynx *(arrows)*.

Box 11-3 Causes of Subglottic Airway Narrowing

- Croup (symmetrical)
- Posttraumatic (symmetrical)
- Congenital (symmetrical; segmental or generalized)
- Tracheomalacia (symmetrical, generalized)
- Tracheitis (symmetrical or asymmetrical)
- Hemangioma (symmetrical or asymmetrical)

CHEST

Plain Film

The chest radiograph is one of the most common radiographic studies performed in the pediatric population and can be one of the more difficult studies to interpret. Because it is a cornerstone in the investigation of pulmonary diseases, it is important that pulmunologists become comfortable with interpreting chest radiographs. Not only should they be comfortable with recognizing abnormalities, but they also need to appreciate when a study is technically suboptimum, as this can make correct interpretation more difficult. In addition, they need to be able to recognize the different appearances of the normal chest radiograph as a child ages. In this section, we initially describe ways to evaluate a radiograph for adequate technique and describe some of the common normal variants before describing a system for evaluating a chest radiograph.

Technique

Due to the challenge of keeping an uncooperative child still, one of the most common technical abnormalities on a chest radiographs is rotation, which may mask an abnormality or produce the appearance of a lesion that is not present. On a correctly centered chest radiograph, the anterior ends of corresponding ribs are equidistant to the ipsilateral pedicle of the vertebra at that level. In addition, the medial ends of the clavicles should be equidistant to the spinous process of the vertebra at that level. Movement of an uncooperative child will also result in blurring of the radiograph.

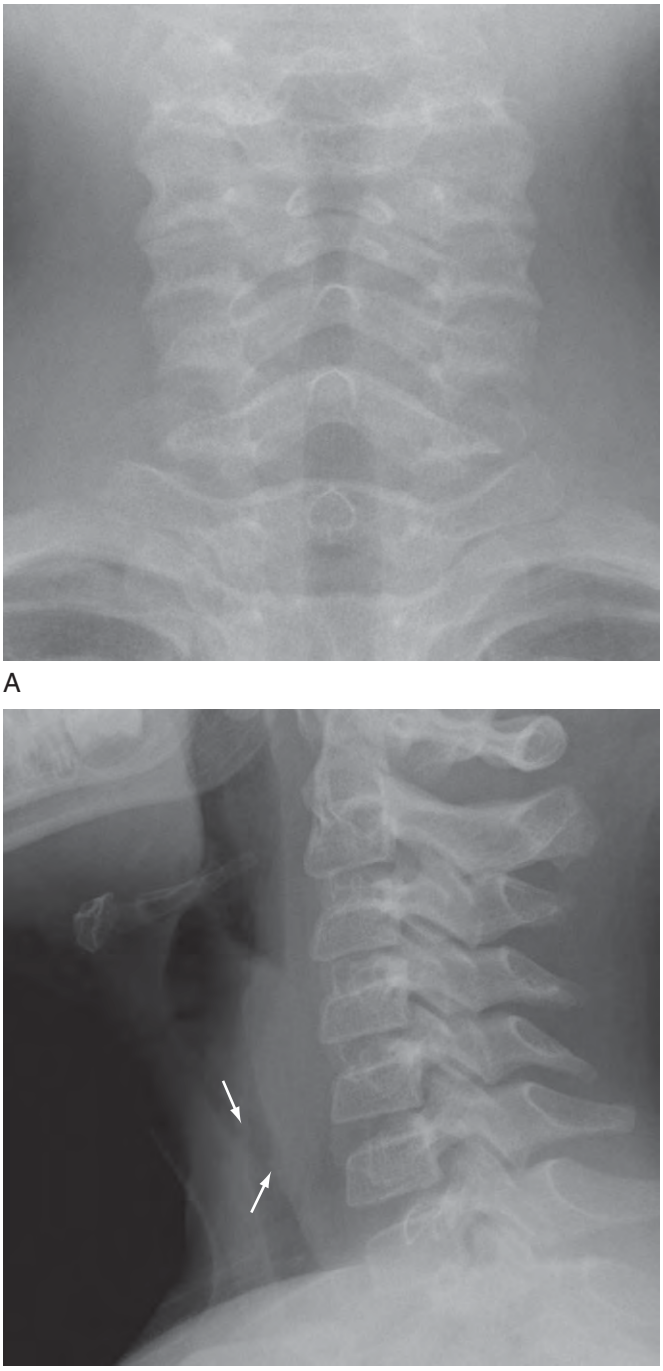
A radiograph obtained with inadequate inspiration will result in symmetrical increased density in the lungs, and will spuriously enlarge the cardiomediastinal silhouette (Fig. 11-24). With adequate inspiration, the anterior ends of 6 ribs should be seen above the dome of the diaphragm.

As children come in all shapes and sizes, obtaining an optimally exposed radiograph can be a challenge. On appropriately exposed radiograph, the pedicles of the vertebral bodies should be visible through the cardiac silhouette and the pulmonary vessels in the middle third of the lungs should be visible.

Normal Variants

As the child grows, there are changes in the normal appearance of the chest radiograph. It is important to be able to recognize these normal variations in appearance, as this will help prevent anxiety and reduce the number of resultant unnecessary and potentially harmful investigations.

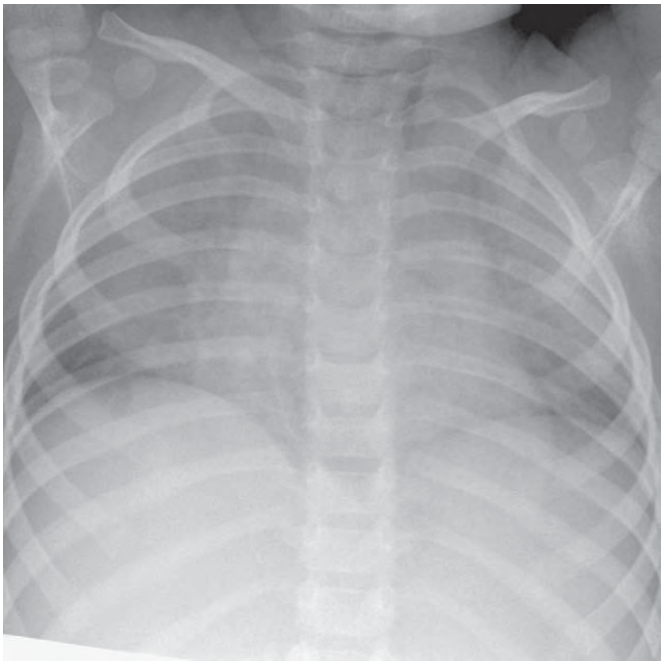
The neonatal chest is relatively box shaped, and as the child grows, it becomes more elongated in the craniocaudal plane. Not only does the shape of the thoracic cavity change, but the appearance of the intrathoracic structures also



A

B

Figure 11-23 Bacterial tracheitis: 7-year-old boy with stridor. Anteroposterior view **(A)** demonstrates symmetrical narrowing of the subglottic airway. Lateral view **(B)** shows a more focal area of narrowing in the subglottic airway with projections *(arrows)* from the mucosa into the tracheal lumen. These projections or webs are not always visible in bacterial tracheitis and can also be seen with adhered mucus.



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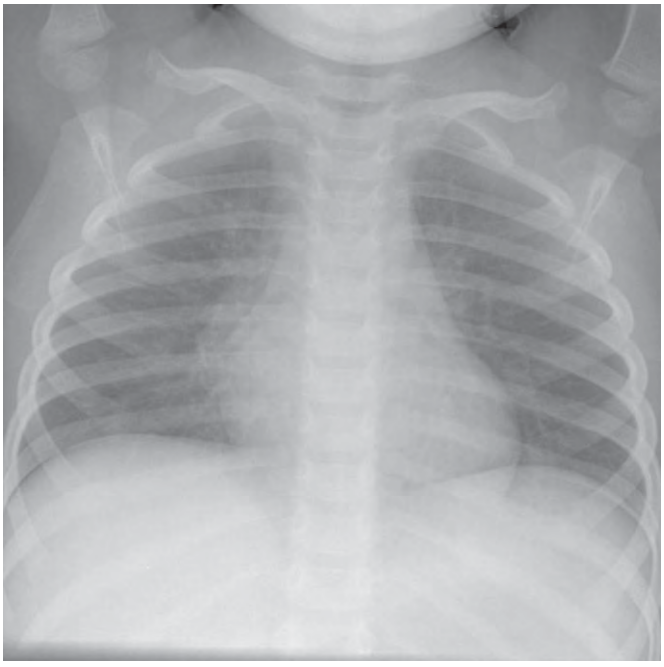


B

Figure 11-24 Effect of poor inspiration. Anteroposterior radiograph **(A)** looks abnormal with diffuse increased haziness throughout both lungs and borderline cardiomegaly. The anterior ends of three ribs can be seen above the diaphragm. A repeat radiograph **(B)** performed immediately following **(A)** during inspiration demonstrates a normal heart size and clear lungs. Five ribs can be seen above the diaphragm.

changes. The most striking changes occur in the normal thymus, and this can be a source of confusion. In the infant, the thymus is at its largest relative to the chest cavity. As the child grows, so does the thymus, albeit at a slower rate, and reaches its maximal size at puberty and then begins to involute through adolescence. In infancy, the thymus has a quadrilateral shape that is often asymmetrical and may make it appear like a mediastinal mass or upper lobe pneumonia on radiographs. Often, it is difficult to separate the thymus from the heart contour, giving the appearance of an enlarged heart. However, close inspection often reveals a small notch between the left lobe of the thymus and the left heart border. In addition, the soft constituency of the thymus allows the right lobe to extend into the horizontal fissure, leading to a characteristic sail-like configuration. Because of the pliability of the gland, it may become molded by the ribcage and adopt a wave-like contour that may be exaggerated on obliqued radiographs (Fig. 11-25). As childhood progresses, the thymic contour becomes narrower as it assumes a triangular configuration and generally is no longer visible on radiographs at age 5 years, although rarely it remains visible until puberty. The thymus may decrease in size during times of stress or chemotherapy for malignancy and may increase in size when the stress has been removed or after chemotherapy has been completed.

A not uncommon mimic of a pneumothorax is normal skinfolds. Unfortunately, this is especially true in supine radiographs such as those obtained in intensive care units, where pneumothoraces secondary to positive pressure ventilation are more common. Usually, they can be differentiated because skinfolds often can be followed beyond the chest wall and do not run parallel to the rib cage. Also, lung vascular markings may be seen beyond a skinfold (Fig. 11-26). If in doubt, a repeat radiograph or a decubitus radiograph may be performed for confirmation.

On supine anteroposterior radiographs, the heart often appears enlarged, especially if the image is not obtained during deep inspiration. In infants, this is confounded by the presence of the relatively large thymus, as discussed earlier. A lateral radiograph is usually sufficient to confirm the normal heart size.

Analyzing a Radiograph

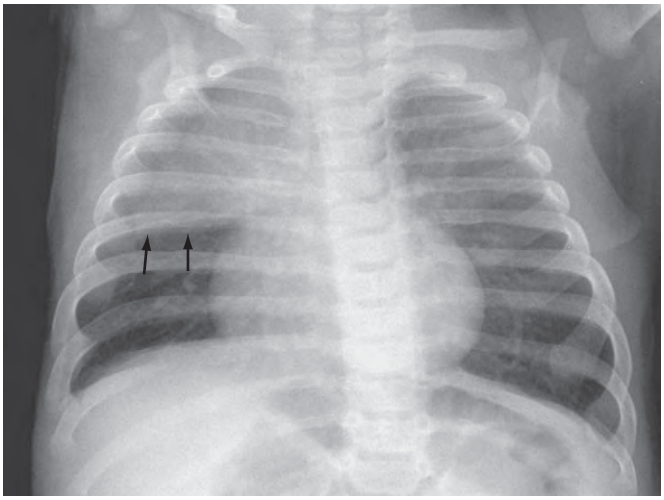
Using a systematic approach for analyzing a chest radiograph is very important as it helps prevent missing a subtle but important abnormality once a trivial but more obvious abnormality has been identified. The order in which you evaluate a radiograph is not as important as having a system that ensures that you examine each region. The ABCs approach is one method that is easy to remember, as follows.

ABDOMEN

Disease processes in the abdomen may present with respiratory symptoms and vice versa. Although the area of the abdomen that is visible is limited, the chest radiograph may contain evidence of dilated bowel loops, free intraperitoneal air, abdominal situs inversus, organomegaly, gallstones, and renal calculi.

AIRWAY

Although the airway is best assessed on dedicated airway radiographs, much information can be obtained from a chest radiograph. On the frontal radiograph, the normal airway deviates to the right, especially at the level of a normal left-sided aortic arch. If the trachea remains in the midline or deviates to the left, this is suspicious for an extrinsic mass or a congenital vascular anomaly such as a right-sided arch or a double aortic arch (Fig. 11-27). Similarly, posterior



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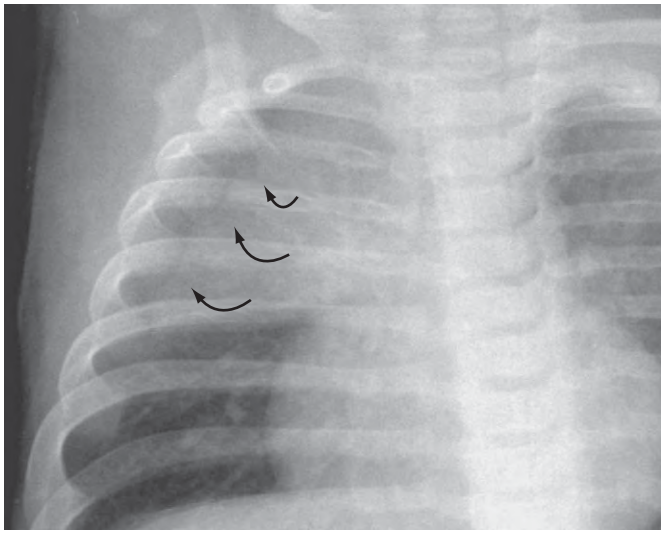

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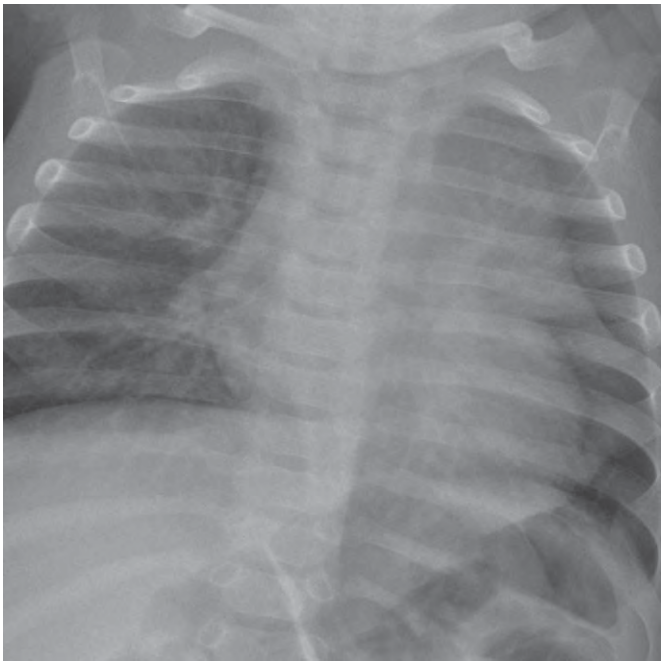


C

Figure 11-25 Varying appearances of the thymus. Anteroposterior radiograph **(A)** demonstrates a prominent right lobe of the thymus. Note the straight inferior border *(arrows)* and oblique lateral border giving the appearance of a sail. Close inspection of the lateral border **(B)** demonstrates an undulating wave-like edge *(curved black arrows)*. Sometimes, the left lobe of the thymus may be prominent **(C),** and in such cases may be separated from the left heart border by a notch.

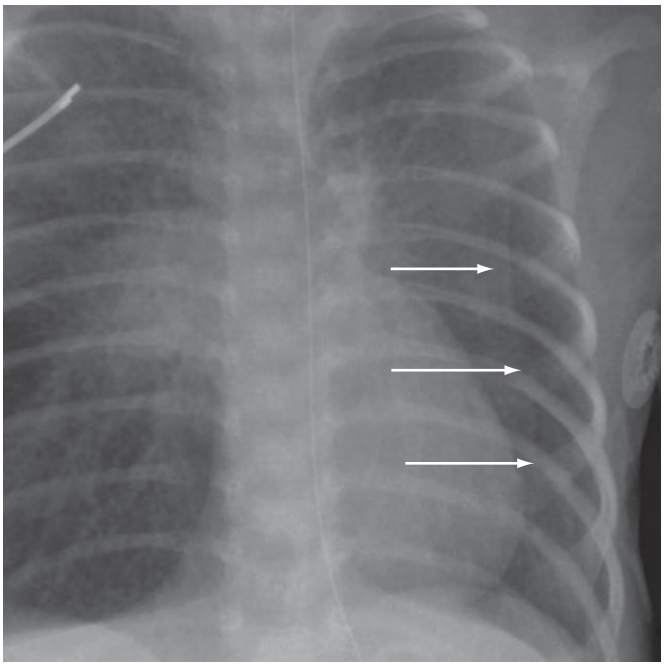
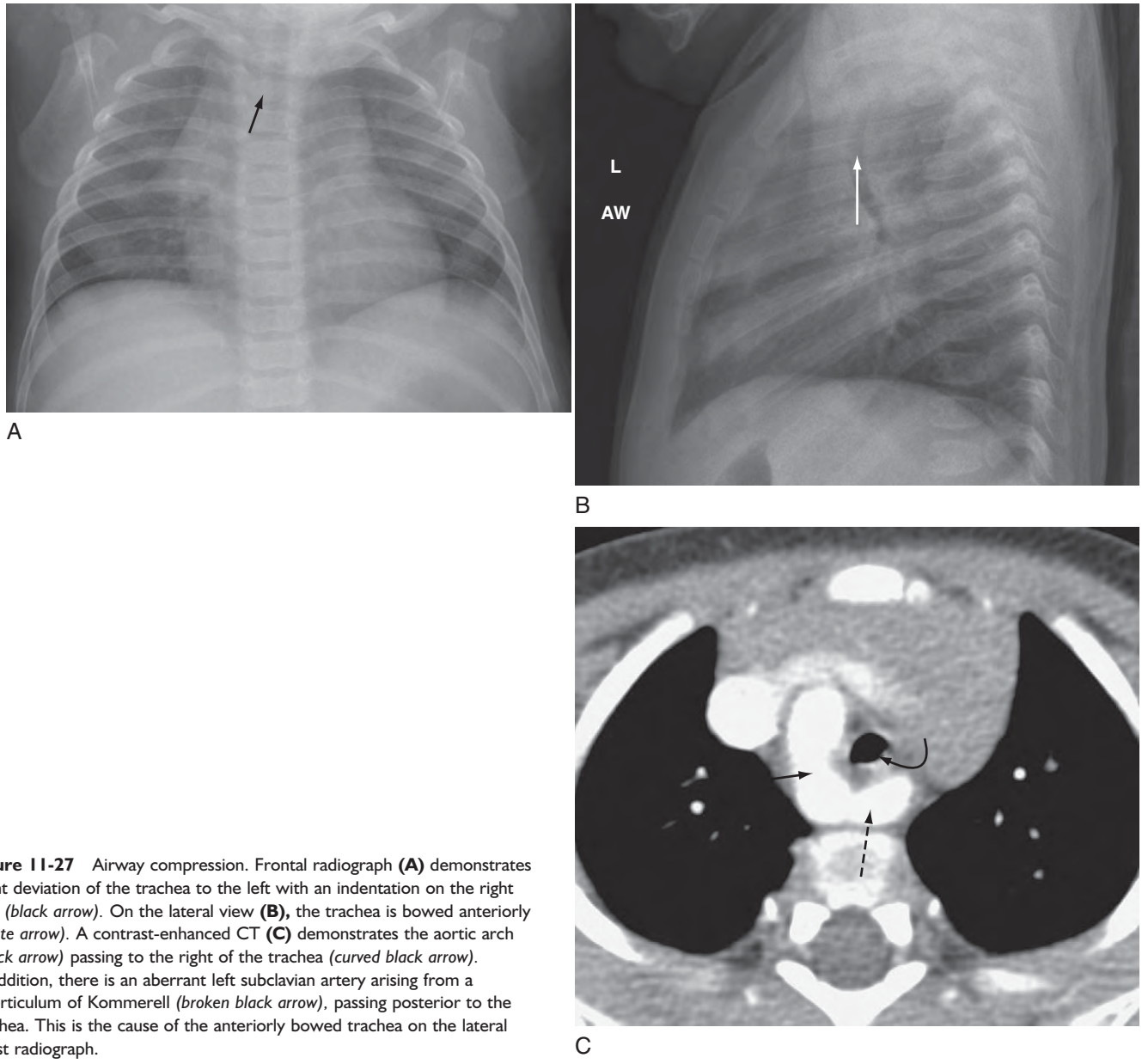


Figure 11-26 Skinfold mimicking a pneumothorax. Radiograph in a 26-day-old girl demonstrates an interface *(arrows)* in the left hemithorax. Lung markings are seen peripheral to the interface, and a subsequent radiograph did not show signs of a pneumothorax.



A

B

C

Figure 11-27 Airway compression. Frontal radiograph **(A)** demonstrates slight deviation of the trachea to the left with an indentation on the right wall *(black arrow)*. On the lateral view **(B),** the trachea is bowed anteriorly *(white arrow)*. A contrast-enhanced CT **(C)** demonstrates the aortic arch *(black arrow)* passing to the right of the trachea *(curved black arrow)*. In addition, there is an aberrant left subclavian artery arising from a diverticulum of Kommerell *(broken black arrow)*, passing posterior to the trachea. This is the cause of the anteriorly bowed trachea on the lateral chest radiograph.

indentation on the trachea on the lateral chest radiograph can be seen with an aberrant subclavian artery.

The trachea should be visible from the glottis to the carina on both the frontal and lateral radiographs as a lucent tube with parallel well-defined walls. Ill definition or obliteration of a portion of the airway should be further investigated.

BONES AND SOFT TISSUES

Lesions of the chest wall may present with respiratory symptoms. Bony lesions may also lead to deformity or chest pain, and in younger children with nonspecific symptoms such as fussiness, a chest radiograph should be carefully examined for signs of child abuse, such as rib fractures (Fig. 11-28).

CATHETERS AND TUBES

It is important to pay careful attention to any catheters, tubes, sutures, monitoring leads, pacing devices, or nerve stimulators, as they are not an uncommon source of morbidity. It is recommended to follow each individual device all the way to the tip (Fig. 11-29).

CHEST

As described previously, the age of the patient influences the size of the normal thymus, which is reflected in the varying appearance of the upper mediastinum in infancy and childhood. After early childhood, any widening of the upper mediastinum should raise a concern for a mass or lymphadenopathy.

The heart size is best evaluated using a combination of the frontal and lateral chest radiographs. On the frontal radiograph, enlargement is considered if the ratio of the transverse diameter of the heart is greater than half the maximum transverse diameter of the chest. It is not unusual for the cardiac silhouette to look enlarged on a supine anteroposterior chest radiograph obtained during inadequate inspiration. On the lateral view, enlargement is confirmed if the posterior

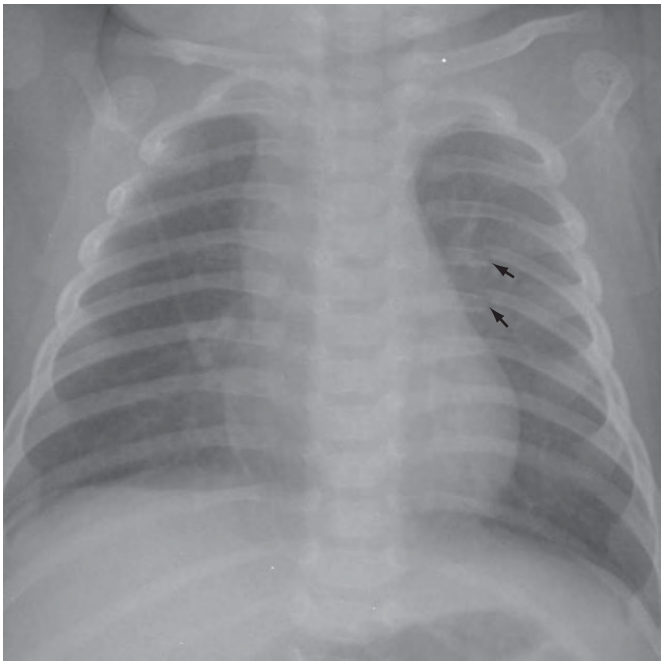


Figure 11-28 Evaluating for rib fractures: 9-month-old girl who was brought to the emergency department with lethargy and fever. A chest radiograph demonstrates left posterior rib fractures *(arrows)*. This appearance and clinical history are of concern for nonaccidental trauma.

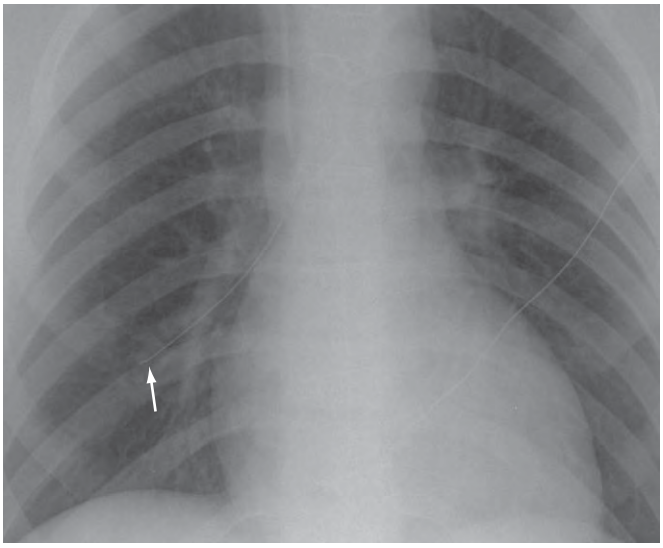


Figure 11-29 Follow tubes and lines to their tip: 17-year-old boy who is recently postsurgery. Chest radiograph demonstrates a nasogastric tube in a right lower lobe bronchus.

border of the heart extends beyond the tracheal air column (Fig. 11-30).

When evaluating the lungs, it is helpful to start by comparing the density of the two lungs at the same level, as these should be symmetrical. There should also be no significant difference in the density of the apex of the lungs compared with the base. The density of the lungs depends on a number of factors but essentially reflects the relative aeration of the lung. An opacity reflects replacement of aerated lung by soft tissue or fluid density material and may be due to atelectasis, consolidation, a mass, etc. The reason the heart, mediastinum, and diaphragm are normally visible is because these structures are bordered by aerated lung, which has a much lower density. When normal low-density air is replaced by fluid or solid material, there is no longer an appreciable difference in density compared with surrounding soft tissue structures such as the heart or diaphragm, and this leads to loss of the visualization of these structures. This is called the silhouette sign (Fig. 11-31). If a bronchus is visible within an opacity, this is referred to as an air bronchogram, formed by fluid-filled alveoli surrounding an air-filled bronchus (Fig. 11-32).

Decreased density reflects a relatively increased ratio of air to fluid/interstitium. This may be due to air trapping (e.g., an inhaled foreign body), an aerated cyst (e.g., a pneumatocele), or a decrease in blood flow to that area (e.g., congenital lobar emphysema) (Fig. 11-33).

In pediatric patients, a pleural effusion is the most common manifestation of pleural disease. In upright patients, a small effusion is usually seen as blunting of the costophrenic angles, while larger effusions will lead to a band of increased density between the lung and the ribs. On the lateral view, a meniscus of fluid is seen in the posterior costophrenic angle ascending along the posterior chest wall for a variable distance. If the patient is supine, then effusions may manifest as general increased density throughout the affected hemithorax due to the fluid layering posteriorly. Occasionally, fluid primarily collects in a subpulmonic location between the lung and the diaphragm and can be recognized by lateral displacement of the apex of the diaphragm from the midclavicular line. A large pleural effusion is one cause of complete opacification of a hemithorax (Box 11-4). A pneumothorax is manifested as a lucent area lateral to the lung that does not contain normal lung markings. In a supine patient, the pneumothorax may only be appreciated as generalized increased lucency of the affected hemithorax. Additional signs of a pneumothorax in a supine patient include deepening of the costophrenic angle or a sharp outline of the heart border or hemidiaphragm (Fig. 11-34).

Box 11-4 Causes of a Unilateral Opaque Hemithorax

With contralateral mediastinal shift:
- Congenital diaphragmatic hernia
- Massive pleural effusion
- Extensive consolidation
- Large mass (e.g., pleuropulmonary blastoma)

With ipsilateral mediastinal shift:
- Lung aplasia/agenesis
- Collapse of ipsilateral lung

IMAGING FOR COMMON PEDIATRIC RESPIRATORY PROBLEMS

Certain clinical scenarios are more commonly encountered than others, and, as such, general algorithms can be applied. Other less common but clinically important questions may benefit from general recommendations.

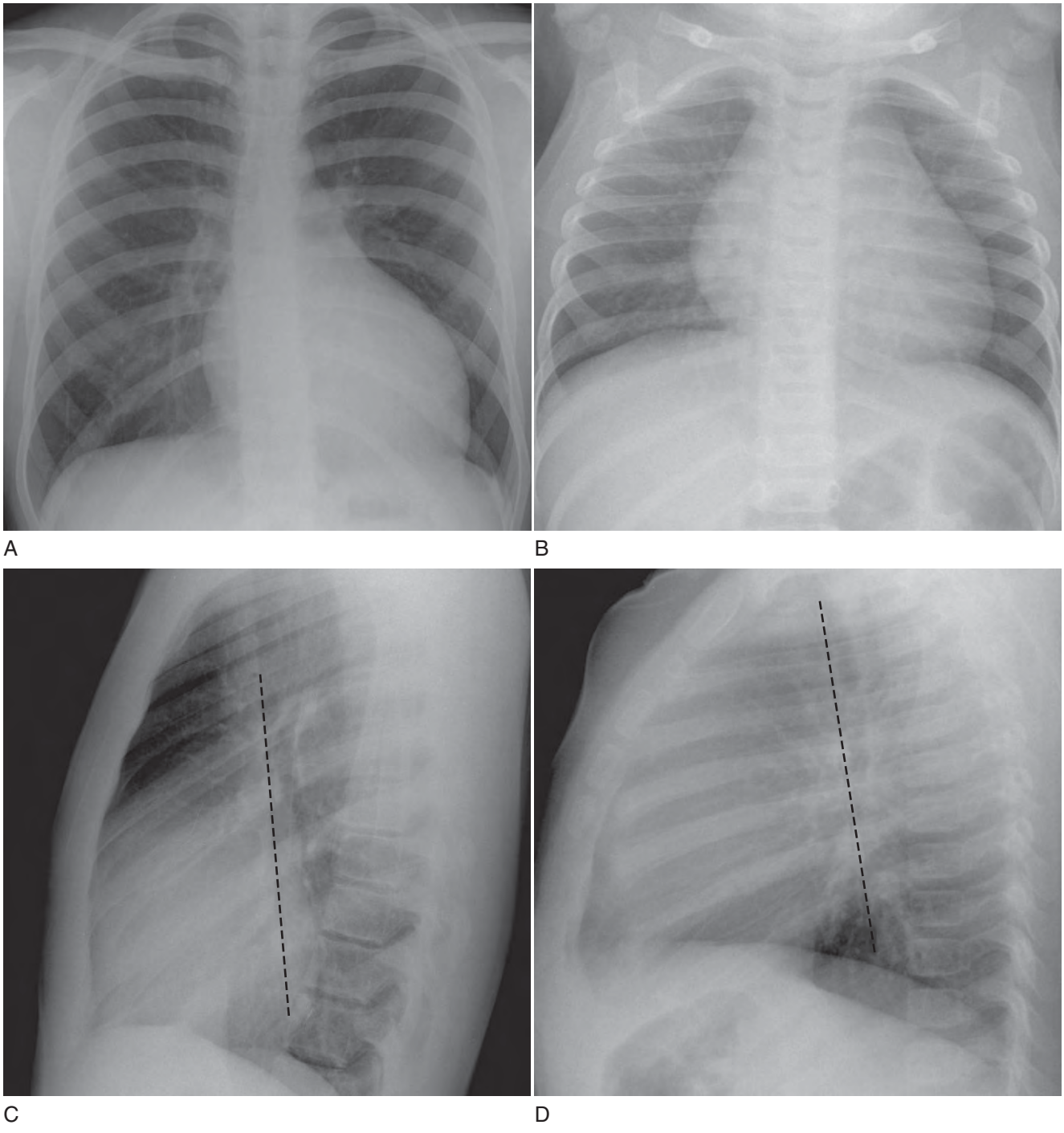


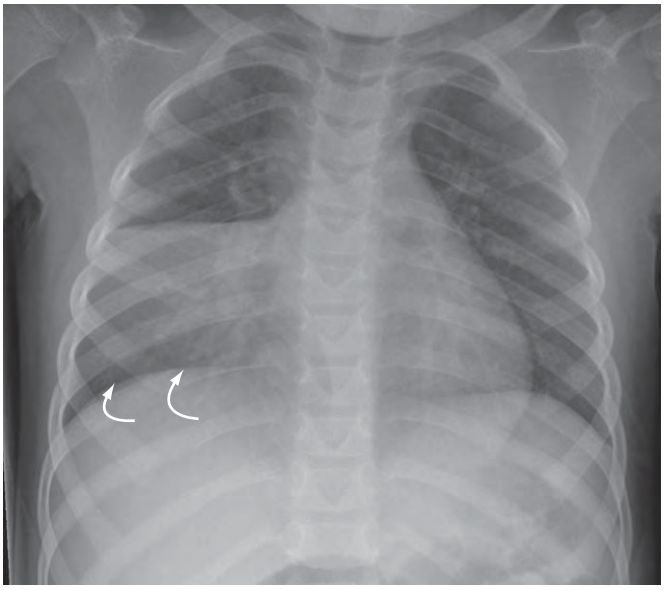
Figure 11-30 Assessment of cardiomegaly. Frontal chest radiographs (**A** and **B**) are both of concern for cardiomegaly. Lateral radiograph **C** demonstrates enlargement of the heart because the ventricular margin passes posterior to a line extended as an inferior continuation of the trachea. In fact, the heart crosses the thoracic vertebrae. Lateral radiograph **D** demonstrates normal heart size as a similar line passes posterior to the ventricular margin. The apparent enlargement was due to a prominent thymus.

Neonate

In general, a single frontal view of the chest suffices to answer most clinical questions. Occasionally, a lateral or other additional view may be helpful. A chest CT scan may be indicated for better definition of a congenital lesion such as a congenital cystic adenomatoid malformation for presurgical planning. Evaluation of a suspected congenital vascular anomaly such as a vascular ring can be evaluated with MR imaging, which will spare unnecessary radiation exposure. However, if a lung parenchymal abnormality is also a concern, then CT is preferable. An esophagogram with barium or low-osmolar contrast material can also be used to define a vascular ring or sling, or a congenital esophageal abnormality such as a tracheoesophageal fistula.

Child with Suspected Pulmonary Infection

Chest radiographs are often performed in young children with an unexplained fever. The yield is generally low, however,



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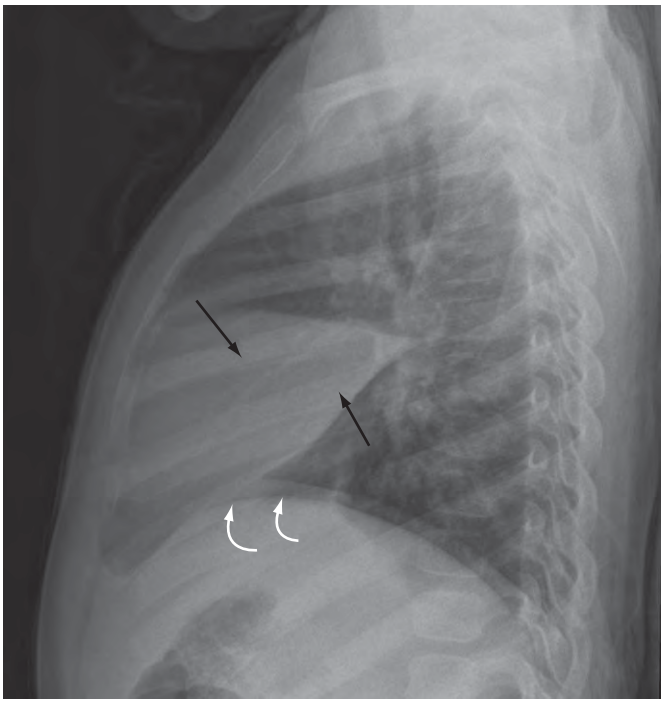


B

Figure 11-31 Silhouette sign. On the frontal radiograph **(A),** the right heart border is not visible because aerated lung has been replaced by fluid-filled lung in the middle lobe. On the lateral view **(B),** this is confirmed as the consolidated middle lobe is seen as a triangular-shaped density overlying the heart *(black arrows)*. Note that the right hemidiaphragm remains visible on both the frontal and lateral radiographs as it is outlined by aerated lung *(curved white arrows)*.

unless there are accompanying respiratory symptoms. A chest radiograph in an older child (older than 3 years) with an unexplained fever is not indicated because the diagnostic yield is so low.

In patients with signs of an acute respiratory infection, a chest radiograph may be performed, although it is not always necessary. More appropriately, a chest radiograph should be performed in those patients who are not responding as expected to standard therapy. If complications such as a

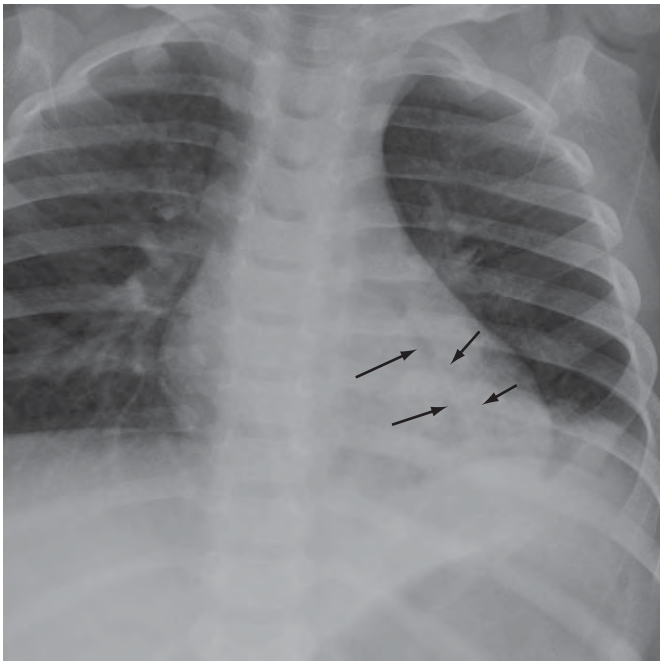


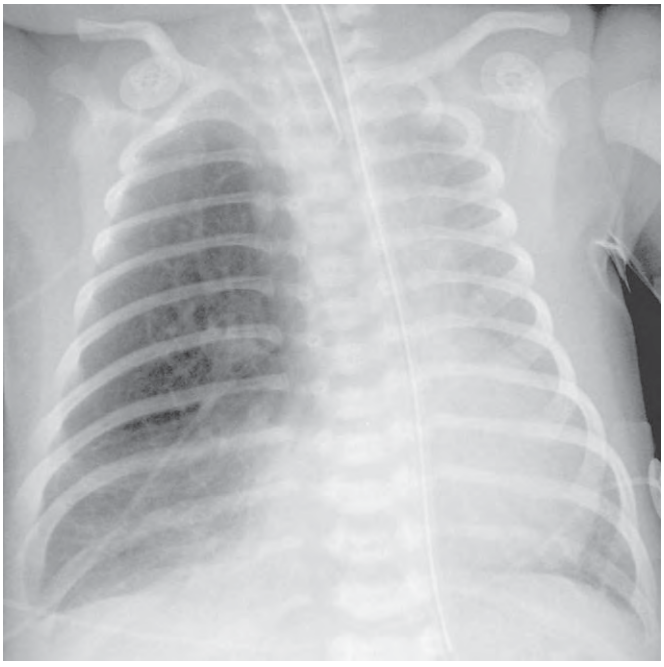
Figure 11-32 Bronchogram sign. Frontal radiograph in a 21-month-old boy with cough and fever demonstrates an irregular increased density in the left lower lobe. Air-filled bronchi are seen *(arrows)* because they are surrounded by nonaerated lung.

cavitary pneumonia or an abscess or other complications such as a loculated parapneumonic effusion or an empyema are suspected, then a contrast-enhanced CT scan may be helpful in evaluating the extent of the disease. If drainage of a parapneumonic effusion is being contemplated, then an ultrasound will help determine if the effusion is simple enough to be drained by placing a chest tube or if it is a complex effusion that needs surgical drainage.

In a patient with a history of recurrent pneumonias, an esophagram or a video swallowing study may demonstrate predisposing causes such as a tracheoesophageal fistula or aspiration. Similarly, a nuclear medicine sulfur colloid study can be used to detect gastroesophageal reflux that may predispose to aspiration. An HRCT scan can demonstrate signs of residual damage from recurrent pneumonia such as scarring and bronchiectasis and may suggest previously unsuspected disorders such as cystic fibrosis (Fig. 11-35).

Wheezing Child

Wheezing is a common presenting complaint in childhood, and although most commonly it is caused by small airway diseases such as a viral infection or asthma, it may also be caused by any obstructing central airway lesion such as a foreign body (Fig. 11-36), a compressing aberrant vessel, or a mediastinal mass. Not every child who presents with asthma or signs of a viral infection needs a chest radiograph, which should be reserved for those who do not respond as expected to standard therapy or demonstrate signs or symptoms of complications such as lobar collapse, pneumothorax, or superimposed infection. A chest radiograph in a wheezing child often shows hyperinglation, which is seen in conditions that cause air trapping but may be seen in multiple other conditions also, in both neonates and older children (Box 11-5).



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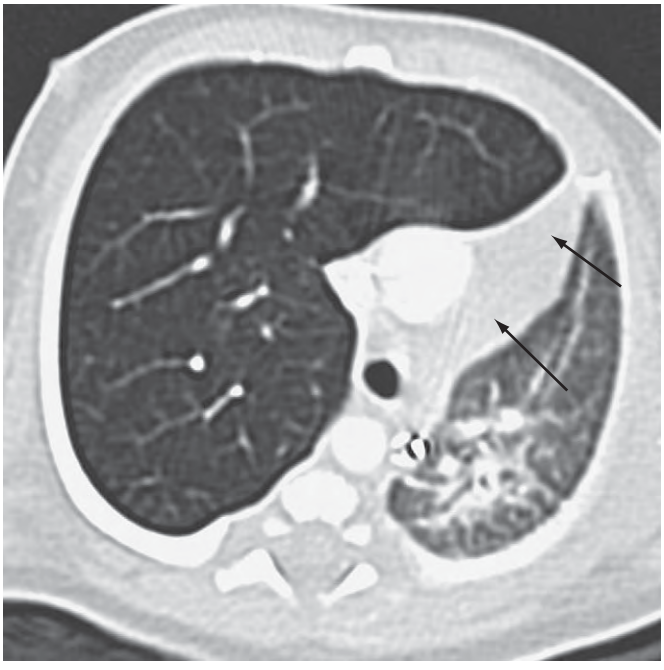


B

Figure 11-33 Hyperinflation: 14-day-old boy with respiratory distress. Chest radiograph **(A)** demonstrates increased lucency in the right upper lobe, causing shift of the mediastinum to the left. Preoperative CT image **(B)** confirms the hyperinflation. Notice the decreased number of vessels in the hyperexpanded right upper lobe and the deviation of the thymus *(arrows)* and other mediastinal structures to the left.

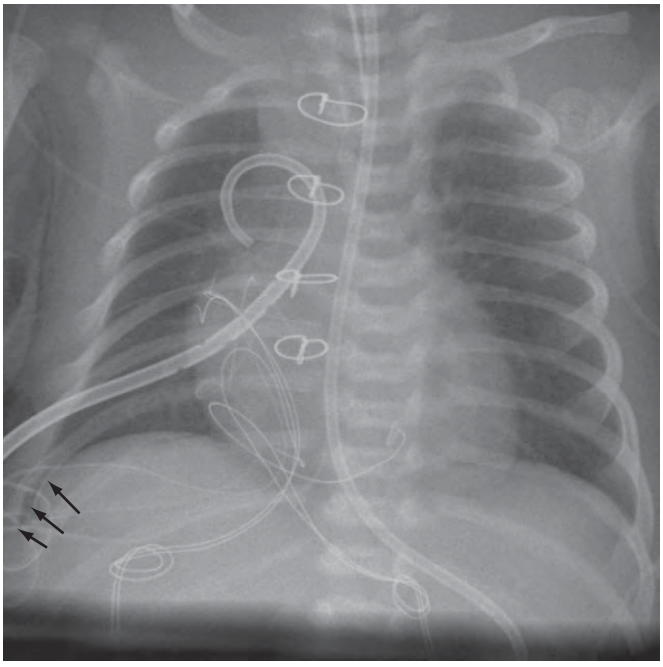


Figure 11-34 Pneumothorax in a supine patient. Chest radiograph demonstrates mild diffuse lucency in the right hemithorax and an asymmetrically deep right costophrenic angle *(arrows)* in a patient postsurgery for congenital heart disease.

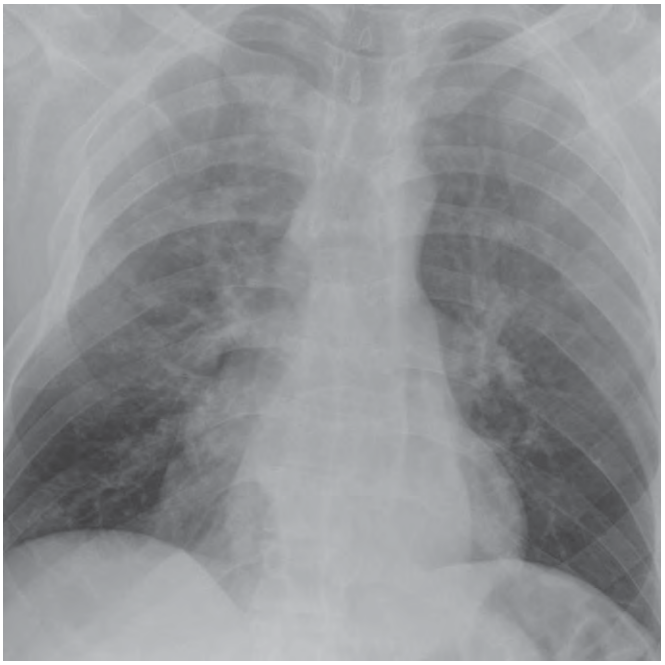
Box 11-5 Causes of Hyperinflation

Neonate

- Untreated hyaline membrane disease
- Meconium aspiration
- Neonatal pneumonia
- Congenital heart disease
- Transient tachypnea (mild)
- Congenital lobar emphysema (unilateral)
- Compensatory hyperinflation with contralateral hypoplasia/agenesis

Child

- Viral infection (bronchiolitis)
- Asthma/reactive airways disease
- Bronchopulmonary dysplasia
- Cystic fibrosis
- Dehydration/acidosis
- Bronchiolitis obliterans
- Foreign body (unilateral)
- Compensatory hyperinflation with contralateral collapse



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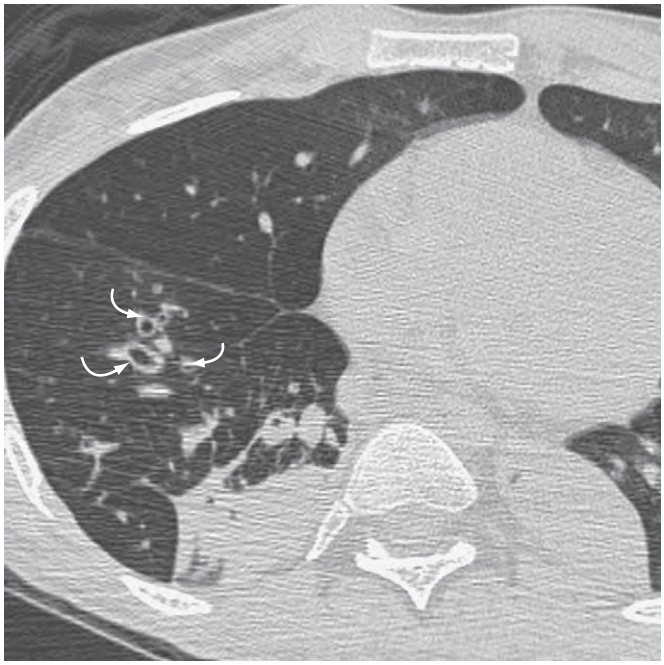

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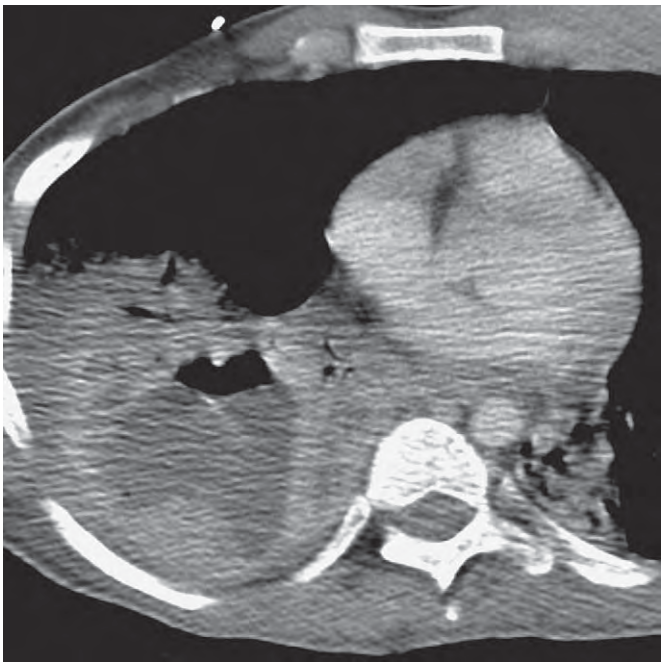

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Figure 11-35 Aspiration: 17-year-old with a history of cerebral palsy and aspiration. A chest radiograph **(A)** demonstrated some subtle ill-defined opacities in the perihilar regions with bilateral lower lobe atelectasis. A CT scan **(B)** performed at the same time demonstrated bronchiectasis in the right lung base *(curved white arrows)*, presumed secondary to recurrent aspiration. A further CT scan **(C)** performed 8 months later demonstrated a cavitary pneumonia in the same location, consistent with aspiration pneumonia.

Complications of Malignancy

In a patient with a known malignancy, pulmonary metastases may be obvious on a chest radiograph. However, spiral CT is needed to evaluate the true extent of metastatic disease. In a patient with a known malignant tumor and a normal chest radiograph, CT should also be performed to assess for metastases. Patients who are immunocompromised due to therapy and have an unexplained fever should be investigated with chest CT even if the chest radiograph is normal, as infections in this population may be subtle (Fig. 11-37). Both metastases and opportunistic infections in oncology patients may appear as multiple pulmonary nodules, which may also be seen in a variety of other conditions (Box 11-6).

Mediastinal and Parenchymal Masses

In the pediatric population, mediastinal masses are usually visible on a chest radiograph, which are often obtained for an unrelated reason. As implied previously, the most common mediastinal mass is the normal thymus, which usually can be diagnosed on a chest radiograph. Confirmation, if needed, may be achieved with MR imaging or CT, but an ultrasound scan can also identify normal thymic tissue.

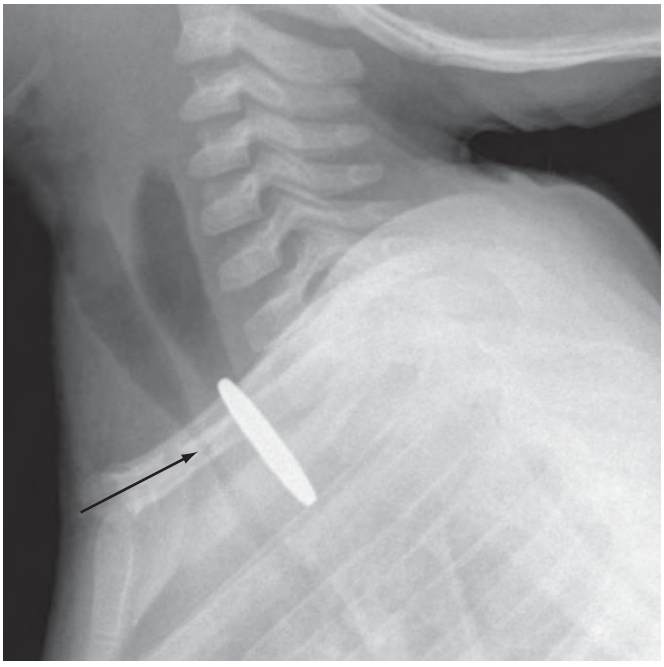


Figure 11-36 Esophageal foreign body: 9-month-old girl with a history of recurrent wheezing, not responding to medical therapy. Lateral radiograph demonstrates the coin in the proximal esophagus, resulting in inflammation and thickening of the esophageal wall. Over time, this has involved the tracheal wall with resultant narrowing of the tracheal lumen *(arrow)*.

Box 11-6 Causes of Multiple Pulmonary Nodules

Infection

Fungal: histoplasmosis, coccidioidomycosis, *Candida,* and cryptococcosis

Bacterial: tuberculosis

Viral: cytomegalovirus, measles

Septic emboli

Metastases/Tumor

Wilms tumor

Osteogenic sarcoma

Hepatoblastoma

Rhabdomyosarcoma

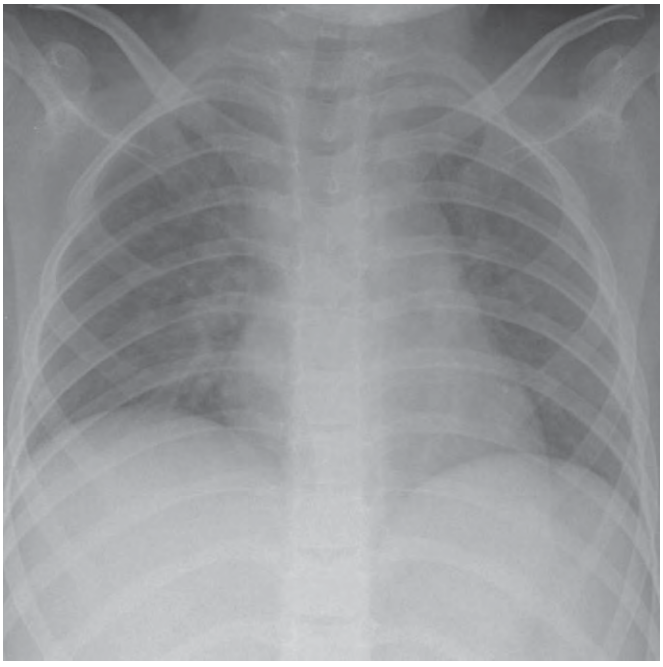
Ewing sarcoma

Lymphoma

Vascular

Wegener granulomatosis

Multiple arteriovenous malformations



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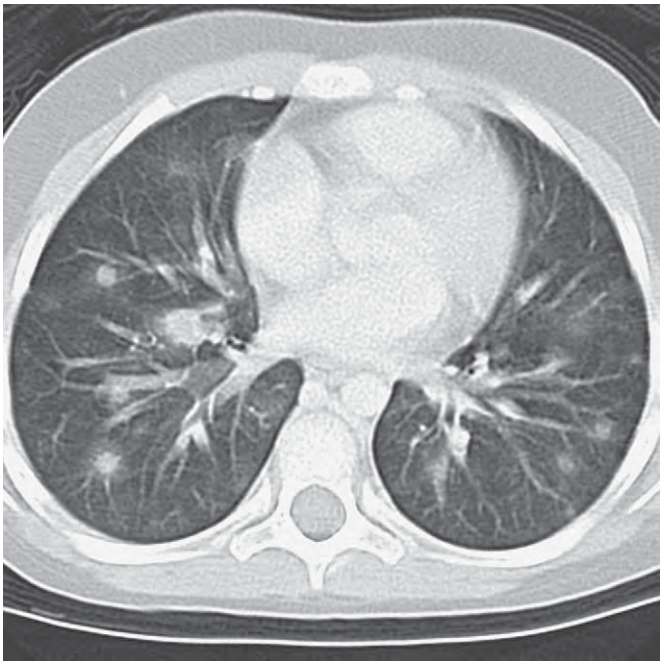

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Figure 11-37 Utility of CT in immunocompromised patients: 7-year-old boy with a history of a bone marrow transplant and a fever. Radiograph **(A)** has low lung volumes but is otherwise normal. A CT **(B)** performed that day demonstrates numerous small ill-defined nodular densities that yielded cytomegalovirus.

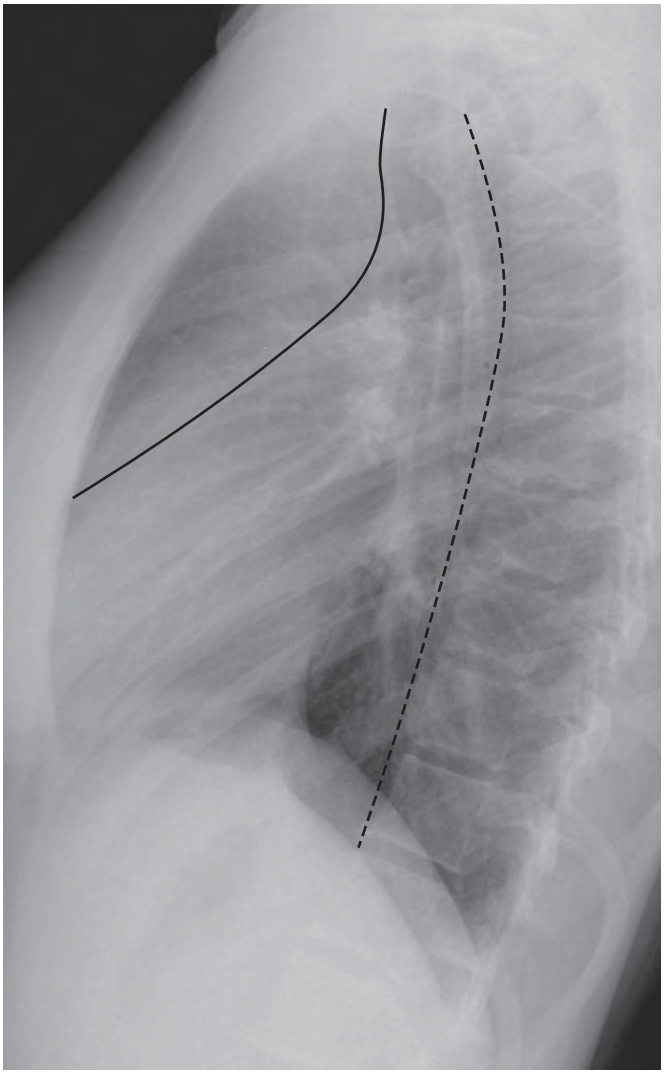


Figure 11-38 Anterior mediastinum is anterior to the trachea and ventral surface of the heart *(solid line)*. Posterior mediastinum is posterior to the anterior surface of the spine *(dashed line)*. Middle mediastinum is between these two lines.

Box 11-7 Causes of Mediastinal Masses by Mediastinal Compartment

Anterior

Normal thymus

Thymic hyperplasia

Lymphoma

Teratoma

Morgagni hernia

Middle

Lymphoma

Lymphadenopathy

Bronchogenic cyst

Hiatal hernia

Posterior

Sympathetic ganglia origin
- Neuroblastoma, ganglioneuroblastoma, ganglioneuroma

Peripheral nerve origin
- Schwannoma, neurofibroma

Bochdalek hernia

Foregut duplication cyst

Investigation of other causes of a mediastinal mass should also be performed with CT or MR for a number of reasons: (1) to try to identify the location of the mass and the organ of origin, (2) to look for signs of involvement of surrounding structures, and (3) to evaluate whether the mass is cystic or solid and, if possible, to identify component tissues in complex masses such as a teratoma.

The mediastinum can be divided into anterior, middle, and posterior compartments, and identifying which compartment a mass arises in helps to narrow the differential diagnosis (Fig. 11-38). Anterior mediastinal masses are most commonly due to lymphoma and germ cell tumors. Usually, these can be differentiated by the presence of some calcification and/or fat in a teratoma (Fig. 11-39). Middle mediastinal masses most commonly are due to lymphoma and foregut duplication cysts (Fig. 11-40), while posterior mediastinal masses are usually neurogenic in origin (Box 11-7).

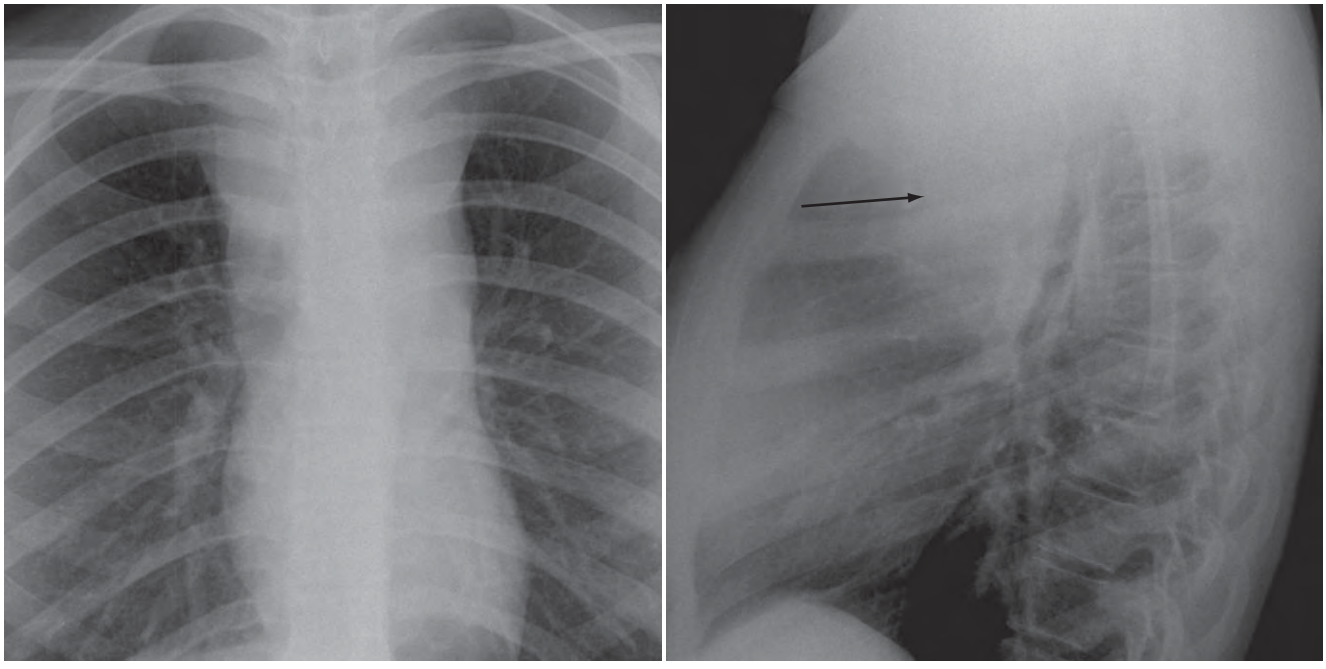
Parenchymal masses other than congenital lesions such as sequestration and congenital cystic adenomatoid malformation and those related to bacterial infection (i.e., round pneumonia) are uncommon in infants and children. Granulomatous infections are common in some geographical areas, but primary lung tumors such as pleuropulmonary blastoma are rare.

CONCLUSION

Plain film radiography continues to be the mainstay of pediatric imaging, and pediatric pulmonologists should be comfortable with evaluating a chest radiograph. Cross-sectional imaging techniques, especially HRCT, are becoming increasingly important as a means of investigating the respiratory tract but should be used only when the clinical information to be gained outweighs the potential risk of radiation and also the risk of any required sedation. Special techniques such as controlled ventilation or decubitus imaging can be used to optimize the quality of the images obtained in sedated children.

Imaging of the airway for intrinsic abnormalities is primarily performed with radiography. Extrinsic airway compression and mediastinal abnormalities can be imaged with CT or MR imaging. The choice of which modality to use should be decided on a case-by-case basis.

Nasal and paranasal structures are optimally imaged with CT and MR imaging.



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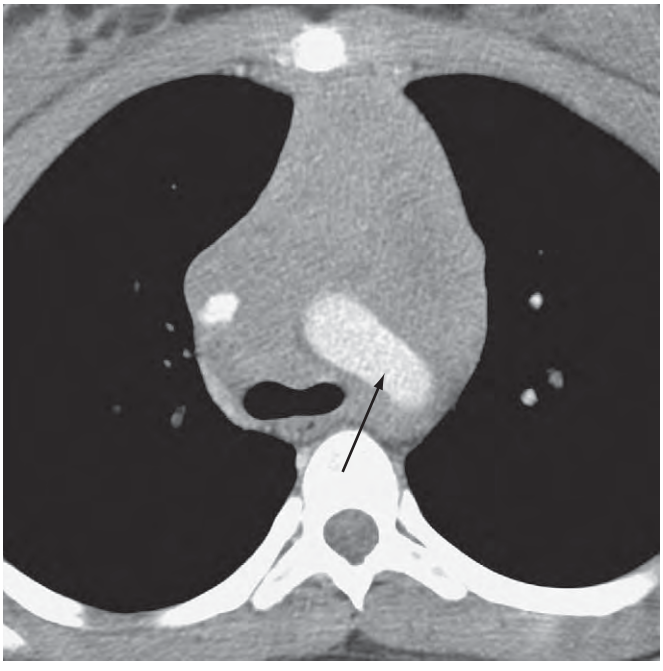

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Figure 11-39 Anterior mediastinal mass: 15-year-old girl with a cough and chest pain. Frontal radiograph **(A)** demonstrates widening of the mediastinum. Lateral radiograph **(B)** localizes this to the anterior mediastinum *(arrow)*. Contrast CT **(C)** demonstrates a homogeneous attenuation mass anterior to the aortic arch *(arrow)* in the anterior mediastinum. This is too large to be a normal thymus in a teenager. Homogeneous anterior mediastinal masses are lymphoma until proven otherwise.

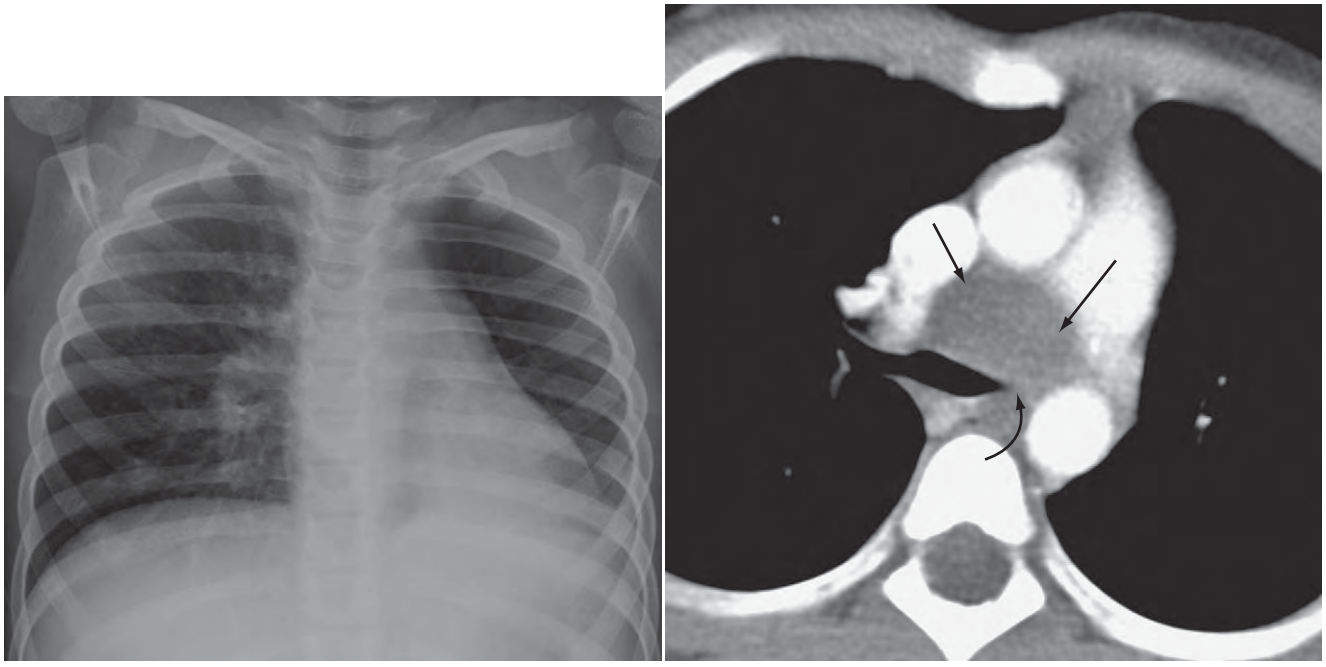

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Figure 11-40 Middle mediastinal mass: teenager with a history of recurrent left lower lobe pneumonia. Radiograph **(A)** demonstrates consolidation in the left lower lobe. CT image **(B)** demonstrates a fluid attenuation mass *(arrows)* on the precarinal region causing compression of the left main bronchus *(curved arrow)*.

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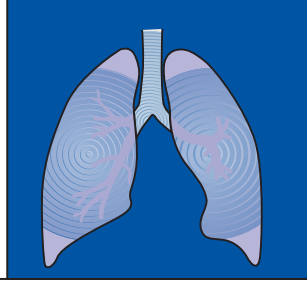

CHAPTER 12 Respiratory Function Testing in Infants and Preschool-Aged Children

Peter D. Sly and Wayne J. Morgan

TEACHING POINTS

- Lung function testing is feasible in infants and preschool-aged children.
- Attention to detail in optimizing the measurement conditions is critical to producing reliable results.
- International efforts at producing standardized measurement techniques and reference values are continuing.
- Before introducing these techniques locally, labs should study healthy children to ensure that the available reference data are applicable to their population.

Measurement of lung function in adults and older children has become a routine part of the management of respiratory diseases. Pulmonary function tests provide objective evidence regarding the nature and control of respiratory diseases and the effect of therapy and provide opportunities to study the mechanisms by which diseases alter lung function. These objective assessments have been unavailable to those managing respiratory diseases in infants and younger children until relatively recently. Many advances have been made in the past decades, and now the techniques and equipment necessary to measure lung function in infants and young children are readily available. Measurements of lung function in preschool-aged children are being used clinically in many parts of the world.

This chapter is not intended to be sufficiently detailed that the reader can learn to measure lung function in infants and young children from these pages. A joint task force from the American Thoracic Society and European Respiratory Society has produced numerous publications about how these tests should be performed.[1-9] The interested reader is referred to these publications for practical details of the various tests.

LUNG FUNCTION TESTING IN INFANTS

Influence of Measurement Conditions on Lung Function

A major requirement for most methods of measuring lung function in infants is to have the infant sleeping. This is necessary to effect reproducible results. However, infants cannot be relied on to sleep naturally on demand or to remain asleep long enough to allow pulmonary function to be measured. Thus, the majority of infant lung function tests are performed with the infant sedated, most commonly with chloral hydrate or a similar sedative. Sedating infants for pulmonary function testing is considered safe, with no reported adverse effects despite many thousands of tests having been performed throughout the world.[10] However, a fall in arterial oxygen saturation has been reported in wheezy infants sedated for pulmonary function testing,[11] so continuous monitoring of oxygen saturation is considered mandatory in such infants.

Standardization of measurement conditions must address both laboratory conditions and the infant's state with respect to factors that influence the results of respiratory function tests, such as feeding, posture, and sleep state.[6]

Measurement Techniques

The techniques used to measure pulmonary function in infants can be conveniently grouped into four groups: measures of lung volume, measurements of ventilation inhomogeneity, measures of forced expiratory flow, and measures of compliance and resistance.

Measures of Lung Volume

Knowledge of lung volume can play an important role in the respiratory care of infants and young children and can assist in the interpretation of measurements of resistance, compliance, and forced expiratory flow. Two main techniques are used for measuring lung volumes in infants: body plethysmography and gas-dilution techniques.

BODY PLETHYSMOGRAPHY

In body plethysmography, the infant is placed inside a rigid, closed container (a plethysmograph) and makes respiratory efforts against an occlusion at the airway opening; the respiratory efforts rarefy and compress the thoracic gas (Fig. 12-1). Calculation of the amount of gas in the thorax during occluded breathing efforts is made by applying Boyle's law. The assumptions underlying this technique are discussed more fully in Chapter 13. There are, however, a number of particular difficulties in applying these assumptions to measurements in infants. The success of the plethysmographic measurement of lung volume relies on the plethysmograph having an adequate frequency response over the range of frequencies used. In an adult plethysmograph, with a volume typically 50 to 100 times that of the adult's intrathoracic volume, the fre-

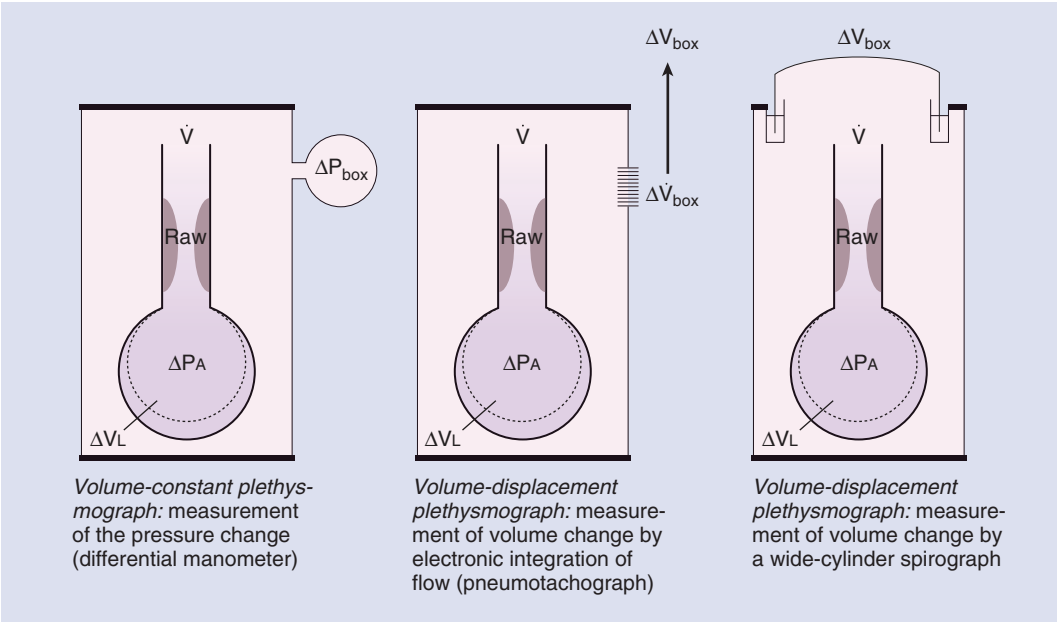

Figure 12-1 Types of plethysmographs. Dotted lines indicate volume change by compression; solid lines indicate volume change by expansion of thoracic gas (ΔV_L). ΔV_{box}, Change in volume in plethysmograph; ΔP_{box}, change in pressure in plethysmograph; $\dot{V}$, gas flow; Raw, airway resistance; ΔP_A, change in alveolar pressure; ΔV_L, change in lung volume. (Redrawn from Tammeling GJ, Quanjer PH: Contours of Breathing. Burlington, Ontario, Canada, Boehringer Ingelheim Pharmaceuticals, 1985.)

quency response is poor (<0.2 Hz) because of the thermal time constant of the box and the necessary presence of a slow leak to allow for gas expansion resulting from the heat generated by the subject. Adults and older children are asked to make occluded breathing efforts at a frequency of approximately 1 Hz. This is primarily to keep the glottic aperture open, aiding the transmission of alveolar pressure to the airway opening and minimizing the difference in airway resistance (Raw) between inspiration and expiration.[12] However, this technique ensures that the box is being operated at a frequency at which the frequency response is adequate and that gas compression within the box is essentially isothermal.

The infant plethysmograph is considerably smaller than the adult, giving it a greater surface area–to-volume ratio. Thus, the mean distance over which heat diffusion must occur between any point inside the plethysmograph and its walls is greatly reduced. This in turn leads to a much reduced thermal time constant,[13] which adversely influences the frequency response of the plethysmograph in the frequency range usually encountered in infants. The thermal time constant of a 60-L plethysmograph, with metal walls, was reported to be 0.16 second.[13] Gas compression within this box was found to be polytropic (i.e., between isothermal and adiabatic) over a frequency range of 0.1 to 3 Hz. Infants, obviously, cannot be requested to breathe at a particular frequency, and the respiratory rate is likely to change during measurements, particularly those that involve giving the infant a bronchodilator or bronchial challenge agent.[13] Changes in the frequency of the occluded breathing efforts result in changes in the value of thoracic gas volume calculated simply because of the polytropic gas compression.

An alternative to the "constant-volume" plethysmograph is the "flow plethysmograph" in which a pneumotachograph measures gas flow between the plethysmograph and the exterior (see Fig. 12-1, center). The flow signal can be integrated to produce the volume change occurring in the box resulting from respiration (i.e., tidal volume). During occluded breathing efforts, this volume should equal the change in volume recorded in a constant-volume plethysmograph (see Chapter 13). In a flow plethysmograph, the gas displacement minimizes polytropic gas compression and eliminates thermal effects. If the resistance and inertance of the pneumotach are too high, the flow signal may be damped, introducing errors into the calculations of lung function. These errors can be improved by using a screen pneumotachograph fitted flush with the plethysmograph wall without any connecting tubing or by correcting for the resistance and inertance of the pneumotachograph.[14]

Transmission of the changes in alveolar pressure to the airway opening during occluded breathing efforts occurs with a time constant dependent on the Raw and upper airway compliance. Infants have higher Raw and more compliant upper airways, both of which increase the time required to transmit alveolar pressure changes to the upper airway. This problem is magnified in conditions with increased Raw, such as wheezing illnesses. Under these conditions, the airway opening pressure may markedly underestimate alveolar pressure, resulting in overestimations of thoracic gas volume and thus limiting the accuracy and usefulness of this technique in infants with airway disease. Recent advances in technology and attention to detail in calculation of results have brought marked improvements in the accuracy of plethysmography in infants.[15]

GAS-DILUTION TECHNIQUES

The most common application of the gas-dilution technique is the helium-dilution technique. This technique is based on

the principle of gas equilibration between an unknown lung volume and a known volume containing helium as an indicator gas. Gas is mixed by ventilatory movements, and the lung volume is calculated from the change in helium concentration. Lung volume can also be measured using the nitrogen-washout technique. With this technique, the infant breathes from a reservoir of nitrogen-free gas, and the washout of nitrogen in the alveolar gas is measured with a rapidly responding nitrogen analyzer.

The major problems with these techniques include the following:

1. Any leak in the circuit results in the final concentration of gas (especially helium) being artificially low, with the consequent overestimation of lung volume. For these tests, the infant breathes through a facemask, increasing the possibility of leaks, which may be difficult to detect.
2. Adequate time must be allowed for the helium to be distributed throughout the lung and for the final helium concentration to become stable. In the presence of small airways and in conditions with increased Raw, the time required for equilibration may be considerable. Long equilibration times may be impractical when testing infants.
3. Gas-dilution techniques measure the lung volume readily communicating with the airway opening, which may be substantially less than the total lung volume. The response to treatments, such as bronchodilators, can be difficult to interpret because a beneficial treatment effect may be measured as a decrease in lung volume if most airways are patent or as an increase in lung volume if the bronchodilator opens previously closed airways, resulting in an increased volume of lung in communication with the airway opening.

Measurements of Ventilation Homogeneity

The realizations that lung disease in infants with cystic fibrosis begins in the lung periphery and that measurements of forced expiration may not be sensitive enough to detect signs of early disease have led to an increase in interest in tests that measure ventilation distribution in infants. The multiple breath nitrogen washout technique has been used for decades in adults and has been investigated in infants.[16] Techniques using the inert gases SF6 and/or helium as a tracer gas are becoming increasingly popular.[17,18] The most common indices of lung function calculated from these multiple breath inert gas techniques are the functional residual capacity (FRC) and the lung clearance index (LCI). The measurements are performed as follows:

- Tidal breathing is monitored and when a stable pattern with a stable end-expiratory level has been achieved the breathing circuit is switched to one containing the tracer gas (e.g., 4% SF6).
- The gas concentration is measured during tidal breathing until a stable plateau has been achieved. This phase is known as the wash-in phase.
- The breathing circuit is then switched to one without the tracer gas and gas concentration monitored until the concentration has dropped to 1/40 of the plateau concentration (the washout phase).
- FRC is calculated from the cumulative expired tracer gas volume divided by the difference in end-tidal tracer gas concentration at the start of the washout and the end-tidal tracer gas concentration at the end of the washout.
- LCI is calculated as the number of lung volume turnovers (cumulative exhaled volume/FRC) required to lower tracer gas concentration to 1/40 of the starting concentration.

LCI is a useful measure of volume homogeneity and is essentially constant at 6 to 7 throughout childhood.[17] LCI also appears to be abnormal in children with cystic fibrosis and is more sensitive to the presence of early lung disease than standard spirometry.[17]

Measures of Forced Expiratory Flow

The primary method used to measure forced expiratory flows in infants has been the rapid thoracic compression (RTC) technique. The RTC technique produces forced expiratory flows by suddenly applying a pressure to the thorax and abdomen at the end of a tidal inspiration, using an inflatable thoracoabdominal jacket connected to a positive-pressure reservoir. Flow is measured at the mouth with an appropriately sized pneumotachograph attached to a mask sealed around the infant's nose and mouth.[19] Flow is integrated to obtain volume, and a flow-volume curve is constructed. Before the RTC maneuver, a reproducible end-expiratory volume (FRC) is established from at least three tidal breaths. An RTC initiated at the end of inspiration then produces a partial expiratory flow-volume curve, with exhalation continuing to a volume below the previous FRC. RTC maneuvers are repeated at increasing jacket pressures until the pressure that produces the highest expiratory flows is determined. The maximum flow occurring at the previously established tidal FRC ($\dot{V}$max FRC) is reported.

Use of the RTC has led to major advances in understanding the normal growth and development of the respiratory system and of the development of respiratory diseases. For example, $\dot{V}$max FRC shows an essentially linear increase with somatic growth and with lung volume throughout the first year of life.[20,21] Seidenberg and coworkers[22] demonstrated that lung function abnormalities persist for up to 3 months in the absence of clinical symptoms after an episode of acute viral bronchiolitis. However, the RTC technique has not proved to be the "panacea" it initially promised to be and has largely been replaced by the raised volume RTC (RVRTC), in which the infant's lungs are inflated to a volume approaching total lung capacity before the forced expiration is initiated[9] (see later).

The utility of measurements of forced expiration relies on expiratory flow limitation being achieved. Although this may be the case with the RTC technique in infants with airway obstruction, flow limitation is unlikely to be achieved in healthy infants. Furthermore, FRC is notoriously variable in infants, even over short periods, which leads to substantial variability in the values of $\dot{V}$max FRC (Fig. 12-2). Many studies have consistently failed to demonstrate a bronchodilator response after therapy with inhaled β-sympathomimetics; yet many clinical studies have shown that infants can benefit from the administration of inhaled bronchodilators. One possible reason for this discrepancy is that bronchodilators alter

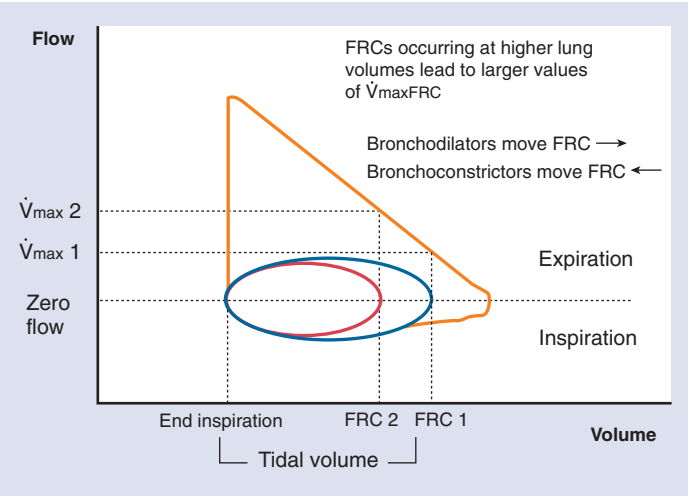

Figure 12-2 Effect of variation of FRC on V̇max FRC as calculated from a partial expiratory flow-volume curve.

FRC, possibly reducing hyperinflation. This would reduce the V̇max FRC, masking the expected increase after bronchodilator treatment (see Fig. 12-2).

In an attempt to overcome many of the problems with the RTC technique, Turner and colleagues[23,24] developed a technique in which the lungs were inflated to a preset pressure using a pump before the RTC. They reason that the use of a standard inflation pressure reduces the variability of the measurements produced. They then measure the volume forcibly exhaled in a given time, usually 0.75 second (Fig. 12-3). This technique is analogous to the 1-second forced expiratory volume (FEV_1) that is routinely measured in older children and adults. In addition, because the forced expiration is induced from a higher lung volume, full forced expiratory flow-volume curves appear to be possible (Fig. 12-4). Other groups have used various methods to inflate the lungs and various inflation pressures have been used. The American Thoracic Society (ATS)–European Respiratory Society (ERS) Task Force has published standardized guidelines for the RVRTC,[9] and the interested reader is referred to that publication for further information.

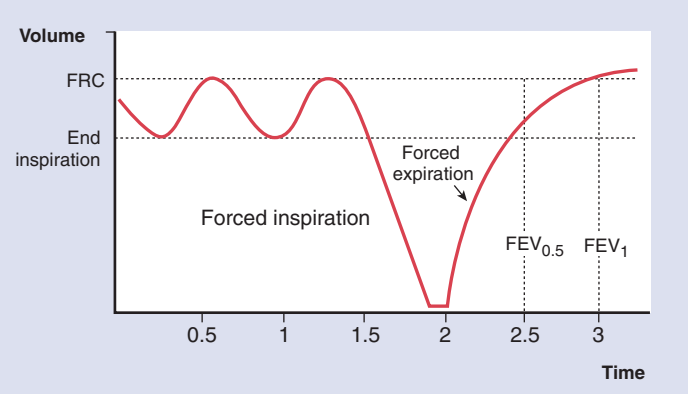

Figure 12-3 Volume-time plot of the raised volume RTC maneuver. $FEV_{0.5}$, $^1/_2$-second forced expiratory volume; FEV1, 1-second forced expiratory volume.

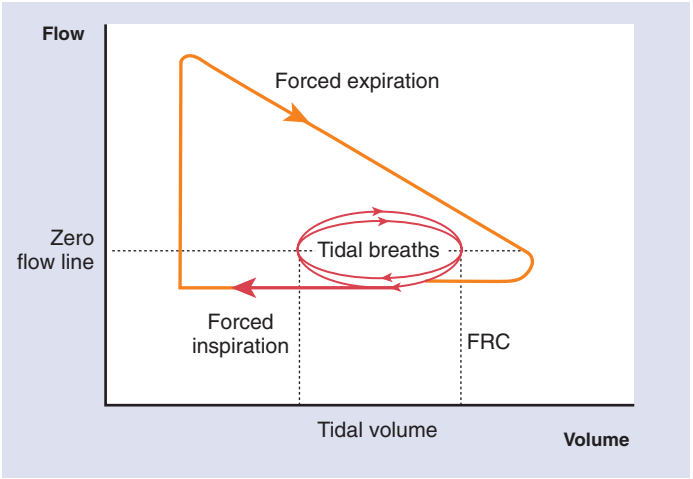

Figure 12-4 Flow-volume plot of the raised-volume RTC maneuver.

Measures of Resistance and Compliance

A number of techniques are available for measuring resistance and compliance in spontaneously breathing infants. The most commonly used tests are occlusion tests, which invoke the Hering-Breuer reflex, and body plethysmography. Other possibilities include the use of forced oscillation techniques. Older techniques involving the measurement of esophageal pressure as an index of pleural pressure have largely fallen out of favor for use in spontaneously breathing infants and are not discussed here further.

TECHNIQUES THAT INVOKE THE HERING-BREUER REFLEX

Techniques invoking the Hering-Breuer reflex rely on the assumptions that this reflex, producing complete relaxation of both inspiratory and expiratory respiratory muscles, can be elicited during airway occlusion and that airway opening pressure comes into equilibrium with alveolar pressure during the occlusion. Occlusion techniques may involve multiple occlusions at different lung volumes or single occlusions at end-inspiration.

Multiple-Breath Occlusion Technique

In the multiple-breath occlusion technique, pressure is measured at the mouth during brief airway occlusions performed on multiple breaths. Occlusions are performed at different volumes above FRC, and the individual measurements are plotted as volume versus pressure. The slope of the line of "best fit" is the compliance of the respiratory system (Fig. 12-5). In the single-breath occlusion technique, the airway is occluded at the end of inspiration, with the subsequent expiration occurring passively. A passive expiratory flow-volume curve is then constructed and a line fitted to the linear portion (Fig. 12-6). Compliance is calculated by dividing the total exhaled volume by the pressure at the airway opening recorded during the occlusion. The slope of the linear part of the passive flow-volume curve is equal to the reciprocal of the expiratory time constant (τrs). Resistance can be calculated by dividing the time constant by the compliance.

The problem with these techniques is ensuring relaxation of the respiratory muscles after airway occlusion and equilibration of airway opening and alveolar pressures. Generally,

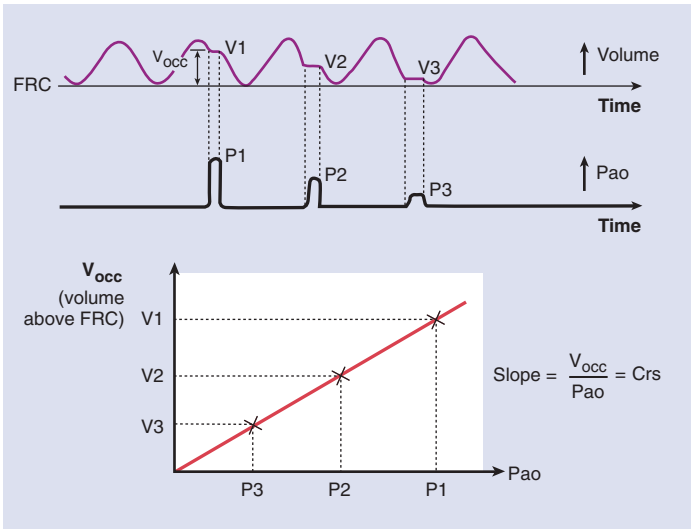

Figure 12-5 Calculation of compliance of the respiratory system using the multiple-breath occlusion technique. V_{occ}, volume at which occlusion is made; V, volume; P, pressure; Pao, pressure at the airway opening; Crs, compliance of the respiratory system.

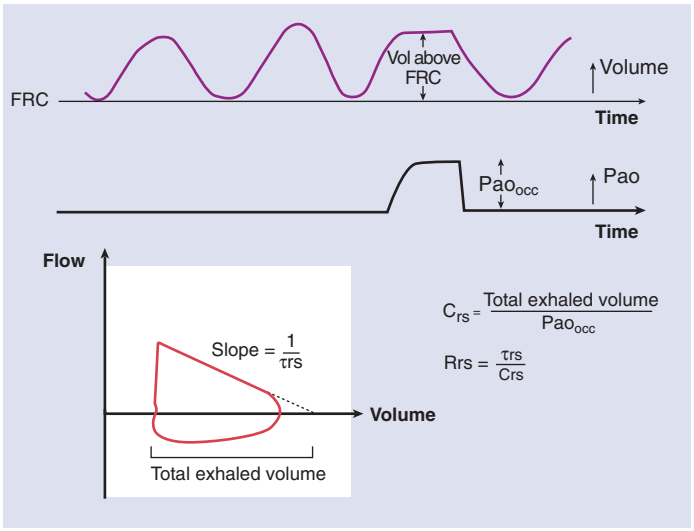

Figure 12-6 Calculation of respiratory compliance (Crs) and resistance (Rrs) using the single-breath occlusion technique. Pao_{occ}, airway opening pressure following occlusion; Pao, pressure at the airway opening; τrs, expiratory time constant.

the presence of a plateau in airway opening pressure indicates that both of these assumptions have been satisfied. The ERS/ATS Task Force has recommended that occlusions should be held for a minimum of 400 milliseconds.[25] The length of the airway occlusion can influence the values of compliance calculated from the subsequent expiration, with compliance decreasing by 0.15 ml/cm H_2O for each 0.1 second of occlusion time.[26] These data strongly argue for standardizing the length of occlusion and discarding data in which a plateau is not achieved. The ERS/ATS Task Force recommends that a plateau should be maintained for at least 100 miiliseconds.[25]

Low-frequency Forced Oscillation Technique

Forced oscillation techniques are described in detail in Chapter 13. These techniques have been used in infants, and impedance spectra have been measured above 4 Hz.[27,28] In infants, the forcing function is generally applied through a facemask and includes the impedance of the nose. When making measurements in infants, the clinician must take extreme care to prevent leaks around the facemask. An adaptation of the forced oscillation technique, using lower frequencies, has been developed for infants.[29] By applying the forcing function during a pause in breathing produced by invoking the Hering-Breuer reflex, reliable impedance data can be obtained from 0.5 to 20 Hz. The impedance spectra showed the same marked frequency dependence (Fig. 12-7) reported in paralyzed animals[30,31] and in adults studied either during voluntary muscle relaxation[32,33] or during mechanical ventilation with paralysis.[34] Fitting the constant phase model[31] to the respiratory system impedance (Zrs) allows partitioning into components representing the airway resistance (together with any Newtonian resistance in the chest wall) and the lung parenchyma, i.e.:

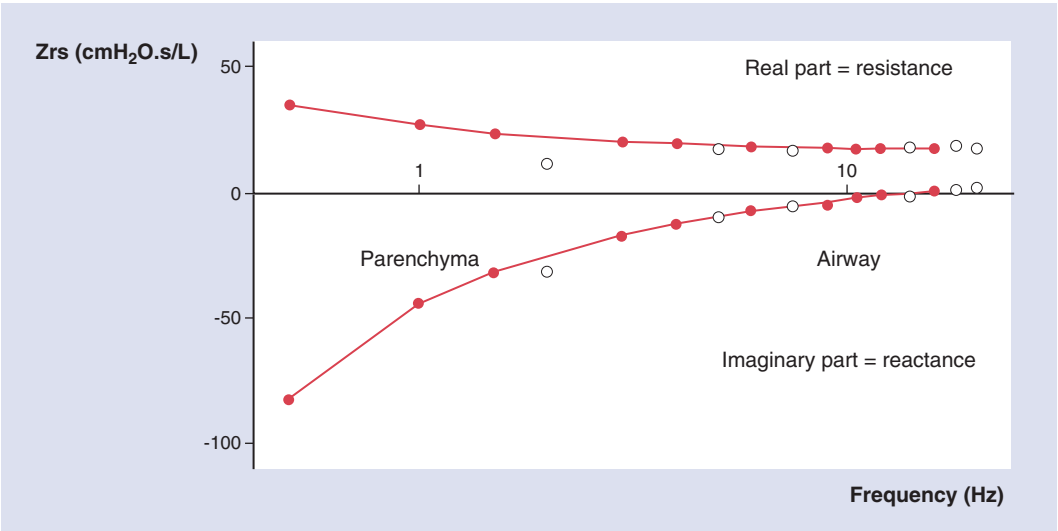

Figure 12-7 Respiratory system impedance (Zrs) measured in an infant. The upper panel shows the resistive component and the lower panel the reactance plotted as a function of frequency.

$$Zrs = Raw + j\omega Iaw + (G - jH)/\omega^{\alpha}$$

where Raw and Iaw are the frequency-independent resistance and inertance of the airways (see earlier); G and H are the coefficients for tissue damping and elastance, respectively; j is the imaginary unit, and ω is the angular frequency. The frequency dependence of the respiratory tissues is governed by the coefficient α, which can be expressed as $\alpha = (2/p)\arctan(H/G)$. As shown schematically in Figure 12-7, Zrs in the lower frequency range (<4 to 6 Hz in infants) is dominated by the mechanical properties of the pulmonary parenchyma, whereas those at higher frequencies are dominated by the mechanical properties of the conducting airways.

Interrupter Technqiue

Respiratory system resistance can also be measured in infants using the interrupter technique. The use of this technique is far more common in preschool-aged children, and the reader is directed to that section for a description of the technique. The major difference in infants is that the measurement is made through a facemask, which adds a compliant compartment (the gas in the facemask) in front of the respiratory system. This can decrease the accuracy of the measurements, especially in the presence of airway obstruction.

Body Plethysmography

Body plethysmography is commonly used to measure Raw in adults and older children but has been modified for infants by the inclusion of a rebreathing bag containing heated, humidified, oxygen-enriched gas at body temperature, pressure, and saturation. This sophisticated technique requires a large amount of expertise and training but can produce simultaneous measurements of lung volume and Raw. The ATS-ERS Task Force expended a great deal of time developing standardized techniques and has worked with industry to ensure that reliable equipment is commercially available. The interested reader is directed to the task force publications[6,15] for further information.

Measures of Tidal Breathing Parameters

Inductance plethysmography is a noninvasive technique that can be used for measuring tidal breathing in infants. The inductance plethysmograph consists of a pair of wire bands that are usually embedded into an elastic material encircling the chest wall and abdomen. The wires are arranged in a sinusoidal fashion and are excited by an oscillator to produce impedance proportional to the area enclosed within the band. By calibrating the impedance signal with known volume changes, it is possible to calculate changes in the cross-sectional areas of the thoracic and abdominal cavities in terms of changes in lung volume. However, the calibration is notoriously unstable and extremely sensitive to changes in body posture. A new generation of respiratory inductance plethysmographs was introduced in the mid-1980s. These devices produce an automatic qualitative calibration during the initial period of operation. Subsequent measurements of tidal breathing excursion are related to that measured during this initial period.[35]

The shape of the tidal breathing flow-volume curve can be influenced by airway function. Martinez and coworkers[36] reported that the time to peak tidal expiratory flow (Tptef) expressed as a percentage of total expiratory time (TE) (Fig. 12-8) (referred to by them as Tme/Te) was low in infants who subsequently developed wheezing lower respiratory illnesses. Martinez and coworkers[36] used a pneumotachograph and facemask in sedated infants to measure Tptef/TE. Stick and associates[37] demonstrated that Tptef/TE could be successfully measured using an uncalibrated respiratory inductance plethysmograph during quiet sleep in infants. The precise physiologic interpretation of Tptef/TE is unclear. In adults, Tptef/TE is correlated with airway conductance, lower values occurring with subjects with airway obstruction and low airway conductance.[38] This can be conceptualized by comparing the normally rounded shape of the expiratory limb of the flow-volume loop seen during tidal breathing (see Fig. 12-8, left), at which Tptef/TE approximates 0.5 with the peaked shape of the expiratory limb of a forced expiratory flow-volume curve (see Fig. 12-8, right), at which Tptef/TE approaches 0.15 to 0.2. For a given level of respiratory drive, as airways become more obstructed the tidal flow-volume curve becomes more like that normally seen during forced expiration, and Tptef/TE decreases. Martinez and coworkers[36] interpreted a low premorbid value of Tptef/TE as being indicative of smaller than usual airways, making the infants more likely to develop wheezing illnesses with the usual respiratory tract viral infections. However, the flow-volume

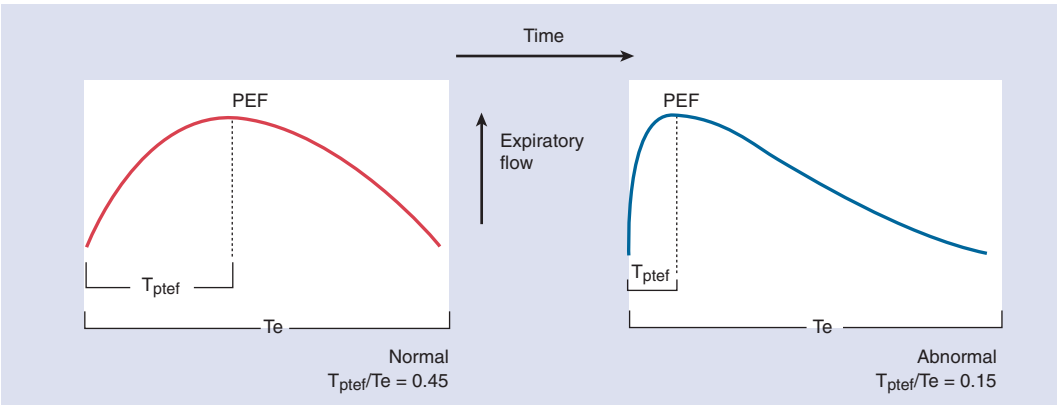

Figure 12-8 Calculation of the ratio of time to T_{ptef}/T_E from tidal expiratory flow and time recordings. PEF, peak expiratory flow.

curve represents an "integrated" output from the respiratory system, and factors other than airway conductance are likely to influence the expiratory flow pattern. Tptef/TE is also influenced by respiratory rate, becoming lower as respiratory rate increases and becoming lower in the prone than the lateral or supine sleeping positions.[39,40] Thus, it is not possible to assign precise physiologic meaning to Tptef/TE.

LUNG FUNCTION TESTING IN PRESCHOOL-AGED CHILDREN

Children under the age of 7 to 8 years are frequently unable to perform the standard lung function tests used in older children and adults. Evaluating lung function in young children is important not only for clinical reasons but also due to the considerable growth and development of the respiratory system that occur, with associated changes in lung mechanics.[41] Children commonly present with recurrent cough and wheeze during this period. Many of these children will lose their symptoms as they grow, yet others will continue to have asthma that persists into adult life.[42] The treatment implications of these two clinical patterns are different, and we are currently hampered by a lack of objective assessments to help distinguish between these two patterns. In addition, children recovering from chronic neonatal lung disease and children afflicted with cystic fibrosis are prone to recurrent or persistent respiratory symptoms. Objective assessments of pulmonary function in these children would be expected to improve clinical management.

The preschool-aged group presents a number of special challenges. Children in this age group are not able to voluntarily perform many of the physiological maneuvers required for the pulmonary function tests used in older children and adults. They have a short attention span and are easily distracted. Due to these issues, the children need to be engaged and encouraged by the operator to participate in the test. A child-friendly laboratory is essential for success, and staff must be prepared to adjust to the child's schedule.

A number of pulmonary function tests have been attempted in conscious children within the preschool-aged group. These include standard spirometry,[43-50] $\dot{V}$maxFRC,[51-53] forced oscillation,[54-60] interrupter resistance,[55,58,59,61-67] specific airway resistance measured in a plethysmograph,[58,59,68] FRC using gas dilution techniques,[53,66,69] and measurements of gas mixing indices.[17,18] Commercial equipment is available for most of these tests, although not specifically designed for preschool-aged children. Equipment dead space, resistance, and software programs designed for adults, not young children, may introduce unpredictable errors into the measurements, and no systematic research on these factors has been conducted.

The emotional developmental stage of the preschool-aged child will be an important determinant of the child's success at performing pulmonary function tests. This influence will be greatest in tests requiring more active cooperation from the child. For example, young children frequently have difficulties in performing the forced expiratory maneuvers required for spirometry. They can either blow "hard" or "long," but frequently cannot blow both "hard and long."[44] Measurements that can be made during tidal breathing, such as with forced oscillation, the interrupter technique, and gas washout techniques, may be more suitable for the child unable to accurately perform spirometry.

The physiological developmental stage of the respiratory system must also be considered in determining which outcome variables are applicable to this age group. For example, recent studies have demonstrated that the ratio of FEV_1 to forced vital capacity in healthy 5- to 6-year-old children is approximately 90% to 95%,[43,46,49,50] implying that young children essentially empty their lungs within 1 second. The physiological and clinical utility of FEV_1 comes from its location on the effort-independent (flow-limited) part of the maximal forced expiratory flow-volume (MEFV) curve (see Chapters 7 and 13). The flow-limited portion of the MEFV curve extends down to lung volumes as low as 85% to 90% of exhaled vital capacity in adults. The ability to maintain flow-limitation at low lung volumes depends largely on the ability of the chest wall muscles to maintain sufficient driving pressure to exceed that needed to ensure flow-limitation. It is highly unlikely that children in the preschool-aged group will have the chest wall muscle strength to maintain flow-limitation to lung volumes as low as 90% exhaled vital capacity. While this concept is not new,[70] the use of variables such as $FEV_{0.75}$ or $FEV_{0.5}$ has not yet been adopted into clinical practice and most commercial equipment does not report such variables.

The most appropriate lung function test for use in the preschool-aged group will depend on the purpose for measuring lung function. The interrupter technique is easily implemented and is suitable for use in epidemiological studies, particularly those involving measurements in the field. However, it may be more suited for studies reporting group mean data than for studies reporting individual data. Measurements capable of reflecting changes in the lung parenchyma, such as gas washout techniques and potentially forced oscillation, are likely to be more suitable for detecting early lung disease in a condition such as cystic fibrosis, which is known to start in the peripheral airways. The clinical and research roles for measuring bronchodilator responses and for provocation testing still need to be evaluated.

SUGGESTED READING

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 175:1304-1345, 2007.

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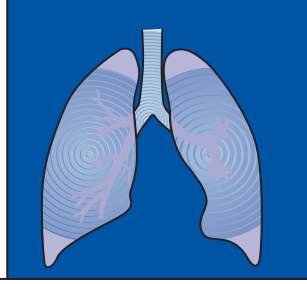

CHAPTER 13 Lung Function in Cooperative Subjects

Peter D. Sly, Rachel A. Collins, and Wayne J. Morgan

TEACHING POINTS

- Descriptive terms have been used to subdivide lung volumes into a number of fractions related to normal physiologic function where each subdivision is called a *volume*, and any combination of two or more volumes is called a *capacity*.
- The lung becomes stiff near total lung capacity with a marked decrease in compliance.
- The energy used to move the lungs during quiet breathing is proportional to volume multiplied by elastance plus flow multiplied by resistance. During tidal breathing, 90% of the energy expended is to overcome elastic forces.
- Lung function can be evaluated in children unable to perform forced expiratory maneuvers by using forced oscillation systems.
- Expiratory flow is proportional to lung elastance and inversely proportional to airway resistance, but is independent of the force driving flow over most of the expired vital capacity as long as reasonable effort is made.
- The forced vital capacity and forced expiratory volume in 1 second (FEV_1) are the most informative measures obtained with spirometry. In young children, timed volumes of shorter duration ($FEV_{0.5}$, $FEV_{0.75}$) provide information comparable to FEV_1 in older children and adults.

The measurement of pulmonary function provides an objective assessment of the state of the respiratory system and useful information for the diagnosis and management of respiratory tract illnesses in adults and children. A basic knowledge of the physiologic principles behind the tests and techniques used for making the measurements is necessary to understand the appropriate use of lung function testing and to intelligently interpret the data produced. The American Thoracic Society (ATS) and European Respiratory Society (ERS) have revised their interpretive strategies.[1]

Many measurements of respiratory function are based on forced expiratory maneuvers. Spirometry has been shown to be feasible in preschool-aged children as young as 3 years[2-5] and can be performed successfully in 70% to 80% of children by the age of 5 to 6[6] with the use of visual incentives and extensive coaching by staff experienced in measuring pulmonary function in children. A well-trained technician experienced in handling children and a laboratory setting that children do not find threatening are essential for gaining the child's confidence and producing reliable measurements of pulmonary function.[7] An ATS/ERS statement[8] outlines general standards for lung function testing and includes guidelines for selection and training of personnel.

This chapter deals with the basic physiologic principles of lung function testing. For applications of these tests in particular conditions, the reader is referred to the chapters dealing with those conditions.

PRINCIPLE 1: LUNG VOLUMES

The measurement of static lung volume (i.e., the amount of gas within the lungs at any given point during inflation or deflation) can provide important information about the state of the respiratory system. Also, because the value of many parameters of lung function, including resistance, compliance, and forced expiratory flows, depends on the lung volume at which they are measured, knowledge of lung volume aids interpretation of other measures of lung function.

Subdivisions of Lung Volume

Traditionally, descriptive terms have been used to subdivide lung volume into a number of fractions related to normal physiologic function (Fig. 13-1). By convention, each subdivision is called a *volume*, whereas any combination of two or more volumes is called a *capacity*. The more commonly used subdivisions follow:

1. *Tidal volume* (V_T) is the volume of gas breathed in and out with each breath.
2. *Vital capacity* (VC) is the maximum volume that can be exhaled after a maximal inspiration (i.e., VC = V_T + inspiratory reserve volume + expiratory reserve volume).
3. *Functional residual capacity* (FRC) is the amount of gas remaining in the lungs at the end of expiration (whether that expiration is during tidal breathing or during periods of increased ventilatory requirements such as exercise).
4. *Total lung capacity* (TLC) is the total amount of gas within the lungs after a maximal inspiration (TLC = FRC + inspiratory capacity).
5. *Residual volume* (RV) is the amount of gas left in the lungs after a maximal expiration (RV = TLC − VC).

The commonly used terms to subdivide lung volume are illustrated in Figure 13-1.

With normal tidal breathing in adults and older children, the normal end-expiratory lung volume (i.e., FRC) coincides with the elastic equilibrium volume (EEV) of the respiratory system. This EEV occurs where the outward elastic recoil of

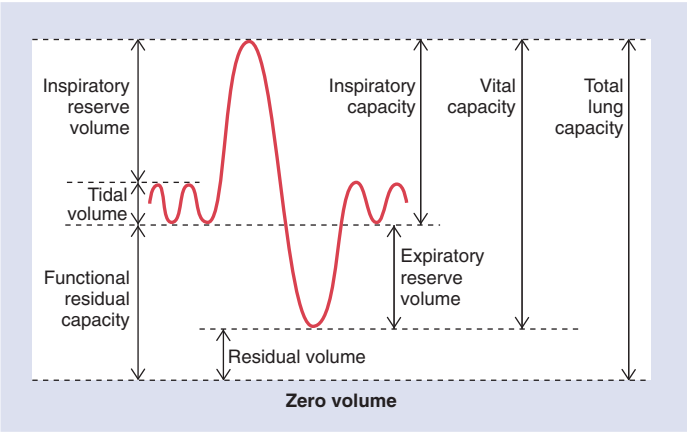

Figure 13-1 The subdivisions of lung volume.

the chest wall is balanced by the inward elastic recoil of the lungs (Fig. 13-2). The EEV is the volume the respiratory system assumes if all muscle forces are relaxed (e.g., during passive expiration) and normally occurs at approximately 40% of VC. However, under various normal and abnormal clinical situations, FRC may be above or below EEV. At times of increased ventilatory requirements, such as during exercise or with lung disease, active expiration can push FRC below EEV. Similarly, if the recoil of the chest wall is decreased (e.g., in normal neonates) or if the lung recoil is increased, such as that seen in diseases characterized by "stiff lungs" (e.g., respiratory distress syndrome), EEV may occur at a lower lung volume, at which there is risk of closure of the small airways. Breathing from low lung volumes is inefficient because extra force is required to open the closed airways. Under these circumstances, FRC is usually actively elevated above EEV by various means, including an increased respiratory rate, thus beginning the next inspiration before EEV has been reached, and a slowed expiration caused by contracting the inspiratory muscles or adductor muscles of the glottis.

PRINCIPLE 2: RESISTANCE AND COMPLIANCE

Elastic Properties of the Respiratory System

The respiratory system is composed of a collection of elastic structures. When a force is applied to an elastic structure, the structure resists deformation by producing an opposing force to return the structure to its relaxed state. This opposing force is known as the *elastic recoil pressure*. The force required to stretch a purely elastic structure depends on how far it is stretched, not how rapidly it is being stretched. Similarly, the pressure required to overcome the elastic recoil of the lung and chest wall depends on the lung volume above or below EEV. The *elastic recoil pressure* (Pel) divided by the lung volume gives a measure of the elastic properties of the respiratory system (*elastance* [E]): E = Pel/V. The reciprocal of elastance is known as *compliance* (C) and describes how much the respiratory system is inflated for a given change in applied pressure: C = V/Pel. When lung volume is plotted on the ordinate and elastic recoil pressure is plotted on the abscissa, the slope of the pressure-volume curve is equivalent to the compliance of the respiratory system (Fig. 13-3).

Dynamics of Respiration

Ventilation of the lungs involves motion of the respiratory system, which is produced by forces required to overcome the elastic, flow-resistive, and inertial properties of the lungs and chest wall. Under normal circumstances, these forces are produced by the respiratory muscles.

The force required to move a block of wood over a surface is determined by the friction between the block of wood and the surface and by how fast the wood is moving. It is not, however, determined by the block's position. Similarly, the pressure required to produce a flow of gas between the atmosphere and the alveoli must overcome the frictional resistance of the airways. This pressure is proportional to the flow ($\dot{V}$) (i.e., the rate at which volume is changing), as follows:

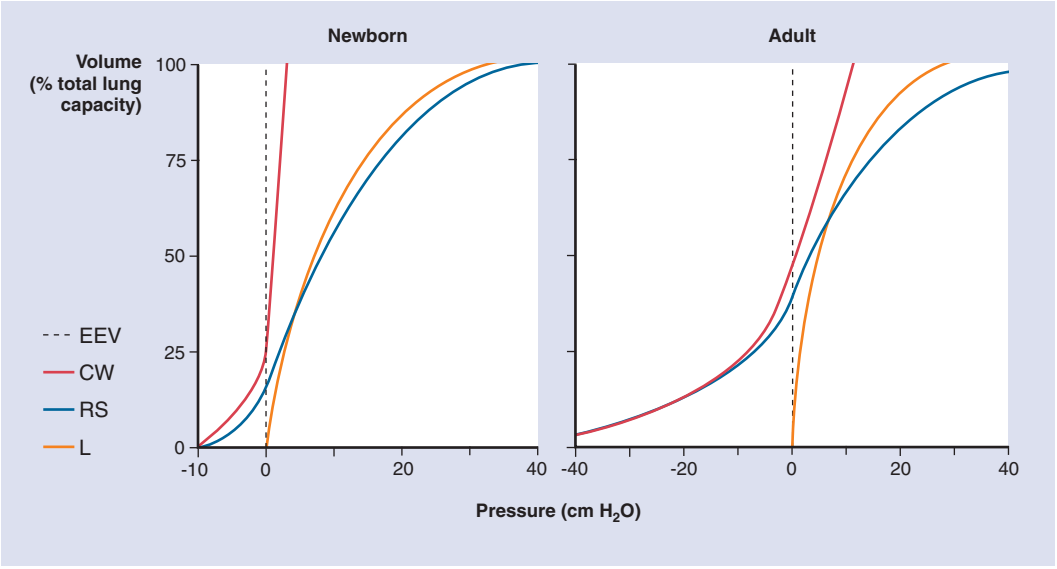

Figure 13-2 Pressure-volume curves of the newborn and adult lung, demonstrating the effect of lung (L) and chest wall (CW) compliance on elastic equilibrium volume (EEV). RS, respiratory system. (Redrawn from Agostini E: J Appl Physiol 14:909, 1959.)

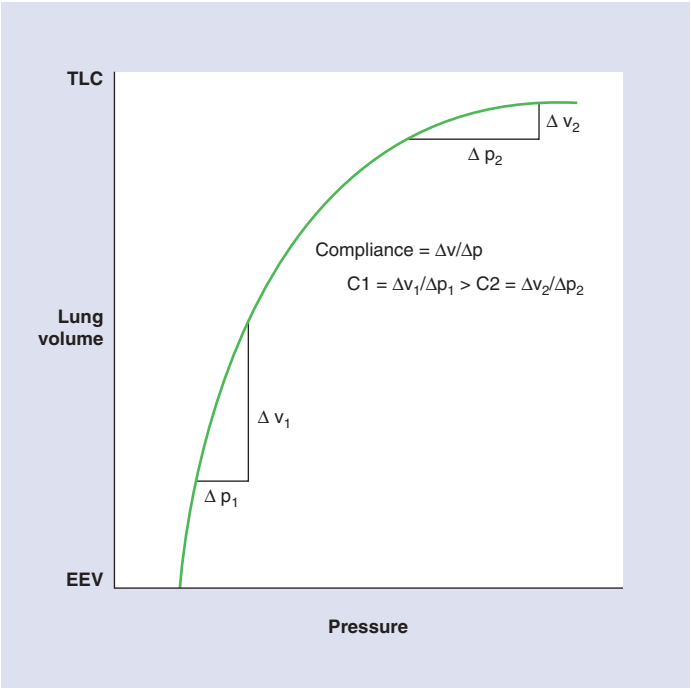

Figure 13-3 Static pressure-volume curve of the lung allows calculation of compliance (C), which decreases at high lung volumes. EEV, elastic equilibrium volume; TLC, total lung capacity.

$$\overline{Pao - P_A = Pfr \propto \dot{V}}$$

where Pao is pressure at the airway opening (usually atmospheric pressure), P_A is alveolar pressure, and Pfr is the pressure required to overcome frictional resistance. The pressure required to produce a unit of flow is known as the *flow resistance* (R), as follows:

$$\overline{R = Pfr/V'}$$

Most commonly used tests of pulmonary function model the respiratory system as a single compartment with a single resistance and a single elastance (Fig. 13-4). The equation of motion describing the balance of forces acting on the system during ventilation follows:

$$\overline{P = EV + R\dot{V} + I\ddot{V}}$$

where P is the applied pressure, I is the coefficient of inertance, E is elastance, $\dot{V}$ is gas flow, and $\ddot{V}$ is gas acceleration. Under most circumstances, the inertance is negligible and therefore ignored. During spontaneous breathing, the applied pressure is produced by the respiratory muscles and can be measured as the transpulmonary pressure. During tidal respiration, approximately 90% of the applied pressure is required to overcome elastic forces, and approximately 10% is required to overcome flow-resistive forces.

Traditionally, the majority of the force developed during breathing has been thought to be required to move gas through the airways, with little energy dissipated by the tissues of the respiratory system. In recent years, the contribution of tissue viscoelasticity to the behavior of the respiratory system has become increasingly apparent. The energy

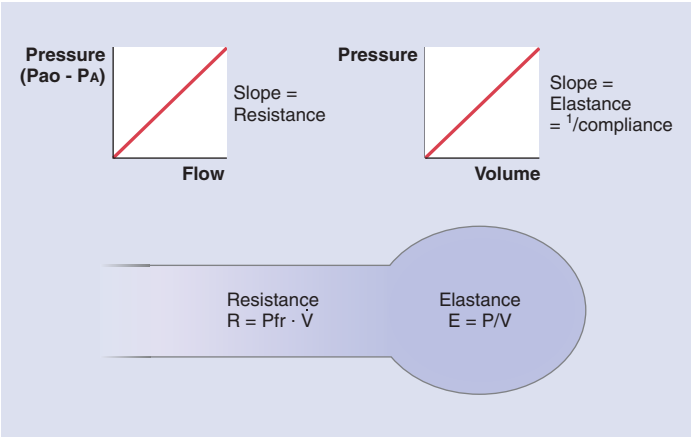

Figure 13-4 Diagram of the single-compartment model of the lung, consisting of a resistance and compliance in series. Pao, pressure at the airway opening.

expended moving the tissues has been called *tissue viscance* or *resistance*, although it is a non-Newtonian resistance. When measured during inspiration, tissue resistance increases with increasing lung volume,[9,10] whereas airway resistance falls. Tissue resistance contributes approximately 65% of respiratory system resistance at FRC in mechanically ventilated animals and increases to as much as 95% at higher lung volumes.[10,11] The contribution of tissue resistance to respiratory system resistance in humans under the same circumstances is not known.

Physiology: Measurement Techniques

MEASUREMENT OF LUNG VOLUMES

Plethysmography

Thoracic gas volume (Vtg) at FRC is usually measured directly in a plethysmograph using techniques based on Boyle's law.[12] In other words, for a given amount of gas at a constant temperature, the product of pressure (P) and volume (V) is constant, as follows:

$$\overline{P \times V = (P + \Delta P) \times (V + \Delta V)}$$

Assuming the product $\Delta P \bullet \Delta V$ is negligible, this equation can be written as follows:

$$\overline{V = -\Delta V/\Delta P \times P}$$

Vtg is measured by having the subject make breathing efforts against an occluded airway while sitting in a plethysmograph. During occluded breathing efforts, the changes in intrathoracic gas volume are assumed to occur by gas compression-decompression alone. From Boyle's law, as previously expressed, the Vtg at which the occluded breathing efforts were made can be calculated, as follows:

$$\overline{Vtg = -\Delta V/\Delta P_A \times P_B}$$

where ΔV is the change in gas volume during the occluded breathing efforts, which is measured with the plethysmograph; ΔP_A is the change in alveolar pressure, which is measured from changes in airway opening pressure during the

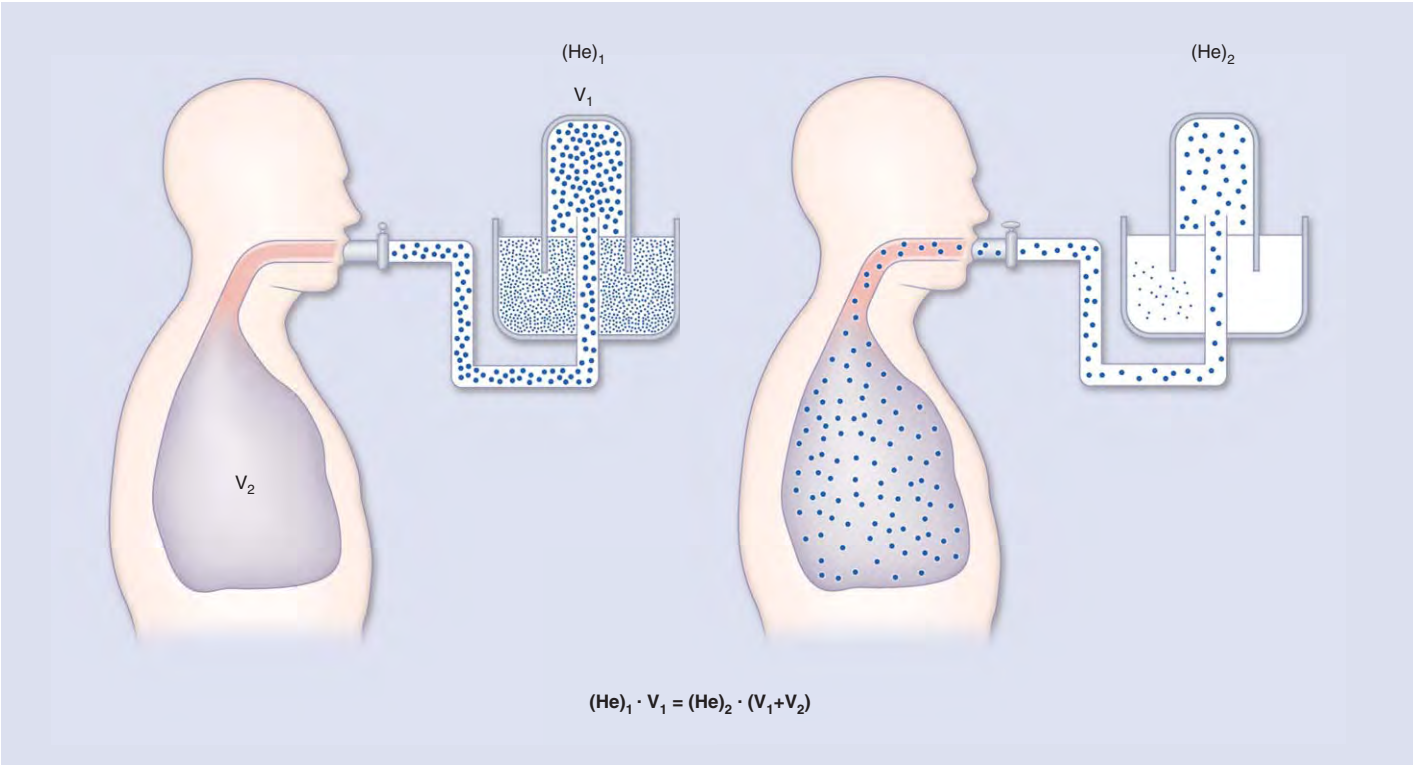

Figure 13-5 The calculation of lung volumes using the helium-dilution technique. He, helium; V, volume.

occluded breathing efforts; and P_B is the barometric pressure in the room minus water vapor pressure at body temperature.

The application of Boyle's law to plethysmography is based on the following assumptions:

1. During occluded breathing efforts, there is no flow along the airways, and the changes in alveolar pressure can be represented by changes in airway opening pressure.
2. Gas compression and decompression, both within the lungs and within the plethysmograph, occur under isothermal conditions.
3. Compression of abdominal gas is negligible.

In healthy subjects seated in an adult-sized plethysmograph, these assumptions are reasonably valid. The major potential source of error comes from the compliance of the upper airways, especially the cheeks.[12] The respiratory system can be represented as two compliant compartments (i.e., the upper airways and the alveolar gas compartment) separated by a resistive element (the airways). Changes in pressure in the alveolar compartment are transmitted to the airway opening with a time constant determined by the airway resistance and the compliance of the upper airway. If either the airway resistance or the compliance of the upper airway increases, the time constant of transmission may become long enough that the changes in airway opening pressure underestimate changes in alveolar pressure, resulting in an overestimation of the true lung volume. For subjects with normal lungs, supporting the cheeks with hands is usually sufficient to ensure accurate measurements of lung volume.

The original plethysmographs were largely constant-volume, "pressure" plethysmographs. However, this type has now been largely replaced by variable-volume "flow" plethysmographs. These plethysmographs include a pneumotachograph in the wall and measure the flow into and out of the box produced by chest wall movement during the occluded breathing efforts. This flow is then integrated to give the volume change resulting from compression of the Vtg during occluded breathing efforts. These flow plethysmographs have the advantage of an improved frequency response at low frequencies without sacrificing performance at higher frequencies. They are suitable for measuring volume variations over a wide range of amplitudes and frequencies and also allow the measurement of forced expiration within the plethysmograph.

Once Vtg has been measured, TLC and RV are calculated from Vtg and measurements of inspiratory capacity and VC. The RV may be falsely elevated if the child does not exhale fully. RV is one of the most variable of all lung function tests in children,[13] and the results must be interpreted with caution. Caution also must be exercised in the measurement and interpretation of lung volumes by plethysmography in the presence of marked airway obstruction.

Gas Dilution

Alternatively, lung volumes can be measured by gas dilution. In theory, these techniques are simple, involving the measurement of the dilution of a known concentration of gas by an unknown volume (the Vtg) (Fig. 13-5). With measurement of the final gas concentration, it is possible to calculate Vtg. Although the helium-dilution method is simple to perform and is relatively inexpensive,[14] it is time consuming, has potentially limiting cooperation, and is likely to significantly underestimate the Vtg in the presence of airway obstruction.

The apparatus required for measuring lung volume by gas dilution is relatively simple; it consists of a spirometer, gas reservoir, gas analyzer, and system for supplying oxygen and removing carbon dioxide during the test. The system functions as a closed circuit, which must be free of leaks. The subject is instructed to breathe to and from the spirometer, and when a regular respiratory pattern has been established, the circuit is switched so that the subject breathes to and from the gas reservoir, which contains a known concentration of the indicator gas. By convention, the indicator gas is introduced at the end of expiration. When the gas concentration in the circuit (including the lungs) reaches a new equilibrium, the final concentration is used to calculate the new volume of the system (i.e., circuit plus lungs). Any leak in the circuit results in a falsely low final concentration and an overestimation of the end-expiratory lung volume. Gas-dilution techniques measure the part of the lung volume that is readily available for gas exchange and does not measure "trapped" gas. Therefore in subjects with significant airway obstruction, the Vtg measured by gas dilution is likely to be significantly lower than that measured by plethysmography.

MEASUREMENT OF RESISTANCE AND COMPLIANCE

Plethysmography

Airway resistance is most commonly measured in children by plethysmography. When a subject breathes within a plethysmograph, volume changes are recorded in proportion to variations in alveolar pressure and in alveolar gas volume (i.e., Vtg), provided volume changes due to other influences, such as changes in gas conditions from body temperature, pressure, and saturation within the lungs to ambient temperature and pressure (saturated) within the box, can be eliminated. Under these circumstances, the change in volume can be expressed as follows:

$$\Delta V = \Delta P_A \times Vtg/P_B$$

Alveolar pressure is the product of resistance to gas flow by flow at the airway opening (Raw), as follows:

$$\Delta V = (Raw + Req) \times \dot{V} \times Vtg/P_B$$

where Req is the resistance of the equipment connected to the airway. Calculation of airway resistance follows:

$$Raw = (\Delta V/\dot{V} \times P_B/Vtg) - Req$$

This technique has been standardized for use in adults and children and includes measuring Vtg, as previously described; opening the shutter; connecting the subject to the box or a gas-conditioning circuit through a flowmeter; and asking the patient to pant while supporting the cheeks with the hands. Panting is usually made at a frequency of 1 to 3 Hz with a V_T of 50 to 150 mL, giving an airway opening flow of 0.3 to 3.0 L/s peak to peak. Precise details are published elsewhere.[12]

Occlusion Techniques and Esophageal Manometry

Measurement of compliance in spontaneously breathing subjects requires either that the subject relax the respiratory muscles against an occluded airway at various points during inspiration and expiration or the insertion of an esophageal balloon. These techniques measure compliance of the respiratory system and lung and are not commonly used in children and are not discussed here. Measurement of airway resistance using occlusion techniques is feasible in preschool-aged children[15] and is discussed in Chapter 12.

Forced Oscillation

Because the forced oscillation technique requires little active cooperation from the subject, it is attractive for use in children, particularly those unable to perform forced expiration adequately. It was introduced in the 1950s as a method for determining the impedance of the total respiratory system (Zrs) by applying sinusoidal variations in pressure to the respiratory system (Prs) and measuring the resulting flow ($\dot{V}$).[16] In essence, Zrs is calculated from Prs/$\dot{V}$ and can be expressed as an amplitude ratio and a phase shift between the signals. This technique can also measure Zrs at different frequencies and thus represents the frequency-dependent behavior of the respiratory system (Fig. 13-6). It assumes that both the measuring system and the mechanical properties of the respiratory system are linear during the time of measurement and for the amplitude of the pressures applied.[17] The ERS guidelines for measurement and reporting of forced oscillation data have been described by Oostveen and associates.[18]

The signal applied to the respiratory system is known as a *forcing function*. Over the years, a number of different forcing functions have been used to measure Zrs. The simplest consists of a single sinusoid, which measures Zrs at that (single) frequency. Measurements can be repeated at different frequencies, and a picture of the frequency-dependent behavior of the respiratory system can be built. Alternatively, multiple sinusoids can be applied at the same time. If this approach is adopted, the clinician must carefully limit the amplitude of the resulting signal because too great an amplitude may be uncomfortable for the subject and result in nonlinear behavior of the respiratory system. Forcing functions can be opti-

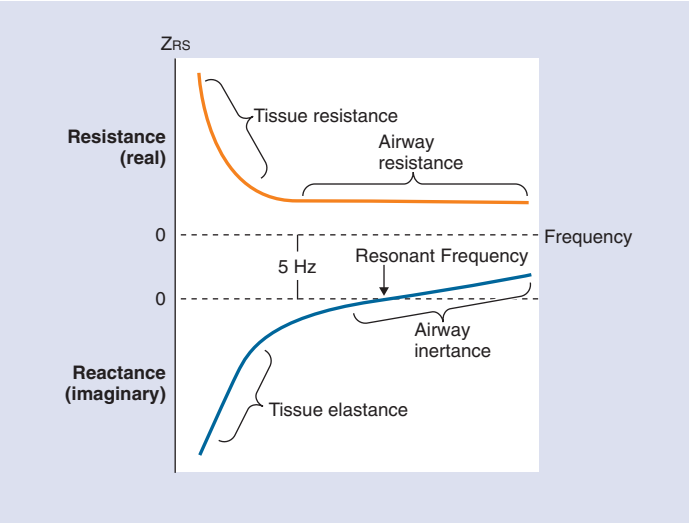

Figure 13-6 Zrs data from the forced oscillation technique. Low-frequency data represent tissue elastance and resistance, and high-frequency data represent airway resistance and inertance. *Real* and *imaginary* are terms defining the phase relationship of the signals.

mized in a number of ways, such as ensuring that the components are not integer multiples of one another[19] or that no component is either the sum or the difference of other components.[20] Both of these optimization procedures are designed to reduce the effects of nonlinearities and to reduce harmonic distortion. For more detailed descriptions, the reader is referred to the specialized literature.

Whatever forcing function is used, some estimate of the reliability of the Zrs data is required. Reliability is generally assessed by determining the "coherence function." This is in essence the correlation between the input signal (the forcing function) and the output signal (the flow, $\dot{V}$). Perfect correlation results in a coherence value of 1.0. By convention, Zrs is considered to be reliable if the coherence is at or above 0.95 at a particular frequency. Measurement noise reduces the reliability of Zrs, which is reflected in a decreased coherence. In this context, the breathing frequency and heart rate can decrease the reliability of Zrs at those frequencies (and at their harmonics) and usually limit the lower end of the frequency spectrum that can be measured in children.[21-23]

Calculation of Zrs from data obtained using forcing functions that contain multiple frequencies is usually performed in the frequency domain. This is done using fast Fourier transformations or similar mathematical techniques. A description of the mathematics involved is beyond the scope of this chapter, but the resultant Zrs spectrum is conventionally expressed as *real* and *imaginary parts*. The real part is related to the component in phase with the pressure signal and reflects the resistive behavior of the respiratory system. The imaginary part is related to the component of flow out of phase with pressure and reflects the elastic and inertive behaviors of the respiratory system (see Fig. 13-6).

Many studies have used parameter-estimating techniques to produce values of resistance, elastance, and inertance from Zrs spectra.[23-31] These studies have demonstrated that the real part of Zrs reflects airway resistance at higher frequencies (above 5 to 10 Hz in adults and older children), whereas the low frequencies (<2 Hz) reflect the resistive properties of the lung tissues and chest wall (see Fig. 13-6). At low frequencies, the imaginary part is dominated by elastic behavior, whereas at high frequencies, inertive behavior dominates. The elastic and inertive behavior of the respiratory system are 180 degrees out of phase with each other (i.e., they have the opposite sign). The frequency at which these properties are equal and opposite and therefore cancel each other out is known as the *resonant frequency* of the respiratory system (see Fig. 13-6). This can be recognized as the frequency at which the imaginary part of Zrs crosses the zero axis. The resonant frequency has been reported to change with age and with lung disease.[21,23,32]

The use of forced oscillation in children has been limited by some of the practical problems encountered when applying this technique and by the lack of user-friendly, commercially available equipment. The following major technical problems need to be overcome:

1. Interference from the breathing frequency
2. Leak around the mouthpiece
3. Upper airway compliance

The breathing frequency causes a loss of coherence from the forcing function for up to five harmonics of the fundamental frequency. In practice, this means that no useful Zrs data are obtained at frequencies below 4 Hz in spontaneously breathing children. Adults are frequently able to hold their breath with their glottis open for long enough to measure Zrs at lower frequencies. This does not appear to be the case in most children.

Leak around the mouthpiece acts as a resistance pathway in parallel with the respiratory system. This resistance mainly affects the lower frequencies and results in overestimation of resistance and underestimation of elastance. The effect of a leak is compounded in situations in which the airway resistance is increased, such as with airway disease or during bronchoprovocation tests.

The compliance of the upper airways acts as a shunt compliance in parallel with the respiratory system. This results in shunting of the forcing function away from the respiratory system, especially at higher frequencies. This in turn results in overestimation of airway resistance and underestimation of inertance (with a shift of the resonant frequency to a higher frequency). The effect of a shunt compliance is increased in situations in which airway resistance is increased (see previous section).

Measurements of Forced Expiration

Measurements of forced expiration have become the major method used to detect the presence of obstructive lung disease. The ATS/ERS guidelines for spirometry have been updated.[33] The use of such measurements is derived from the observation that expiratory flow is independent of the force driving flow over most of the expired VC as long as reasonable effort is made[34] (Fig. 13-7). This observation led directly to the description of the maximum expiratory flow volume (MEFV) curve, which emphasized that at most lung volumes, there was a limit to maximum expiratory flow ($\dot{V}$max). The peak expiratory flow (PEF) is discussed later, and flows near RV may be effort dependent because expiratory muscle contraction may not be able to provide sufficient force to maintain flow limitation at this low lung volume.

FLOW LIMITATION

The mechanism for expiratory flow limitation is complex. Elegant descriptions can be read in the *Handbook of Physiol-*

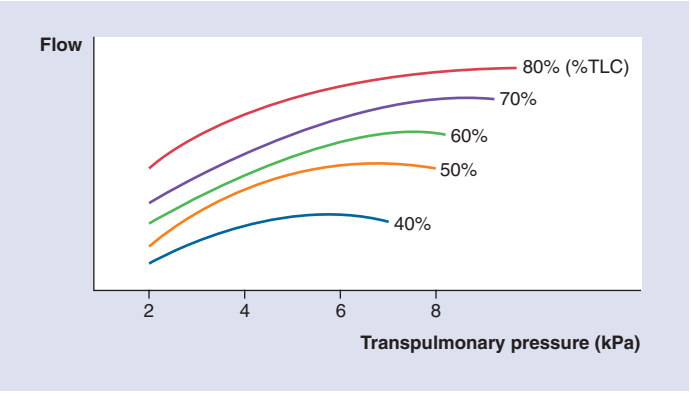

Figure 13-7 Isovolume pressure-flow curves in a normal adult at different proportions of total lung capacity. (Redrawn from Tammeling GJ, Quanjer PH: Contours of Breathing, Burlington, Ontario, Canada, 1985, Boehringer Ingelheim Pharmaceuticals.)

ogy published by the American Physiological Society.[35] In fluid dynamic terms, a system cannot carry a greater flow than the flow for which fluid velocity equals wave speed at some point in the system. The wave speed is the speed at which a small disturbance travels in a compliant tube filled with fluid. In the arteries, this is the speed at which the pulse propagates. In the airway the speed is higher than this, mainly because the fluid density is lower. The wave speed (c) in a compliant tube with an area (A) that depends on a lateral pressure (P) filled with a fluid of density (ρ), is given by:

$$c = (AdP/\rho dP)^{1/2}$$

where dP/dA is the slope of the pressure-area curve for the airway (i.e., an expression of airway wall compliance). $\dot{V}max$ is the product of the airway area and fluid velocity at wave speed, as follows:

$$\dot{V}max = cA$$

At high lung volumes, the flow-limiting site in the human airways is typically in the second and third airway generations. As lung volume decreases, airway caliber decreases, the flow-limiting site moves peripherally, and $\dot{V}max$ decreases. At low lung volumes, the density dependence of $\dot{V}max$ is small, and the viscosity dependence is large and becomes the predominant mechanism limiting expiratory flow.

Flow limitation in a compliant tube is accompanied by "flutter" of the walls at the site of flow limitation.[36] This flutter conserves the energy in the system because the driving pressure in excess of that required to produce $\dot{V}max$ is dissipated in causing the wall flutter. In the presence of airway obstruction, this flutter may become large enough to generate sound, which is heard as wheezing. Thus, expiratory wheezing is a sign of expiratory flow limitation.

MEFV CURVES

Most children can accomplish forced expiratory maneuvers by the age of 7 years. To produce reliable MEFV curves, children need to be able to give a maximal effort without hesitation for at least 3 seconds. In young children, a learning effect may be operative, so more than the standard three tests may be required to obtain consistent, representative data. The VC and the forced expiratory volume in 1 second (FEV_1) are the most informative measures. Indices derived from expiratory times of less than 1 second may be useful in young children who are unable to produce prolonged expirations,[6] however, the discriminative ability of these indices is yet to be determined (see Chapter 12 for further discussion). Forced expiratory flows at lower lung volumes are more sensitive, but their variability is greater. The forced expiratory flow occurring between 25% and 75% of expired VC is frequently used as an indication of "small airway" disease. This practice is based on the assumption that the site of flow limitation is likely to exist in the small airways over this volume range. There is no direct evidence to support this assumption, especially in children. Figure 13-8 shows the relationship between the spirogram (a volume-time plot of forced expiration) and an MEFV curve.

PEAK EXPIRATORY FLOW

Peak expiratory flow (PEF) is the maximum flow achieved during a forced expiration starting from the level of maximal lung inflation.[37] Primarily a measure of large airway caliber, PEF can be used to identify and assess airflow limitation in clinical practice and epidemiologic studies and can aid

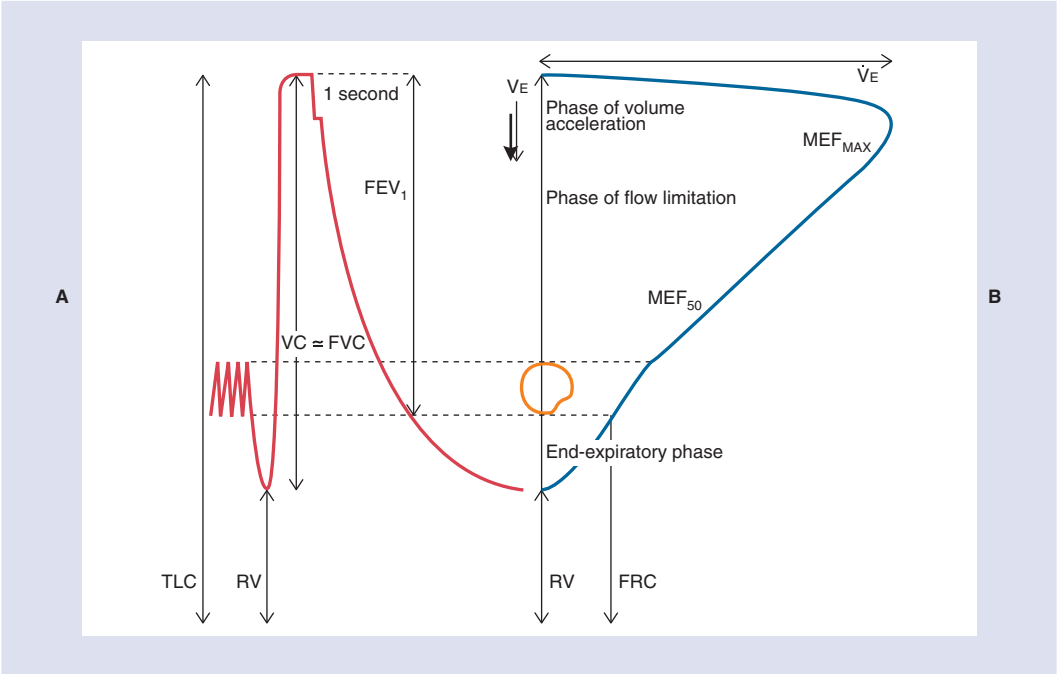

Figure 13-8 **A,** Spirogram. **B,** Maximum expiratory flow volume curve. FEV_1, forced expiratory volume in 1 second. (Redrawn from Tammeling GJ, Quanjer PH: Contours of Breathing, Burlington, Ontario, Canada, 1985, Boehringer Ingelheim Pharmaceuticals.)

in the monitoring of disease progress and the effects of treatment.

In healthy subjects, PEF is determined by lung volume, airway caliber, lung elastic recoil, expiratory muscle strength, and the duration of pause at TLC before forced expiration. Traditionally, PEF was not thought to be flow limited because a plateau is not seen on isovolume pressure-flow curves, presumably because of the inability of the respiratory muscles to generate sufficient force. More recently, it has been demonstrated that PEF is determined by a wave-speed ($\dot{V}ws$) flow-limiting mechanism in the central airways, occurring when the velocity of the accelerating flow reaches $\dot{V}ws$ at some point in the airway.[38] The three main contributing factors to PEF in this model are Pel, the resistance upstream of the flow-limiting segment (Pfr), and the relationship between distending pressure and airway cross-sectional area (A) at the most upstream position at which $\dot{V}$ equals $\dot{V}ws$. According to this model, PEF will be large when Pel is large, Pfr is small, A is large, and airway wall compliance is small. Breath-hold at TLC before performance of the expiratory maneuver results in stress-relaxation of the viscoelastic elements of the lung and decreased airway wall compliance, reducing the maximum achievable wave speed and thus PEF.[39]

Flow limitation at PEF does not mean that it is independent of effort. The magnitude of PEF depends on how this maximum flow is reached. If expired volume from the TLC at which PEF is reached is small, PEF will be higher because at higher lung volume, the higher elastic recoil pressure and lower upstream resistance result in a greater wave speed and a higher PEF. In any interpretation of changes in PEF, the magnitude of effort and the volume at which PEF is reached are critical.

Miniature PEF meters are cheap and portable and can be used in the home, but there is little evidence to suggest that home PEF monitoring improves clinical outcomes. Issues with equipment accuracy, compliance, and lack of technical expertise all contribute to the unreliability of home PEF monitoring, and evidence suggests that patient education and symptom monitoring may be more useful in disease management.[40]

PEF increases with height during childhood; however, there is a wide range of normal values at any given height, making expression of a measured PEF as a percentage of predicted normal based on population studies unlikely to be useful. PEF may be more usefully expressed relative to each child's "personal best" determined by monitoring it for 1 to 2 weeks at a time when the child is well. This value can then be used as a basis for comparison during exacerbations of asthma.

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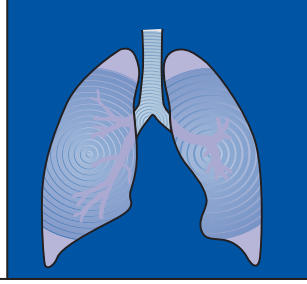

CHAPTER 14

Gas Exchange and Acid-Base Physiology

Gas Exchange, Oxygen Delivery, and Ventilation

Marc D. Berg and Robyn J. Meyer

TEACHING POINTS

- Major contributors to oxygen delivery are hemoglobin level, oxygen saturation, and cardiac output.
- Interference with any step in oxygenation, including pulmonary gas exchange, loading, transport, unloading, and tissue gas exchange, may cause hypercapnia and hypoxic cellular damage.
- Arterial hypoxemia may be caused by diffusion defects, shunting, or hypoventilation.
- Arterial carbon dioxide is determined mainly by the degree of alveolar ventilation in relation to the patient's carbon dioxide production.

BASIC PHYSIOLOGY OF GAS EXCHANGE

Normal Gas Exchange

In the body, gas exchange occurs via simple diffusion at the lung (pulmonary gas exchange) and at the tissue (intracellular gas exchange). Once a gas has diffused into the blood at one of these sites, it is dissolved into plasma and bound to hemoglobin (loading). The gas then circulates with blood (transport) until it reaches the other site of gas exchange. The gas is then released from the blood (unloading), thus completing the process of gas exchange. Eventually, oxygen is consumed in the tissue, and carbon dioxide is eliminated through the lungs.

Oxygenation, the process by which oxygen is added to the pulmonary blood, occurs at the alveolus. The term *ventilation* generally refers to the removal of carbon dioxide from the alveoli. The rate of gas diffusion through the alveolar-capillary membrane is determined by several factors, including (1) the pressure difference of each gas between both sides of the membrane, (2) the solubility of the gas, (3) the surface area of the membrane, (4) the distance through which the gas must diffuse, and (5) the molecular weight of the gas.[1]

Different gases at the same pressure diffuse at different rates proportional to their diffusion coefficients. Solubility and molecular weight are two important factors that determine the diffusion coefficient of a gas. If the diffusion coefficient for oxygen is 1, the relative diffusion coefficients for different gases in the body fluid are as follows: carbon dioxide, 20.3; carbon monoxide, 0.81; nitrogen, 0.53; and helium, 0.95. Therefore, carbon dioxide diffuses more rapidly than oxygen across membranes. The rate of equilibration of these gases at the alveolar level, however, is roughly equal because the driving pressure of oxygen is much higher than that of carbon dioxide. The driving pressure is determined by the difference in partial pressure in the alveolus versus the end-capillary.

In normal spontaneous respiration, oxygenation and ventilation occur simultaneously. Any change in ventilation also has an impact on oxygenation. Room air at sea level contains oxygen at a partial pressure of 160 mm Hg. The conducting airways then completely saturate the inspired gas with water vapor, dropping the inspired partial pressure of oxygen (PIO_2) to 150 mm Hg. Assuming a normal ventilation/perfusion ratio in the lung, this results in an alveolar partial pressure of oxygen (PAO_2) of 100, compared with deoxygenated pulmonary arterial blood with a partial pressure of oxygen (PO_2) of about 40 mm Hg; that is, there is a driving pressure for diffusion across the pulmonary alveolar-capillary membrane of 60 mm Hg. This driving pressure coupled with the thin (0.5 μm) alveolar capillary membrane allows complete equilibration of oxygen partial pressure between the alveolus and pulmonary capillary approximately one third of the distance across the alveolus. Room air contains essentially no carbon dioxide and allows the removal of carbon dioxide from pulmonary arterial blood with an equilibration at about 40 mm Hg in the pulmonary blood leaving the alveolus.

Oxygenation improves as PAO_2 increases due to increases in the concentration of inspired oxygen (FIO_2), barometric pressure, or the alveolar ventilation/perfusion ratio. The amount of surface area available for gas exchange increases with increases in mean airway pressure as additional alveoli are recruited. Moreover, the thickness of the interstitial space, the area between the alveolar and capillary basement membranes, is also affected by alveolar pressure. Higher alveolar pressures decrease the thickness of the interstitial space, allowing more effective gas exchange. Although alveolar pressure generally improves oxygenation, it is important to note that excessive distention of the alveolus with very high alveolar pressure may actually worsen oxygenation. This occurs through a tamponade of pulmonary capillary blood

flow secondary to the high alveolar pressure that is transmitted to the pulmonary capillary bed. This leads to the development of ventilation-perfusion ($\bar{V}/\dot{Q}$) mismatch and, as perfusion approaches zero, alveolar dead space. Alveolar dead space is the ventilation of nonperfused alveoli.

Ventilation improves with increased minute ventilation, which is the product of tidal volume and respiratory rate. Any increase in alveolar dead space (V_D) without a concomitant increase in tidal volume (V_T) leads to an increased dead space–to–tidal volume ratio (V_D/V_T) and reduced alveolar ventilation ($\bar{V}_A$). Alveolar ventilation decreases the partial pressure of carbon dioxide (P_{CO_2}) in the alveoli, thereby maintaining a lower alveolar P_{CO_2} (P_{ACO_2}) (40 mm Hg) relative to the pulmonary artery P_{CO_2} (45 to 47 mm Hg). Because the diffusion coefficient of carbon dioxide is 20 times greater than that of oxygen, this small gradient of P_{CO_2} (5 to 7 mm Hg) is all that is needed to support diffusion across the alveolar membrane and remove the carbon dioxide produced during cellular metabolism. At rest, this efficient diffusive process is completed in approximately one-third of the distance through the alveolar capillary bed, thus there is substantive reserve for complete diffusion with increased venous P_{CO_2} or blood flow such as during exercise.

Oxygen Delivery

Loading

P_{AO_2} can be calculated using a simplified version of the alveolar gas equation[2]:

$$\begin{aligned} P_{AO_2} &= F_{IO_2} \cdot (P_B - P_{H_2O}) - PaCO_2/R \\ &= 0.21 \cdot (760 - 47) - 40/0.8 \\ &= 150 - 50 \\ &= 100 \text{ mm Hg} \end{aligned}$$

where F_{IO_2} is fractional concentration of oxygen in room air (~0.21), P_B is barometric pressure at sea level (~760 mm Hg), $PaCO_2$ is partial pressure of arterial carbon dioxide (~40 mm Hg), and R is respiratory quotient (~0.8).

The approximate P_{AO_2} in room air is 100 mm Hg at sea level, and the P_{O_2} of the venous blood entering the pulmonary end-capillary bed averages 40 mm Hg at sea level. Oxygen diffuses into the blood from alveoli with the pressure difference of approximately 60 mm Hg. The P_{O_2} in pulmonary end-capillary blood rises quickly to the level of P_{AO_2}. Bronchial circulation, which accounts for 2% of the total pulmonary blood flow, bypasses the pulmonary circulation. This is known as an intrapulmonary shunt as deoxygenated blood passes through the lungs without receiving oxygen, mixes with newly oxygenated blood and returns to the left atrium to be pumped to the body. Because of this pulmonary shunt effect, the P_{O_2} in arterial blood decreases by approximately 5 mm Hg to 95 mm Hg.

Normally, about 97% of the oxygen in the blood is transported in chemical combination with hemoglobin in the red blood cells, and the remaining 3% is carried in the dissolved state in the water of plasma and cells. Therefore, under normal conditions, oxygen is transported to the tissues almost entirely by hemoglobin. Each hemoglobin molecule can loosely bind to four oxygen molecules. The percentage of the hemoglobin bound with oxygen increases as blood P_{O_2} increases. The affinity of hemoglobin for oxygen increases after the hemoglobin has previously bound with other oxygen molecules.[3] The relationship between oxygen affinity and hemoglobin is described by the oxygen-hemoglobin dissociation curve. This curve is an S-shaped curve that increases maximally between a P_{O_2} of 10 and 50 mm Hg. In a healthy individual, arterial blood has a P_{O_2} of 95 mm Hg, and the oxygen saturation is about 97%. A normal systemic venous P_{O_2} is about 40 mm Hg, with an oxygen saturation of about 75%. The ability of hemoglobin to bind oxygen changes in various conditions, and the oxygen saturation will vary at the same P_{O_2} (Fig. 14-1). The following factors affect oxyhemoglobin affinity: the hemoglobin amino acid sequence (hemoglobinopathy, carboxyhemoglobin, methemoglobin), temperature, P_{CO_2}, pH, and concentration of 2,3-diphosphoglycerate. For example, when blood carbon dioxide is removed by the lung and the blood pH increases, the oxygen-hemoglobin dissociation curve shifts to the left, and more oxygen binds to hemoglobin for transport (Bohr effect), thus improving oxygen loading in the lung.[4] Conversely, oxygen affinity to hemoglobin decreases with decreased pH and increased P_{CO_2} in the tissues, causing the oxygen-hemoglobin dissociation curve to shift to the right, thus facilitating the unloading of oxygen to the tissue (Fig. 14-2).

Transport

Once hemoglobin binds oxygen to become oxyhemoglobin, blood flow transports the oxyhemoglobin to the tissue, where oxygen is needed for efficient energy production.

The total amount of oxygen transported to the tissue is calculated as follows:

$$\begin{aligned} \dot{D}_{O_2} &= CO \cdot Ca_{O_2} \\ &= CO \cdot (Hgb \cdot Sa_{O_2} \cdot 1.34) + (Pa_{O_2} \cdot 0.003) \\ &\sim CO \cdot Hgb \cdot Sa_{O_2} \end{aligned}$$

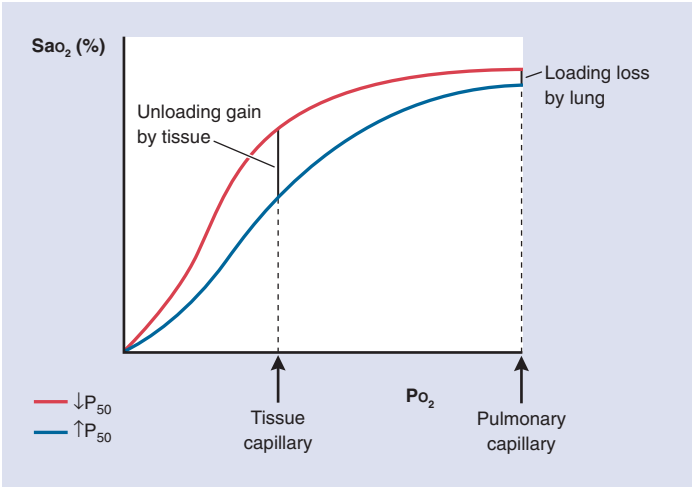

Figure 14-1 The effect on oxygen loading and unloading caused by an increase in oxygen affinity (decrease in P_{O_2} required to saturate 50% of functional hemoglobin [P_{50}]) and a decrease in oxygen affinity (increase in P_{50}). The loading loss and unloading loss and gain are indicated by the heights of the heavy vertical bars between the two curves. Sa_{O_2}, arterial oxygen saturation. (Data from Klocke RA. In Bryan-Brown CW, Ayres SM [eds]: New Horizons: Oxygen Transport and Utilization. Fullerton, CA, Society of Critical Care Medicine, 1987, p. 243.)

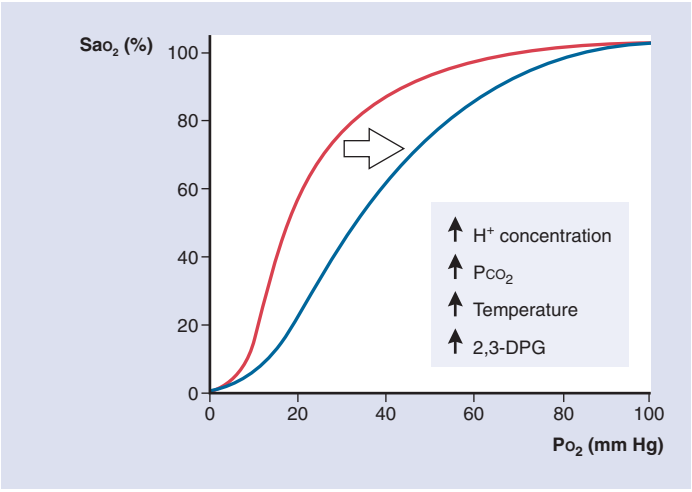

Figure 14-2 Shift of the oxygen-hemoglobin dissociation curve to the right by an increase in the number of hydrogen ions (H^+), the number of carbon dioxide molecules, the temperature, or the concentration of 2,3-diphosphoglycerate (2,3-DPG). (Data from Klocke RA. In Bryan-Brown CW, Ayres SM [eds]: New Horizons: Oxygen Transport and Utilization. Fullerton, CA, Society of Critical Care Medicine, 1987, p. 243.)

where $\dot{D}O_2$ is the total amount of oxygen delivered per minute (in liters per minute), CO is cardiac output (in liters per minute), CaO_2 is arterial oxygen content (in milliliters per liter), Hgb is hemoglobin (grams per deciliter of blood), SaO_2 is arterial oxygen saturation, and PaO_2 is the partial pressure of arterial oxygen (in mm Hg). The dissolved oxygen per PO_2 per deciliter of blood is 0.003 mL/mm Hg/dL of blood.

Example: What is the amount of oxygen delivered when the cardiac output is 5.0 L/min with a hemoglobin level of 15 g/dL, an arterial oxygen saturation of 98%, and an arterial PaO_2 of 100 mm Hg?

$$
\begin{aligned}
DO_2 &= CO \cdot CaO_2 \\
&= CO \cdot (Hgb \cdot SaO_2 \cdot 1.34) + (PaO_2 \cdot 0.003) \\
&= 5\ \text{L/min} \cdot [(15\ \text{g/dL} \cdot 0.98 \cdot 1.34\ \text{mL/g}) + \\
&\quad (100\ \text{mm Hg} \cdot 0.003\ \text{mL/mm Hg/dL})] \\
&= 5\ \text{L/min} \cdot (19.7\ \text{mL/dL} + 0.3\ \text{mL/dL}) \\
&= 5\ \text{L/min} \cdot 20\ \text{mL/dL} \\
&= 1000\ \text{mL of oxygen/min}
\end{aligned}
$$

It is worth noting that the major factors affecting oxygen delivery include cardiac output, hemoglobin level, and oxygen saturation, whereas the effect of dissolved oxygen from arterial PaO_2 is minuscule, 19.7 versus 0.3 mL/dL.

Unloading

When oxyhemoglobin reaches the low PO_2 environment in the tissue, the hemoglobin quickly unloads oxygen. The amount of oxygen unloaded depends on the PO_2 gradient between blood and tissue. When the tissue consumes more oxygen, the tissue PO_2 decreases. Thus, the PO_2 gradient between the blood and tissue increases and allows the hemoglobin to unload more oxygen. If the blood PO_2 is higher than the level necessary to fully saturate hemoglobin with oxygen, however, the amount of oxygen that the hemoglobin unloads changes little (see Fig. 14-2). As noted above, the Bohr effect facilitates unloading of oxygen in the tissue, where carbon dioxide and hydrogen ion levels increase, thus reducing hemoglobin's affinity for oxygen.

Carbon Dioxide

Loading

Unlike oxygen, which primarily binds with hemoglobin, carbon dioxide is carried in four different forms. First, a significant portion of carbon dioxide is transported in the dissolved state, although a small portion of the dissolved carbon dioxide is removed with a small arteriovenous difference. The amount of dissolved carbon dioxide in venous blood is 2.7 mL/dL (PCO_2 of 45 mm Hg) and 2.4 mL/dL at the level of the alveoli (PCO_2 of 40 mm Hg). Because the rate of carbon dioxide diffusion into alveoli depends on the difference between alveolar and venous blood levels of carbon dioxide, the small difference between the levels of dissolved and alveolar carbon dioxide (only 0.3 mL/dL) does not lead to clinically significant carbon dioxide removal.

Second, the dissolved carbon dioxide in the blood reacts with water to form carbonic acid. This mechanism accounts for a very small amount of carbon dioxide transport. There is a direct relationship between carbonic acid and dissolved carbon dioxide. At 37° C, each carbonic acid molecule is in equilibrium with 340 molecules of carbon dioxide. As the level of carbon dioxide increases, the level of carbonic acid also increases. Because PCO_2 and carbonic acid values are higher in venous blood than in arterial blood, venous blood is slightly more acidic (pH, 7.38) than arterial blood (pH, 7.40).

Third, a majority of carbon dioxide travels to the lung in the form of bicarbonate. This is a reversible reaction and accounts for about 70% of the carbon dioxide transported from the tissue to the lung. Although some of the carbon dioxide that enters the blood forms bicarbonate, the amount formed tends to be very small because of the slow reaction rate in plasma. Carbon dioxide diffuses into erythrocytes, where carbonic acid formation rapidly occurs because of carbonic anhydrase in the red blood cells (Fig. 14-3). The carbonic acid dissociates into hydrogen ions and bicarbonate. The hydrogen ion is rapidly buffered by binding to hemoglobin. Bicarbonate diffuses into the plasma via a bicarbonate chloride carrier protein while the chloride moves into the red blood cell to maintain electrochemical neutrality.

Fourth, carbon dioxide reacts directly with amine radicals of hemoglobin molecules to form the compound carbaminohemoglobin. The reaction is slow and accounts only for 20% of carbon dioxide to be removed. The loading process of carbon dioxide in the tissue is facilitated by the Haldane effect; the carbon dioxide–carrying capacity of hemoglobin increases when the oxygen molecule is unloaded at the tissue level.

Transport

Carbon dioxide, which is produced in the tissue, diffuses into the blood, and blood flow carries the three different forms of carbon dioxide to the lung for elimination. Blood flow is a major determining factor in gas transport when the amount of gas loaded remains constant. Besides cardiac output, vascular supply, blood viscosity (e.g., polycythemia), and red cell deformability (e.g., sickle cell disease, microcyte) affect

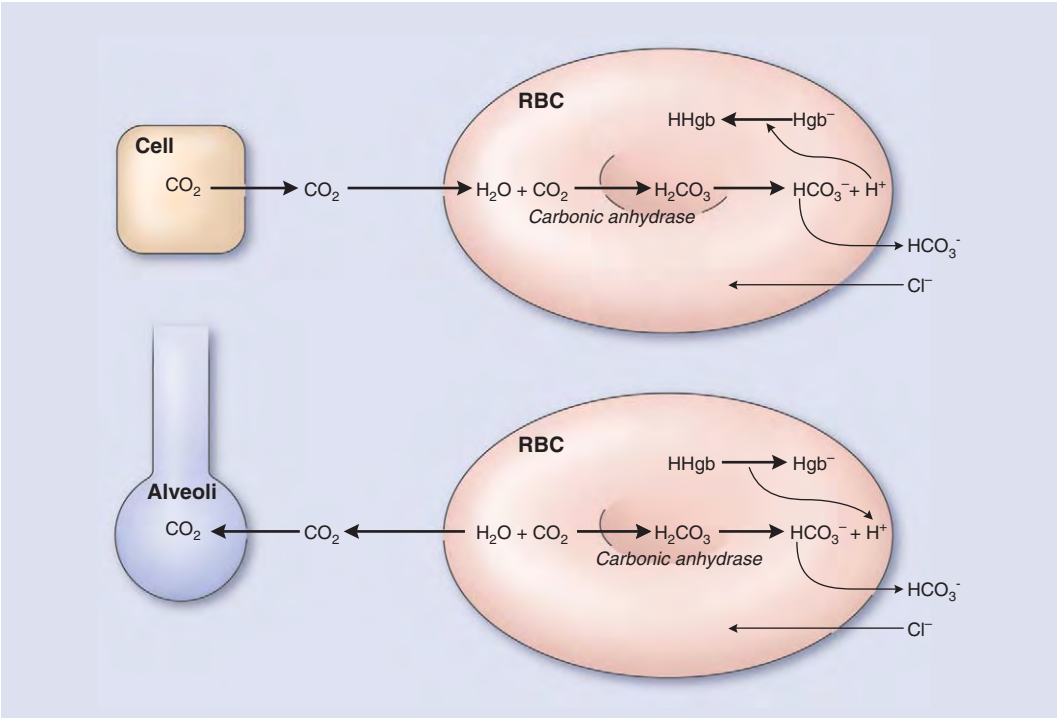

Figure 14-3 Carbon dioxide transport is facilitated by red blood cells (RBCs). A major portion of the carbon dioxide produced by tissues is transported to the lungs as bicarbonate (HCO_3^-). As carbon dioxide enters the red blood cell, carbonic acid (H_2CO_3) is formed and subsequently dissociates to form bicarbonate and a hydrogen ion (H^+). As the hydrogen ion binds with hemoglobin (Hgb), bicarbonate leaves the cell in exchange for chloride (Cl^-) (chloride shift). At the alveolar level, the red blood cell undergoes the same process in reverse. HHgb, hydrogen ion bound to Hgb. (Modified from Malley WJ: Clinical Blood Gases. Philadelphia, WB Saunders, 1990, p 113.)

microcirculation and play important roles in gas exchange at the tissue level.[5]

Unloading

Carbon dioxide arrives in the lung as dissolved carbon dioxide, carbonic acid, carbaminohemoglobin, and bicarbonate ions for elimination by pulmonary gas exchange. In a normal adult, normal ventilation disposes of an average of 10,000 to 15,000 mmol of carbon dioxide per day. As the dissolved carbon dioxide diffuses across the alveolar membrane and plasma carbon dioxide levels decrease, carbonic acid in the red blood cells is converted into carbon dioxide and water by carbonic anhydrase (see Fig. 14-3). Carbonic anhydrase inhibitors may increase carbon dioxide tension in the tissues and decrease carbon dioxide tension in the alveoli, although the mechanism of action for these drugs is more complex.[6] A transient decrease in the rate of carbon dioxide elimination results but is rapidly overcome by compensatory mechanisms. When carbon dioxide moves out of the erythrocyte, bicarbonate moves back in exchange for chloride. The bicarbonate is necessary to replenish the bicarbonate consumed in the hydrolysis reaction. Carbaminohemoglobin unloads the carbon dioxide in the lung, where the P_{CO_2} is lower. The process of carbon dioxide loading and unloading is facilitated by the Haldane effect; the binding of oxygen with hemoglobin displaces carbon dioxide and hydrogen ions from the hemoglobin. The concept of the Haldane effect, like that of the Bohr effect in oxygen carriage, is that the affinity of hemoglobin for carbon dioxide varies with chemical conditions such as P_{O_2}. When hemoglobin is oxygenated in the lung to release hydrogen ions, carbonic acid and ultimately carbon dioxide are produced, with the effect being a reduced affinity to carbon dioxide in the lung resulting from oxygenation. The opposite occurs in the tissue, where hemoglobin releases oxygen and takes up or buffers hydrogen, leading to increased affinity for carbon dioxide.

Abnormal Gas Exchange

When any step in the process of gas exchange between the lung and the tissue is inhibited, less oxygen reaches the tissue. The lack of oxygen causes hypoxic cellular damage. Moreover, the level of intracellular carbon dioxide increases and ultimately creates a hypercapnic or respiratory acidosis. Hypoxic injury and hypercapnic acidosis can be caused by defective pulmonary gas exchange, loading, transporting, unloading or defective tissue gas exchange. If not corrected in time, these conditions can cause irreversible tissue injury. Therefore, it is important to understand the pathophysiology of the hypoxia and hypercapnia to elucidate their causes and give specific therapy before any permanent tissue damage occurs.

HYPOXIA

Pathophysiology

Cells require a continuous supply of energy to perform their functions within an organ and to maintain adequate control

over membrane permeability.[7] A failure of cellular energy metabolism results in organ dysfunction and cell death as control is lost over solute and metabolite exchange across the cell membrane.[8]

Generation of energy occurs in both the presence and absence of oxygen, although aerobic metabolism using oxygen is greatly more efficient. Approximately 20 times more energy is produced in mitochondria by oxidative phosphorylation when substrate consumption is coupled to the consumption of oxygen than when it is without oxygen (i.e., anaerobic).[9] Adenosine triphosphate (ATP) in mitochondria diffuses to the sites of energy use in the cytosol, where a large amount of chemical energy is released from the hydrolysis of one of ATP's high-energy phosphate bonds. The adenosine triphosphatases (ATPases) are the enzymes that control the hydrolysis of ATP, resulting in the formation of adenosine diphosphate (ADP), inorganic phosphate (Pi), and a hydrogen ion (H^+), as follows:

$$ATP \rightarrow ADP + Pi + H^+$$

ADP, Pi, and the H^+ return to the mitochondria, where they serve as substrates for the formation of other ATP molecules.

Measuring the metabolic by-products of the anaerobic reactions, such as the arterial lactate level, may be useful in monitoring the adequacy of global tissue oxygenation. These metabolic by-products, however, do not reflect the hypoxic status of individual organs because of the variable regional blood flow to each organ, changes in tissue lactate accumulation, and washout.[10] Lactate is metabolized by various organs and produced in the liver in response to circulating catecholamines. Lactate metabolism in the body is complicated and lactate values must be interpreted in the context of other clinical and laboratory measures of tissue oxygenation. Lactate levels have been found to be predictive of mortality in some studies[11] but not in others.[12] Sublingual capnometry is a newer technique that shows potential to provide a better noninvasive measure of tissue hypoxia.[12] Phosphorus-31 magnetic resonance spectroscopy can monitor ATP formation, which is indicative of the adequacy of tissue oxygenation.[13] This method has some advantages over other techniques because it measures the level of high-energy phosphate regionally, such as in skeletal muscle, the brain, and the heart. The major drawback is that the patient needs to be in a magnetic cylinder, making it impractical to use in many critically ill patients.

CAUSES OF TISSUE HYPOXIA

Normally, the amount of oxygen delivered to the tissue is 3 to 4 times the amount of oxygen the tissue consumes. There is a significant reserve before the oxygen level reaches the critical point where tissue hypoxia occurs (Box 14-1). Therefore, arterial hypoxemia, which is the state of low blood oxygen content resulting from low P_{O_2}, does not necessarily create tissue hypoxia. As long as capillary P_{O_2} at the tissue level remains higher than the minimum tissue P_{O_2} of 20 mm Hg, there will be oxygen to diffuse from the capillary blood into the tissue for consumption (consumable oxygen).[14] Assuming that Pa_{O_2}, hemoglobin, tissue oxygen consumption, and oxygen diffusion rates remain constant, the blood flow through the tissue determines capillary and venous P_{O_2} (Fick principle). Hypoxic lactic acidosis does not develop in hypoxemia when there is enough tissue perfusion to maintain capillary P_{O_2} above the tissue requirements for oxygen.

In acute hypoxemia, the P_{O_2} chemoreceptors of the carotid arteries and aortic arch quickly recognize low blood P_{O_2}. The respiratory center and the heart are stimulated to increase minute ventilation and cardiac output, respectively, thereby preventing tissue hypoxia. In chronic hypoxemia with chronic lung diseases or cyanotic heart diseases, hemoglobin levels increase to maintain the amount of oxygen for transport. Mitochondria can become more efficient to produce energy with a limited oxygen supply to prevent tissue hypoxia.[15]

Tissue ischemia is low oxygen delivery to the tissue due to decreased blood flow. In contrast to hypoxia, tissue ischemia can cause hypoxic injury even with a normal Pa_{O_2}.[16] When cardiac output decreases, there is not enough tissue perfusion to maintain the P_{O_2} gradient for diffusion between the blood and the tissue. Thus, ischemia is much worse than hypoxemia in the development of hypoxic cellular injury leading to the aphorism "blue blood is better than no blood."[17]

BOX 14-1 Causes of Hypoxia

Pulmonary Gas Exchange

- Inadequate oxygenation of the airway
- Decreased ventilation and perfusion (e.g., intrapulmonary shunt)
- Disruption of alveolar-capillary diffusion (e.g., pulmonary edema, pneumonia)

Loading

- Dysfunctional hemoglobin (e.g., carboxyhemoglobin, methemoglobin)
- Changes in the factors shifting the oxygen-hemoglobin dissociation curve (e.g., pH, P_{CO_2}, 2,3-diphosphoglycerate level, body temperature)
- Venous-to-arterial shunts ("right-to-left" cardiac shunt)

Transport

- Hemoglobin and hematocrit
- Red blood cell deformability
- Low cardiac output: generalized or local ischemia
- Tissue edema

Unloading

- Changes in the factors shifting the oxygen-hemoglobin dissociation curve (e.g., pH, P_{CO_2}, 2,3-diphosphoglycerate level, body temperature)

Tissue Gas Exchange

- Capillary "shunt" resulting from peripheral vasodilation (e.g., septic shock)
- Poisoning of cellular enzymes (e.g., cyanide poisoning)
- Diminished cellular metabolic capacity (e.g., beriberi)

HYPERCAPNIA

Pathophysiology

Carbon dioxide is produced in the tissues as the result of aerobic metabolism and removed from the body through tissue gas exchange, loading, transport, and unloading and, finally, pulmonary gas exchange. The disruption of any of these processes causes carbon dioxide to accumulate in the body fluid and thus produces hypercapnia.

Because of the free diffusibility of carbon dioxide across cell membranes, a sudden increase in extracellular P_{CO_2} decreases the intracellular pH.[18] Because of the abundance of carbonic anhydrase in the cytosol, carbonic acid is formed, thus rapidly causing intracellular acidosis.[19] Most effects of hypercapnia occur at the cellular level. The reduced intracellular pH decreases oxidative metabolism and inhibits the activity of contractile elements by interfering with both excitation–contraction coupling and actin–myosin interaction.[20] Myocardial and skeletal muscle contractility decreases, although most of this impairment is reversible.[21]

In the intact animal, the depressant effect of hypercapnia is offset by the stimulating action of carbon dioxide on the central and autonomic systems. Carbon dioxide is a potent vasodilator. Hypercapnia dilates the coronary arteries and cerebral arteries and may improve blood flow through the normal myocardium and normal brain tissue. Conversely, hypercapnia may reduce perfusion through the injured ischemic areas; this is the "steal phenomenon."[22,23] Increased P_{CO_2} diminishes cerebral vascular tone. Cerebral blood volume increases, potentially raising intracranial pressure.[24,25]

Hypercapnic acidosis constricts pulmonary arteries and renal arteries, leading to pulmonary artery hypertension and decreased renal blood flow.[26-28] Additional cardiovascular effects of hypercapnia include increased cardiac output, tachycardia and systemic hypertension, in part due to catecholamine release. In high-risk patients, extreme levels of hypercapnia can lead to myocardial depression and arrhythmias.[29] Increased P_{CO_2} and low pH shift the oxygen-hemoglobin dissociation curve to the right, which decreases oxygen affinity for the hemoglobin molecule. When the Pa_{O_2} is in the normal range, the rightward shift of the oxygen-hemoglobin dissociation curve is advantageous because there is easier unloading of oxygen to the tissue. However, when the Pa_{O_2} is low, it is more difficult to load oxygen at the pulmonary alveolar-capillary level because of decreased oxygen affinity (see Fig. 14-2).

The concomitant tissue hypoxia potentiates the adverse effects of acute hypercapnic acidosis[30]; if tissue oxygenation is maintained, however, hypercapnia and intracellular acidosis are better tolerated. With time, the acidosis resolves through the excretion of hydrogen ions from the kidneys and the increased resorption of bicarbonate ions.[31,32] Clinically, permissive hypercapnia, which allows a P_{CO_2} rise with alveolar hypoventilation, is an accepted mode of ventilation to prevent further lung injury when oxygenation is well maintained and severe systemic acidosis is avoided.[33-36]

Causes of Hypercapnia

Arterial P_{CO_2} (Pa_{CO_2}) is proportional to carbon dioxide production ($\dot{V}_{CO_2}$) and inversely proportional to alveolar ventilation ($\dot{V}_A$):

$$Pa_{CO_2} = K \cdot \dot{V}_{CO_2} / \dot{V}_A$$

The constant K has the value of 0.863 mm Hg when carbon dioxide is expressed in milliliters per minute under standard conditions (dry gas at standard temperature and pressure) and alveolar ventilation is expressed in liters per minute under body conditions (saturated gas at body temperature and pressure).

The disruption of any of these processes causes the accumulation of carbon dioxide in the body fluid to produce hypercapnia (Box 14-2). In hypoxia resulting from poor perfusion through the pulmonary membrane or through the tissues, serious hypercapnia usually does not occur because carbon dioxide diffuses 20 times as rapidly as oxygen. However, in hypoxia caused by hypoventilation, carbon dioxide transfer between the alveoli and the atmosphere is affected as much as oxygen transfer.

Diminished blood flow in circulatory deficiency removes less carbon dioxide from the tissues, resulting in tissue hypercapnia. However, the transport capacity of the blood for carbon dioxide is about 3 times that for oxygen, so tissue hypercapnia is much less severe than tissue hypoxia.

BOX 14-2 Causes of Hypercapnia

Carbon Dioxide Production

- Increased body temperature: approximately 10% per degree of temperature
- Excessive muscular activity: shivering, rigor, seizure
- Physiologic stress
- Sepsis
- Parenteral nutrition with glucose

Decreased Carbon Dioxide Clearance

- Increased tissue carbon dioxide levels
- Tissue-gas exchange
- Poor tissue perfusion (e.g., ischemia)
- Disrupted diffusion (e.g., tissue edema)
- Loading
- Capillary shunt resulting from peripheral vasodilation (e.g., septic shock)
- Transport
- Low hemoglobin level or hematocrit
- Decreased red blood cell deformability
- Low cardiac output
- Increased blood carbon dioxide levels
- Unloading
- Venous-to-arterial shunts ("right-to-left" cardiac shunt)
- Pulmonary gas exchange
- Decreased ventilation (e.g., respiratory depression, neuromuscular disorder, chest deformity)
- Increased dead space (e.g., upper airway obstruction, lower airway obstruction: reactive airway disease)
- Disruption of alveolar-capillary diffusion (e.g., pulmonary edema, pneumonia)

DISORDERS OF OXYGENATION AND VENTILATION

Oxygen

Each arterial blood gas value should first be evaluated in the context of normal values. Arterial oxygen values, which are affected by age and altitude, can also be altered by the F_{IO_2}, the condition of the alveolar air-blood barrier, and pulmonary blood flow. At sea level, a Pa_{O_2} of 97 mm Hg (range = 80 to 103 torr) is considered normal. A patient with normal lungs receiving supplemental oxygen should have a Pa_{O_2} approximately 5 times the F_{IO_2} (Table 14-1). The Pa_{O_2} decreases in the elderly and varies depending on whether an individual is sitting or supine.[37]

If arterial hypoxemia is present, it may be caused by hypoventilation, absolute (right to left) shunting, diffusion defects, or relative shunting (low $\dot{V}/\dot{Q}$ ratio). Hypoventilation can be rapidly diagnosed by the presence of elevated arterial P_{CO_2} values. Calculation of the alveolar-arterial ($A_{-}a$) oxygen tension gradient while the patient is breathing room air can be helpful in discriminating hypoventilation from shunting. An $A_{-}a$ gradient greater than 20 mm Hg suggests causes other than hypoventilation (i.e., $\dot{V}/\dot{Q}$ reduction, diffusion block, and right-to-left shunt all increase $A_{-}a$ gradient).

Table 14-1
Predicted Effect of F_{IO_2} on Blood Oxygen Content

F_{IO_2}	Predicted Arterial P_{O_2}
30%	150 mm Hg
40%	200 mm Hg
50%	250 mm Hg
80%	400 mm Hg
100%	500 mm Hg

From Shapiro BA, et al: Clinical application of blood gases, 5th ed. St Louis, Mosby, 1994, p. 65.

An *absolute shunt* is defined as blood passing from the right to the left side of the heart without being oxygenated. Absolute shunting does not respond to increases in the inspired oxygen level because the shunted blood never comes in contact with oxygen. Shunting may also occur at the level of the alveoli. Blood cannot be oxygenated when the alveolus is blocked, collapsed, or filled with fluid. There is also anatomic shunting resulting from persistent pulmonary hypertension and congenital heart defects.

When there is no extrapulmonary right-to-left shunt, the P_{O_2} represents pulmonary gas exchange, whereas a venous blood gas value represents the balance between oxygen delivery and oxygen uptake; i.e., tissue gas exchange. Pulmonary gas exchange relies on pulmonary function, and tissue gas exchange is particularly affected by tissue perfusion. Therefore, the interpretation of blood gas values will be different based on where the blood sample was taken.

When there is a right-to-left shunt, total cardiac output ($\dot{Q}t$) is composed of shunted blood ($\dot{Q}s$) and pulmonary end-capillary blood flow ($\dot{Q}c$) (Fig. 14-4), as follows:

$$\dot{Q}t = \dot{Q}s + \dot{Q}c$$

The total amount of oxygen ejected from the left side of the heart is equal to the amount of oxygen carried in pulmonary end-capillary blood plus the amount of oxygen carried in shunted blood, as follows:

$$\dot{Q}t \cdot Ca_{O_2} = \dot{Q}s \cdot C\bar{v}_{O_2} + \dot{Q}c \cdot Cc'_{O_2}$$

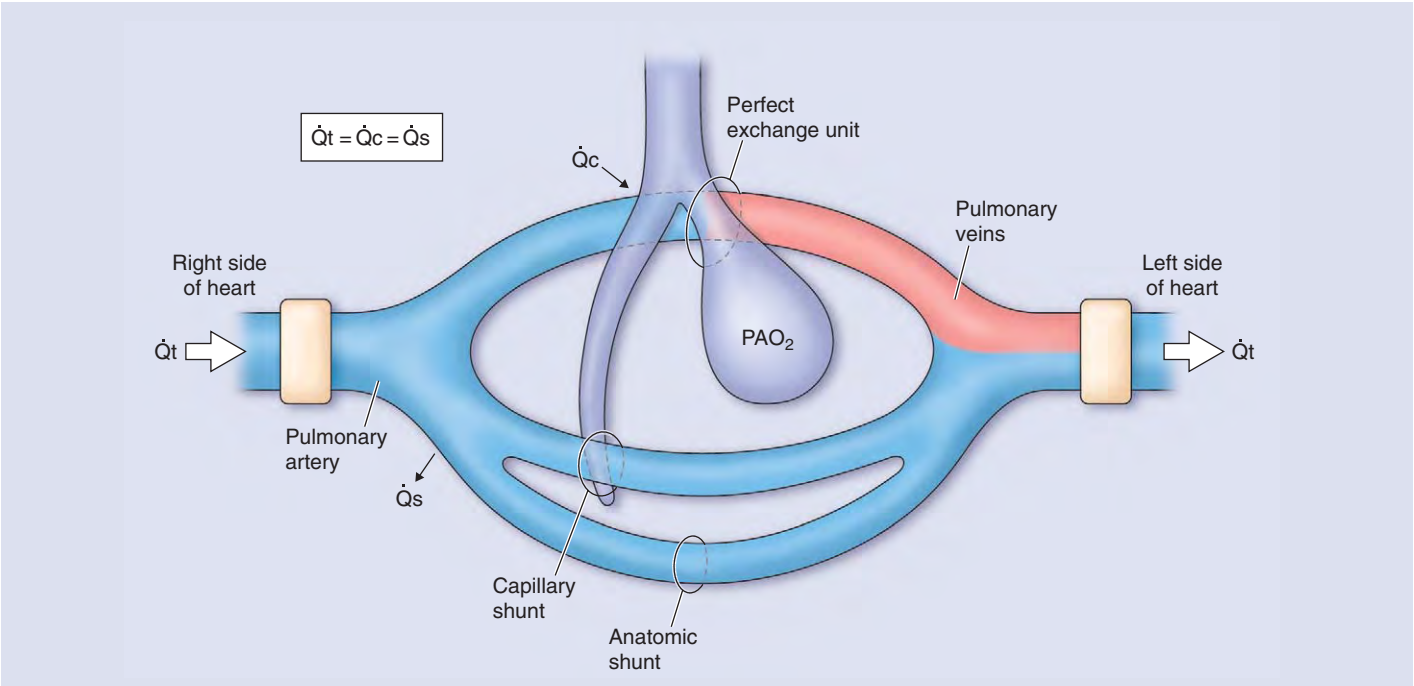

Figure 14-4 A visual concept of physiologic shunting. Pa_{O_2}, partial pressure of alveolar oxygen. (Data from Shapiro BA, et al. In Shapiro BA, et al [eds]: Clinical Application of Blood Gases, 5th ed. St Louis, Mosby, 1994, p 88.)

where Ca_{O_2}, Cc'_{O_2}, and $C\bar{v}_{O_2}$ are the arterial, pulmonary end-capillary, and mixed venous oxygen contents, respectively.

The shunt equation is used to solve for $\dot{Q}s/\dot{Q}t$, as follows:

$$\dot{Q}s/\dot{Q}t = Cc'_{O_2} - Ca_{O_2}/Cc'_{O_2} - C\bar{v}_{O_2}$$

As before, oxygen content is measured directly or calculated according to the following formula:

$$O_2 \text{ content} = (Sa_{O_2} \cdot Hgb \cdot 1.34) + (0.003 \cdot Pa_{O_2})$$

The pulmonary end-capillary oxygen content is not measured clinically; instead, it may be calculated by assuming that it is equivalent to the P_{AO_2}.

The classic shunt ($\dot{Q}s/\dot{Q}t$) (i.e., anatomic shunt plus capillary shunt) is not exposed to P_{AO_2} and therefore is not affected by F_{IO_2}.[38] This shunt is commonly calculated while the patient breathes 100% inspired oxygen and represents only complete $\bar{V}/\dot{Q}$ mismatch (i.e., $\bar{V}/\dot{Q}=0$; a complete absence of gas exchange between the pulmonary capillary and the alveolus) and not the venous admixture seen in states of impaired ventilation and perfusion matching (i.e., $\bar{V}/\dot{Q}<1$, but not 0). When the patient is breathing less than 100% inspired oxygen, the calculated intrapulmonary shunt represents the venous admixture with low $\bar{V}/\dot{Q}$. This is called *physiologic shunt* ($\dot{Q}sp/\dot{Q}t$). When $\dot{Q}sp/\dot{Q}t$ is applied to patients with diseased lungs, it represents the degree of impairment of the lung as an oxygenator. When mixed venous blood is not available to be used in the calculation (i.e., the patient does not have a pulmonary artery catheter), a modified version of the shunt equation can be used. Several formulas have been proposed, one such employs the algebraic combination of the Fick equation and the shunt equation to arrive at a formula for the calculation of $\dot{Q}sp/\dot{Q}t$ without a direct measurement of mixed venous blood (Cv_{O_2}).[39] The resulting equation is:

$$\dot{Q}s/\dot{Q}t = \dot{Q}c \cdot [Cc'_{O_2} - Ca_{O_2}/\bar{V}_{O_2}]$$

Many studies have been published assessing the reliability of the newer oxygen tension–based indexes in reflecting $\dot{Q}sp/\dot{Q}t$.[40-45] These include the alveolar-arterial P_{O_2} gradient ($P_{AO_2} - Pa_{O_2}$), the arterial-alveolar oxygen tension ratio (Pa_{O_2}/P_{AO_2}), the ratio of arterial oxygen tension to inspired oxygen concentration (Pa_{O_2}/F_{IO_2}), the oxygenation index ($[F_{IO_2} \cdot Paw \cdot 100]/Pa_{O_2}$) where Paw is the mean airway pressure, and the respiratory index ($P_{AO_2} - Pa_{O_2}/Pa_{O_2}$).[40-44,46] The clinical application of $P_{AO_2} - Pa_{O_2}$ is limited in patients who have a Pa_{O_2} much less than 150 mm Hg and in whom the F_{IO_2} is varied. With a Pa_{O_2} less than 100 mm Hg, changes in the oxygen content increasingly become a function of changes in hemoglobin saturation rather than in dissolved oxygen. In contrast to the $P_{AO_2} - Pa_{O_2}$, the Pa_{O_2}/P_{AO_2} is relatively unaffected by changes in the F_{IO_2}. So that calculation of the P_{AO_2} could be avoided, the Pa_{O_2}/F_{IO_2} index was introduced. This index is affected by changes in arterial Pc'_{O_2} values, and values less than 2 have been reported to correlate well with $\dot{Q}sp/\dot{Q}t$ values of more than 20%. While applicable only to mechanically ventilated patients, the oxygenation index accounts for the significant effect of mean airway pressure on oxygenation. Last, $P_{AO_2} - Pa_{O_2}/Pa_{O_2}$ was introduced to minimize the inherent problems of $P_{AO_2} - Pa_{O_2}$, and it is a better indicator than $P_{AO_2} - Pa_{O_2}$ in estimating $\dot{Q}sp/\dot{Q}t$.

Carbon Dioxide

The arterial concentration of carbon dioxide (Pa_{CO_2}) is determined mainly by the degree of alveolar ventilation ($\dot{V}A$) in relation to the patient's carbon dioxide production ($\dot{V}_{CO_2}$) as follows:

$$P_{ACO_2} - \dot{V}_{CO_2}/\dot{V}A$$

Alveolar ventilation is lowered by increased alveolar dead space, which occurs when alveoli are ventilated but not perfused. This circumstance is reflected in a measured gradient between P_{ETCO_2} and mixed alveolar P_{CO_2}. P_{ETCO_2} is lower than alveolar P_{CO_2} because of the addition of alveolar dead space gas, which does not contain carbon dioxide.[47]

P_{ACO_2} is difficult to measure directly, and the assumption is made that it is equal to Pa_{CO_2}. This assumption is valid because carbon dioxide is highly diffusible across the alveolar-capillary membrane, which quickly equilibrates P_{ACO_2} and pulmonary end-capillary Pc'_{CO_2}. The difference between mixed venous P_{CO_2} (46 mm Hg) and pulmonary end-capillary P'_{CO_2} (40 mm Hg) is small. Consequently, even a large admixture of venous blood to the pulmonary end-capillary from a large shunt produces only a small increase in arterial P_{CO_2}. Further, eupneic respiratory drive responds to Pa_{CO_2}, and this leads to an increase in ventilation with a reduction in Pa_{CO_2} to normal. Thus, children with right to left shunts rarely have increased Pa_{CO_2} in the absence of pulmonary disease and ventilatory compromise.

Under normal conditions the balance between carbon dioxide production and alveolar ventilation is set so that arterial P_{CO_2} is maintained at 40 mm Hg (37 to 45 mm Hg).[48] An arterial blood gas P_{CO_2} of less than 37 mm Hg with a pH of more than 7.45 is consistent with hyperventilation. A patient with a P_{CO_2} greater than 45 mm Hg with a pH less than 7.35 probably has significant ventilatory failure. Many patients with lung disease breathe more rapidly (tachypnea) or more deeply (hyperpnea) or a combination of both in order to maintain a normal P_{CO_2}. Small changes in P_{CO_2} evoke a rapid increase in ventilation to restore the P_{CO_2} toward normal. Stimuli such as hypoxemia, fever, anxiety, central nervous system disease, septicemia, and medications can increase ventilation,[49] whereas central nervous system depression and pulmonary disease may cause an increase in the P_{CO_2}. The P_{CO_2} rises or decreases until it achieves a new equilibrium; at equilibrium, carbon dioxide production equals excretion. Because respiration is so efficient, modest changes in carbon dioxide production usually do not alter the P_{CO_2}.

Carbon dioxide production increases in response to several conditions, including exercise, burns, and sepsis. Carbon dioxide production can transiently rise as a result of a sodium bicarbonate infusion. After accepting a hydrogen ion, bicarbonate can be converted into carbon dioxide and water via the reaction catalyzed by carbonic anhydrase as presented

later in the chapter. Therefore, infusion of sodium bicarbonate can increase the P_{CO_2} level in an individual whose minute ventilation cannot be increased. In an intensive care unit setting, carbon dioxide production may rise as the respiratory quotient (RQ) rises when patents are metabolizing a larger percentage of carbohydrates (i.e., more carbon dioxide is produced when metabolizing carbohydrates than protein or fat). In an individual with normal lung function, minute ventilation can be increased to compensate for the increased carbon dioxide production.

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Acid-Base Physiology

Peter D. Yorgin

TEACHING POINTS

- Homeostasis of the extracellular fluid hydrogen ion concentration is achieved by carbon dioxide–bicarbonate, phosphate, and protein buffering systems.
- Interpretation of blood gas pH requires the assessment of the primary disturbance, P_{CO_2} and HCO_3^- values, and determination of the appropriate compensatory response to the primary disturbance.
- Use of the modified Henderson-Hasselbalch equation can help to assess the accuracy of blood gas data and is useful in determining the appropriate compensatory response.
- Serum anion gap, urine anion gap, and delta anion gap are useful tools in assessing the cause of a metabolic acidosis.
- Chemical diuretics cause significant hypokalemic metabolic alkalosis through the urinary loss of chloride.

The human body has respiratory, renal, blood, and cellular buffering systems that intricately maintain acid-base homeostasis of the extracellular fluids. The redundancy of these systems allows for the robust protection of acid-base homeostasis during health and illness. Nevertheless, genetic defects, acquired disease, and even iatrogenic factors can cause acid-base disorders. This chapter reviews the systems responsible for acid-base homeostasis, provides clinical examples to illustrate common acid-base disorders, and emphasizes the concepts necessary to assess acid-base status. This chapter is not meant to be an exhaustive review of acid-base physiology but instead has been written to be useful to clinicians seeking a practical approach to acid-base problems. Excellent comprehensive reviews of acid-base physiology can be found elsewhere.[1,2]

GENERAL ACID-BASE CONCEPTS

pH

pH is a convenient means of easily expressing the concentration of hydrogen ion (H^+) in a solvent. The pH system was developed because expressing H^+ concentrations using molality can be difficult. For example, a pH of 7 could be written as 0.0000001 mol/L. pH utilizes a logarithmic scale to express H^+ molality in a solution. pH can be expressed in the form of an equation:

$$pH = -\log[H^+]$$

A solution with a pH of 6 has 10 times the amount of H^+ than does a solution with a pH of 7. If water is the solvent, the pH of an acidic solution is less than 7 (H^+ concentra-

tion = 10^{-7} mmol/L), and a pH greater than 7 is alkaline. An acid is a compound that donates a H^+, or proton, to a base, which is a proton acceptor. An acid is considered to be dissociated after the proton has been donated. Solutions of weak acids and salts of their conjugate bases form buffer solutions. An alkali is a base that donates hydroxide ions (OH^-).

In a healthy individual, the extracellular fluid pH is maintained within a narrow range, pH 7.38 tp 7.42 (H^+ concentration = $10^{-7.38\text{-}7.42}$ mol/L). The evaluation of blood pH is helpful in the evaluation of numerous disorders but particularly so in patients with pulmonary and renal diseases.

pH CAN BE DETERMINED IF P_{CO_2} AND HCO_3^- VALUES ARE KNOWN: THE HENDERSON-HASSELBALCH EQUATION

The pH of blood can be directly measured, using a pH probe (and the Nernst equation), by photochemical sensors (optodes),[3] or it can be calculated using the Henderson-Hasselbalch equation,[4] which describes the relationship between carbonic acid and bicarbonate (HCO_3^-):

$$H_2CO_3 \rightarrow H^+ + HCO_3^-$$

The equation is modified so that the concentration of H^+ can be determined by knowing both the HCO_3^- and H_2CO_3 concentrations. Because a positive value expressed in pH is desirable, the log of both sides of the equation must be obtained.

$$-\log[H^+] = pH = pK + \log[HCO_3^-]/[H_2CO_3])$$

$$pH = pK + \log([HCO_3^-]/H_2CO_3])$$

The pK, in this situation, represents the pH value at which HCO_3^- and H_2CO_3 are found in equal concentrations. The pK practically represents the pH at which there is the greatest amount of buffering capacity. The pK of the CO_2-HCO_3^- buffering system is 6.1. At a pH of 7.40, carbonic acid concentrations are very low and cannot be measured easily. Conversely, P_{CO_2} values are higher and can be easily measured. In most equations, the carbonic acid value is replaced by a solubility coefficient multiplied times the partial pressure of carbon dioxide (CO_2). Using the solubility coefficient, which is 0.0308 for results in mmol/L at 37° C, pH can be defined:

$$pH = pKa + \log([HCO_3^-]/[(0.0308)(CO_2)])$$

THE CO_2-HCO_3^- BUFFERING SYSTEM IS THE FIRST LINE OF DEFENSE AGAINST ACID-BASE PERTURBATIONS

Slight changes in the blood and interstitial fluid H^+ concentration have profound effects on the rate of chemical reactions within the cell. Buffers, found within cells and in blood, quickly limit the change in H^+ concentrations, unlike the renal and respiratory systems, which take time to respond. Buffers have the capacity to combine with an acid or a base and limit the change in H^+ concentrations to less than what would occur without the buffer. An acid-base buffer is usually composed of two or more chemical compounds.

The CO_2-HCO_3^- extracellular buffering system protects against dramatic changes in blood H^+ concentration. The CO_2-HCO_3^- extracellular buffering system has two buffering molecules: carbonic acid (H_2CO_3) and HCO_3^-. Under appropriate conditions, H^+ and HCO_3^- can combine to form carbonic acid. Carbonic acid, in a reversible process, dissociates to yield H_2O and CO_2.

$$H^+ + HCO_3^- \leftrightarrow H_2CO_3 \leftrightarrow H_2O + CO_2$$

If an acid is added to the CO_2-HCO_3^- buffering system, more carbonic acid is generated, as shown in the following reaction:

$$H^+ + HCO_3^- \leftrightarrow H_2CO_3$$

If a base is added to the CO_2-HCO_3^- buffering system, more HCO_3^- is generated, as shown in the following reaction:

$$H_2CO_3 + OH^- \leftrightarrow H_2O + HCO_3^-$$

A MODIFIED VERSION OF THE HENDERSON-HASSELBALCH EQUATION HAS UTILITY FOR THE CLINICIAN

Because the Henderson-Hasselbalch equation can be difficult to use in clinical situations, other, more clinician-friendly formulas have been developed.[5] The Henderson formula makes use of the fact that H^+ concentrations change in a linear fashion in pH around 7.40 (Fig. 14-5). Therefore, the equation can be restated:

$$H^+ \text{ concentration} \cong (K) \text{ lungs/kidneys}$$

where (K) equals 24. Or

$$H^+ \text{ concentration} \cong 24\ (P_{CO_2}/HCO_3^-)$$

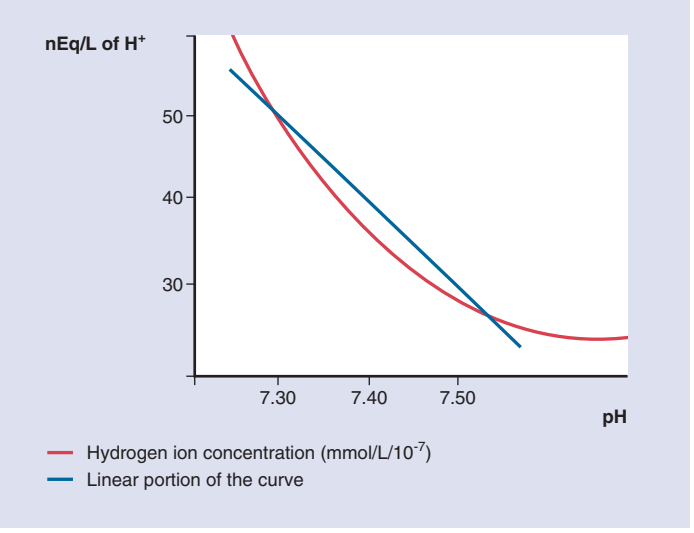

Figure 14-5 Relative to pH, the hydrogen ion concentration (mmol/L/10^{-7}) of blood changes in a linear fashion in a limited area surrounding a pH of 7.40. The Henderson formula can be of great clinical use because of this relationship.

The H^+ concentration at a normal pH (7.40) is 40 nmol/L, which is 0.000000040 mol/L (see Fig. 14-1). An individual with a P_{CO_2} of 40 and an HCO_3^- of 24 mmol/L would have a calculated H^+ concentration of 40 nmol/L (normal) = pH 7.40. For any increase in the H^+ concentration by 1 nmol/L, the pH will decrease by 0.01; for any decrease in the H^+ concentration by 1 nmol/L, the pH will increase by 0.01. If the H^+ concentration was 50 (an increase of 10), then the pH would be 7.30 (a decrease of 0.1 pH unit).

Example: A 2-month-old boy presents with respiratory distress and a large left lower lobe infiltrate on chest radiograph. The blood gas pH is 7.16 with a P_{CO_2} of 63 mm Hg. The reported HCO_3^- (24 mmol/L) may be incorrect or may indicate the presence of mixed acid-base disorder. Is the blood gas correct?

Solution: To determine the H^+ concentration, the equation would be arranged as follows:

$$H^+ \text{ concentration} = [24(63 \text{ mm Hg } (P_{CO_2})]/ 24 \text{ mmol/L } (HCO_3^-)$$

H^+ concentration = 63 = pH of ~7.17. The blood gas reported is internally consistent.

The serum HCO_3^- value is lower than one would expect in a child with a respiratory acidosis. There should be a compensatory metabolic alkalosis. What should the HCO_3^- value be if the pH was 7.40 with a P_{CO_2} of 63 mm Hg?

Solution: The equation can be altered in the following fashion to determine the HCO_3^- if the infant had a normal metabolic response:

$$HCO_3^- = (K)\ P_{CO_2}/H^+ \text{ concentration}$$

The normal H^+ concentration is 40 (equivalent to a pH of 7.40). Therefore, the appropriate serum HCO_3^- value should be 37.8 mmol/L. In this case, the infant has a mixed acid-base disorder consisting of respiratory acidosis and metabolic acidosis. An attempt should be made to identify the source of the metabolic acidosis.

Phosphate and Protein Buffering Systems

The results of actual blood gas analyses are often slightly different than when the results are calculated using the Henderson-Hasselbalch equation because phosphate and protein provide buffering capacity. The phosphate buffering system functions like the CO_2-HCO_3^- buffering system. Two compounds, $H_2PO_4^-$ and HPO_4^-, act as buffers. When a strong acid is added, the following reaction occurs:

$$HCl + Na_2HPO_4 \rightarrow NaH_2PO_4 + NaCl$$

In this reaction, a strong acid, hydrochloric acid, is converted into a weak acid, NaH_2PO_4, thereby causing only a minor change in the pH. If a strong base is added to the buffer system, the following reaction occurs:

$$NaOH + NaH_2PO_4 \rightarrow Na_2HPO_4 + H_2O$$

With this reaction, a strong base is exchanged for a weak base, causing only a minor shift toward an alkaline pH.

The phosphate buffer system has a pKa of 6.8, which means that there are similar concentrations of $H_2PO_4^-$ and HPO_4^- at the pH of 7.40. Therefore, the phosphate buffering system has its best buffering capacity in the normal blood pH range. Yet, the concentrations of $H_2PO_4^-$ and HPO_4^- are much less than those of the HCO_3^- system and therefore contribute less buffering capacity.

The Role of Intracellular Buffering

Cells and the calcium salts in bone make contributions to the buffering of extracellular fluid. Intracellular proteins act as potent buffers and perhaps account for as much as three quarters of all chemical buffering in the body. Some amino acids, such as histadine-related compounds, form free radicals that can disassociate to form base and H^+. Hydrogen ions can bind to imidazole groups of histidine residues in proteins that are found in muscle.[6] Intracellular H^+ concentrations are primarily affected by CO_2 concentrations, which rapidly diffuse through the cell membrane to affect intracellular pH.[7] Bicarbonate, which can move into the cell via an electrogenic Na-HCO_3^- cotransport mechanism, also influences intracellular pH.[8] The calcium salts in bone tend to contribute little to acid-buffering capacity unless calciuria ensues.[8] The calciuria due to long-term acidosis can lead to bone demineralization.

The plasma HCO_3^- increases immediately in response to an increase in P_{CO_2} (Table 14-2). The immediate HCO_3^- changes are modest (4 to 5 mmol/L) and incomplete compared with those in response to a chronic respiratory abnormality. The small changes in serum HCO_3^- are due to intracellular nonbicarbonate buffers.[9,10] During an acute decrease in P_{CO_2}, the production of lactic and citric acid increases slightly, thereby decreasing serum HCO_3^-.[11,12]

Pulmonary Regulation of Acid-Base

The pulmonary compensatory response to acute metabolic acidosis or alkalosis is swift (see Table 14-2). If a strong acid is added to blood, the pH begins to drop as HCO_3^- is consumed and P_{CO_2} begins to rise. Blood pH cannot directly influence the central respiratory center due to the blood-brain barrier. Instead, as P_{CO_2} increases, CO_2 carbonic acid

Table 14-2
Rules of Acute Respiratory Compensation

Change	Rule	Example
↑P_{CO_2}	For every 1–mm Hg increase in P_{CO_2}, the pH will decrease by 0.008 pH unit.	P_{CO_2} 40 → 60 pH 7.40 → 7.24
Compensation to ↑P_{CO_2} ↓P_{CO_2}	The HCO_3^- will increase by 0.1 mmol/L for every 1–mm Hg increase in P_{CO_2}. For every 1–mm Hg decrease in P_{CO_2}, the pH will increase by 0.007 pH unit.	HCO_3^- 24 → 26 P_{CO_2} 40 → 20 pH 7.40 → 7.54
Compensation to ↓P_{CO_2}	The HCO_3^- will decrease by 0.25 mmol/L for every 1–mm Hg decrease in P_{CO_2}.	HCO_3^- 24 → 19

and H^+ levels increase in the cerebrospinal fluid. Hydrogen ions directly stimulate the central respiratory center, causing ventilation to increase. Additional ventilatory stimuli are supplied by peripheral chemoreceptors that respond to the rising H^+ concentrations. Because the lungs represent an open system by which CO_2 can be rapidly disposed, the blood pH can be rapidly corrected to 7.40 by decreasing the P_{CO_2} value to less than 40 mm Hg.

When a strong base is added to blood, the pH rises rapidly and carbonic acid and P_{CO_2} levels decrease. Ventilatory drive decreases in response to decreased serum and cerebrospinal fluid H^+ levels, causing an increase in P_{CO_2}. The compensatory respiratory acidosis response is characterized by an increase in the P_{CO_2} until the pH is normalized at approximately 7.40. The compensatory response is limited by coincident hypoxia; as ventilation decreases, so does the P_{O_2}.

Renal Regulation of Acid-Base

The kidneys maintain acid-base balance via three major mechanisms: HCO_3^- reabsorption, H^+ excretion, and HCO_3^- excretion. Renal acid-base homeostasis starts with the process of glomerular filtration. The concentration of low-molecular-weight constituents of glomerular filtrate, including HCO_3^-, is very similar to that of plasma. Large negatively charged molecules, such as albumin, are not filtered due to the negatively charged proteins, including nephrin and podcin, found in the slit diaphragms between podocytes. After emerging from Bowman's capsule, the filtrate first comes in contact with the convoluted proximal tubule (Fig. 14-6). The proximal tubule reabsorbs approximately 75% of the filtered HCO_3^-, causing the filtrate pH to drop from 7.25 to 6.7 in the proximal tubule. The proximal renal tubular cell cytoplasm is negatively charged (–70 mV) due to the presence of a Na^+,K^+-ATPase pump in the basal membrane,[13] which pumps out three sodium (Na^+) molecules in exchange for two potassium (K^+) molecules[13,14] (Fig. 14-7). The intracellular negative charge inhibits the direct diffusion of HCO_3^-, which is negatively charged, through the luminal membrane of the cell. Conversely, the movement of H^+ from the urine into the renal tubular cells by diffusion is aided by a low tubular pH and intracellular negative charge.

Bicarbonate is reclaimed in the proximal tubule by an elegant mechanism (see Fig. 14-7). On the luminal surface, H^+ is secreted in exchange for Na^+ via an Na^+/H^+ antiporter.[14,15] There also is Na^+-independent H^+ secretion into the tubule lumen via an electrogenic ATP-dependent pump.[16,17] The Na^+-H^+ antiporter appears to have the greatest role in mediating HCO_3^- absorption in the proximal tubule.

In the lumen, H^+ combines with HCO_3^- to form H_2CO_3 (carbonic acid). Luminal carbonic anhydrase[18] facilitates the dehydration of carbonic acid into H_2O and CO_2.[19,20] Although HCO_3^- is unable to pass into the proximal tubular cell, CO_2 easily diffuses into the cell, where it combines with H_2O in the presence of intracellular carbonic anhydrase to form H_2CO_3. The carbonic acid is converted into HCO_3^- and H^+. The HCO_3^- leaves the cell across the basolateral membrane in exchange for Cl^-[21] or leaves with Na^+ via electrogenic Na^+-$3HCO_3^-$ cotransport.[22] The H^+ can be secreted into the tubule lumen again, where it once again can facilitate the reabsorption of HCO_3^-. Bicarbonate reabsorption in the proximal tubule is regulated in part by luminal HCO_3^- concentration, glomerular filtration rate (GFR), peritubular fluid pH, extracellular fluid volume, and K^+ depletion[23] (Table 14-3).

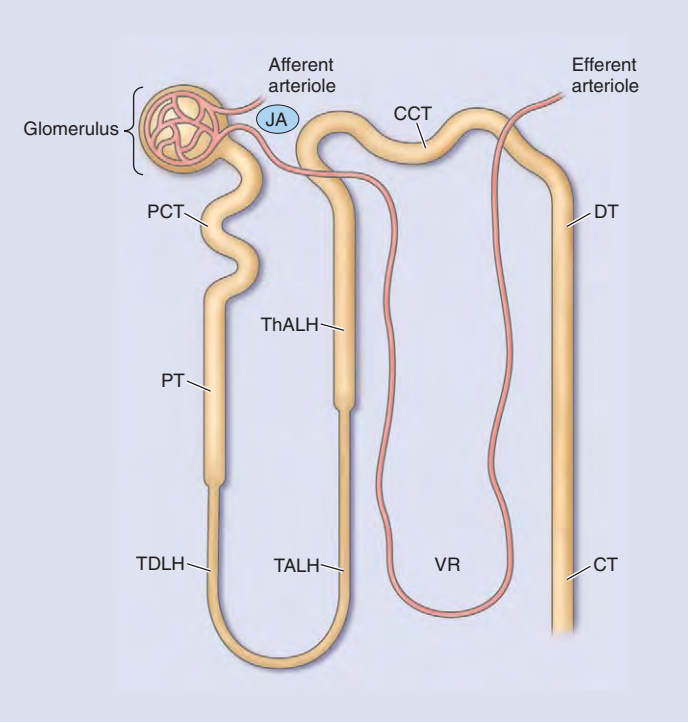

Figure 14-6 Nephron diagram. Blood is brought to the glomerulus by the afferent arteriole and leaves via the efferent arteriole. In some nephrons the efferent arteriole changes course, becoming the vasa recta (VR), which courses through the interstitial area between the ascending loop of Henle and the distal/collecting tubule. Other portions of the nephron are designated by the following abbreviations: CCT, cortical convoluted tubule; CT, collecting tubule; DT, distal tubule; JA, juxtaglomerular apparatus; PCT, proximal convoluted tubule; PT, proximal tubule; TALH, thin ascending loop of Henle; TDLH, thin descending loop of Henle; ThALH, thick ascending loop of Henle.

The distal tubule reabsorbs the remaining HCO_3^- and acidifies the urine. The collecting duct has two types of cells: principal cells and intercalated cells.[18] The principal cells primarily absorb Na^+ in exchange for K^+. There are two types of intercalated cells, one that excretes HCO_3^- and another that excretes H^+.[24] The urine is acidified by luminal vacuolar H^+-ATPase[25] and H^+,K^+-ATPase (Fig. 14-8). The H^+,K^+-ATPase is expressed only in response to K^+ depletion. This pump plays a role in the metabolic alkalosis that is caused by protracted severe hypokalemia, which is seen in patients with diuretic-induced hypokalemia. Alkalemia acts as a stimulus

Table 14-3
Factors That Affect Renal Bicarbonate Reabsorption

Factor	Effect
Increased GFR	↑ Bicarbonate absorption
Increased luminal pH	↑ Distal tubule acidification
Increased peritubular pH	↓ Bicarbonate absorption
Extracellular volume	↓ Bicarbonate absorption (slight)
Potassium depletion	↑ Bicarbonate absorption

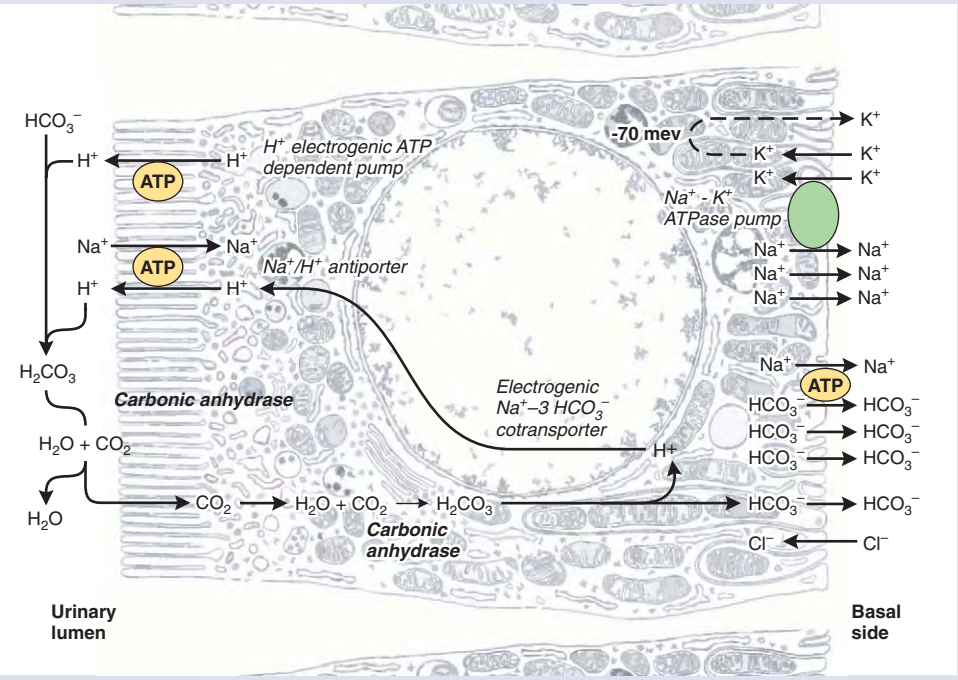

Figure 14-7 One of the major functions for the proximal renal tubule cells is to reabsorb bicarbonate. Hydrogen ion into the tubule lumen combines to form carbonic acid. Carbonic acid, in the presence of carbonic anhydrase, is split into water and CO_2. The CO_2 freely diffuses into the cell, where it combines with water, in the presence of carbonic anhydrase, to form carbonic acid. The carbonic acid splits to form H^+ and HCO_3^-. The HCO_3^- is transported across the basolateral membrane in exchange for chloride or with sodium. ATP, adenosine triphosphate; CO_2, carbon dioxide; HCO_3^-, bicarbonate; H_2CO_3, carbonic acid; H_2O, water; K^+, potassium; mEv, millivolts; Na^+, sodium.

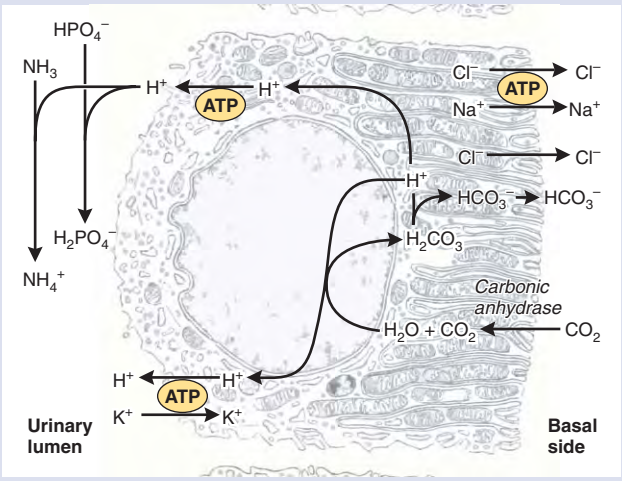

Figure 14-8 One of the major functions of the distal tubule is to acidify the urine. Hydrogen ions are secreted into the tubule lumen, where binding with ammonia and phosphoric acid allows for the reclamation of bicarbonate. ATP, adenosine triphosphate; CO_2, carbon dioxide; HCO_3^-, bicarbonate; H_2CO_3, carbonic acid; H_2O, water; K^+, potassium; Na^+, sodium.

to increase HCO_3^- secretion in the distal tubule. Most distal renal tubular cells, however, secrete H^+. The secretion and loss of H^+ indirectly increase the amount of serum HCO_3^- reabsorbed. Bicarbonate is transferred across the basement membrane in exchange for Cl^-.

Despite the large amount of H^+ in the urine, little of it is excreted as HCl (hydrochloric acid) due to the presence of ammonium and phosphate buffers. If urinary HCl concentrations were high, the conditions needed to form stones, including uric acid stones, would be enhanced, and the low urinary pH could be injurious to the renal tubule and uroepithelium. The H^+ combines with either ammonia or phosphate to buffer the pH.

Ammonia is produced by the conversion of glutamine to ammonia in most renal tubule cells except those in the thin segment of the loop of Henle. The secreted H^+ combines with ammonia, to form ammonium (NH_4^+). Renal tubular ammonia release increases concomitantly with increases in H^+ secretion. This observation is of particular importance when discriminating between renal tubular acidosis and other, mostly gastrointestinal, causes of nonanion gap metabolic acidosis. When a patient has a chronic metabolic acidosis, the ammonium concentration in the urine increases.[26]

Approximately 20% of all filtered phosphate is not reabsorbed before the distal tubule. Phosphate can combine with either one or two H^+ and is typically excreted with Na^+.[27]

Table 14-4
Rules of Chronic Acid-Base Compensation

Chronic Change	Rule	Example
↑P_{CO_2}	For every 1–mm Hg increase in P_{CO_2}, the pH decreases by 0.0025 pH unit.	P_{CO_2} 40 → 60 pH 7.40 → 7.35
Compensation for ↑P_{CO_2} ↓P_{CO_2}	The HCO_3^- will increase by 0.4 mmol/L for every 1–mm Hg increase in P_{CO_2}.	HCO_3^- 24 → 28
	For every 1–mm Hg decrease in P_{CO_2}, the pH increases by 0.003 pH unit.	P_{CO_2} 40 → 20 pH 7.40 → 7.46
Compensation for ↓P_{CO_2} ↑HCO_3^-	The HCO_3^- will decrease by 0.5 mmol/L for every 1–mm Hg decrease in P_{CO_2}.	HCO_3^- 24 → 14
	For every 1–mm Hg increase in HCO_3^-, the pH increases by 0.003-0.008 pH unit.	HCO_3^- 24 → 34 pH 7.40 → 7.43-48
Compensation for ↑HCO_3^- ↓HCO_3^-	The P_{CO_2} will increase by 0.2-0.9 mm Hg for every 1–mm Hg increase in HCO_3^-.	P_{CO_2} 40 → 48
	For every 1–mm Hg decrease in HCO_3^-, the pH decreases by 0.012 pH unit.	HCO_3^- 24 → 14 pH 7.40 → 7.28
Compensation for ↓HCO_3^-	The P_{CO_2} will decrease by 1.25 mm Hg for every 1–mm Hg decrease in HCO_3^-.	P_{CO_2} 40 → 28

Each time H^+ is buffered by the ammonia or phosphate buffering system, a new HCO_3^- molecule is produced by the renal tubule cell and released into the blood.

Chronic Buffering Processes

With any level of chronically elevated or decreased P_{CO_2}, serum HCO_3^- changes cause the pH to return toward normal (Table 14-4) but not completely back to normal. Several hours to days are needed for the full renal response, a compensatory metabolic acidosis, to hypocapnea to begin.[28] A decrease in P_{CO_2} causes a decrease in renal tubular HCO_3^- reabsorption.[29-33] Hydrogen ion secretion by the proximal and distal renal tubules is also diminished.[34,35] The increase in serum chloride (Cl^-) occurs through a shift of Cl^- out of the red blood cells, extracellular volume contraction, and enhanced renal Cl^- reabsorption.

When P_{CO_2} rises, the kidney compensates by secreting more H^+[36,37] and by increasing the amount of HCO_3^- reabsorbed.[29,31,32,38-40]

INTERPRETATION OF ACID-BASE STATUS FROM BLOOD GAS RESULTS

General Approach to Evaluating Acid-Base Status

To effectively assess acid-base status, the clinician is greatly assisted by reviewing simultaneous blood chemistry and blood gas results. The following steps are most helpful in yielding a diagnosis:

1. Assess the serum pH, because it indicates whether a patient is acidemic or alkalemic.
2. Assess the P_{CO_2} and serum total CO_2-HCO_3^- values relative to the pH to determine the primary cause of the pH disturbance.
3. Calculate the expected respiratory or renal compensation. If memorization of the compensation rules seems overwhelming, the modified version of the Henderson-Hasselbalch equation can be used to determine the appropriate respiratory or renal response when one assumes a normal pH.
4. Calculate the anion gap and delta anion gap to distinguish the cause for metabolic acidosis and to determine if there is an additional acid-base disorder.

pH

The first step in analyzing a blood gas is to determine whether the patient is acidemic or alkalemic. The normal pH of extracellular fluids is 7.38 to 7.42. Any increase in P_{CO_2} or decrease in HCO_3^- such that the pH is lower than 7.38 is referred to as an *acidemia*. Any uncompensated decrease in P_{CO_2} or increase in HCO_3^- such that the pH is higher than 7.42 is characterized as an *alkalemia*. When there is a perturbation in the blood pH, the etiology is either respiratory or metabolic. For example, if the patient is acidemic, then there will be an excess of P_{CO_2} or a decrease in HCO_3^-.

Any change in the H^+ concentration in blood causes a defense of the pH by compensatory mechanisms. For example, if there is a perturbation in P_{CO_2}, then the serum HCO_3^- will increase or decrease to compensate, thereby normalizing the pH. When a primary respiratory or metabolic process overwhelms the compensatory mechanism, the blood pH changes.

Example: A neonate with respiratory distress has the following blood gas: pH: 7.33, P_{CO_2}: 52 mm Hg, HCO_3^-: 26 mmol/L. What is the primary disturbance?

Diagnosis: In this particular case, the patient is acidemic due to a primary *respiratory acidosis* with an incomplete *compensatory metabolic alkalosis*.

pH has a significant effect on serum K^+ values. As extracellular H^+ increases, H^+ moves into cells in exchange for K^+. Therefore, in response to acidemia, the serum K^+ rises by 0.6 mEq/L for every decrease in blood pH of 0.1. Conversely, every pH increase of 0.1 leads to a decrease in serum K^+ of 0.2 to 0.4 mEq/L.

P_{CO_2}

The partial pressure of carbon dioxide (P_{CO_2}) in the blood and its relationship to gas exchange is discussed in detail earlier in Gas Exchange, Oxygen Delivery, and Ventilation. However, the P_{CO_2} has profound effects on blood pH and is measured directly with a CO_2 electrode, which is a core element of a multianalyte blood gas machine (normal range: 35 to 40 mm Hg). The actual HCO_3^-, standard HCO_3^-, and base excess are then computed from the pH and P_{CO_2} using the Siggaard-Andersen nomogram (see Fig. 14-8). The arterial P_{CO_2} will vary inversely with alveolar ventilation in a linear manner:

$$Paco_2 \sim K \times \dot{V}CO_2/\dot{V}A$$

where $\dot{V}CO_2$ is the volume of CO_2 produced by the body's metabolism per minute (L/min), and $\dot{V}A$ is the alveolar ventilation (L/min).

Thus, assuming a constant metabolic production of CO_2, a reduction in alveolar ventilation by half will lead to a doubling of P_{CO_2} from 40 mm Hg to 80 mm Hg, causing a respiratory acidosis. Conversely, a doubling of alveolar ventilation will lead to a reduction of P_{CO_2} from 40 mm Hg to 20 mm Hg, causing a respiratory alkalosis.

Blood measurement technique can invalidate the obtained P_{CO_2} result. Air bubbles in the specimen should be avoided because they will cause a spurious fall in P_{CO_2} and an increase in P_{O_2}. The anticoagulant heparin is acidic and in excess can lead to false reduction in the P_{CO_2} and HCO_3^- results. Conversely, when there is delayed measurement, continued metabolism by the erythrocytes reduces pH and P_{O_2} and increases P_{CO_2}. For this reason, specimens are kept on ice prior to measurement.

BICARBONATE

Serum HCO_3^- or total CO_2 values are routinely measured using analytical clinical laboratory or blood gas equipment. Some laboratories will report serum total CO_2 values instead of HCO_3^-. The total CO_2 value includes HCO_3^-, H_2CO_3, dissolved CO_2, carbonate, and CO_2 bound to amino acids. Total CO_2 can be determined by adding a strong acid to blood. Because 95% of the total CO_2 value is HCO_3^-, the total CO_2 value is usually 2 mmol/L higher than the calculated HCO_3^- value. Serum HCO_3^- levels can be estimated from total CO_2 values. Serum HCO_3^- and total CO_2 can be determined from known pH and P_{CO_2} values using the Henderson-Hasselbalch equation.

Serum total CO_2 and HCO_3^- values change in response to blood CO_2 levels due, in part, to the H^+ accepting capacity of hemoglobin and other proteins. When CO_2 is bubbled through a HCO_3^- solution without hemoglobin, the HCO_3^- concentration does not change. Therefore, hemoglobin plays a role in mediating HCO_3^- response to P_{CO_2}. If sodium bicarbonate is infused into blood, P_{CO_2} values increase.

Example: A 17-year-old girl with diabetic ketoacidosis has a serum HCO_3^- of 5 mmol/L, pH of 7.11, and P_{CO_2} of 16.5 mm Hg. After fluids and 100 mEq of sodium bicarbonate were infused, a repeat blood gas shows a HCO_3^- value of 13 mmol/L, P_{CO_2} of 30, and pH of 7.25. Why is the P_{CO_2} rising when the pH is still less than 7.38?

Diagnosis: As sodium bicarbonate is infused, the P_{CO_2} rises because of a decrease in respiratory drive from the rising pH and due to the conversion of H^+ and HCO_3^- to H_2O and CO_2.

In children and adults, the normal serum HCO_3^- value is 24 mmol/L (range, 22 to 29 mmol/L). In newborns, the values are significantly lower due to an expanded extracellular volume, decreased renal tubule ammonia production, a lower HCO_3^- reabsorption threshold, and a limited ability to excrete H^+.[41] A modest metabolic acidosis tends to facilitate an increase in the respiratory drive in the postnatal period. Mean serum HCO_3^- values are lower in preterm infants (18 to 20 mmol/L) than those born at term (20 to 22 mmol/L).

There has been a significant amount of controversy as to whether to correct metabolic acidosis with a sodium bicarbonate or other buffers in critical care situations.[42] Most investigators have concluded that HCO_3^- therapy is not indicated for the treatment of physiologic metabolic acidosis, even lactic acidosis, because it resolves without buffer treatment. There is value, however, in giving buffer therapy to patients with renal tubular acidosis and diarrheal HCO_3^- losses.

BASE EXCESS

Base excess or base deficit is characterized by the amount of base that is required to normalize the pH of the blood. Normal values range from −2 to +2 mEq/L. Base excess can be determined by plotting the values on the Sigaard-Andersen nomogram (Fig. 14-9) or by calculating the formula where the base excess is based on P_{CO_2} and pH or P_{CO_2} and HCO_3^-.

$$\text{Base excess} = 0.9287\ [HCO_3 - 24.4 + 14.83\ (pH - 7.4)]$$

$$\text{Base excess} = 0.02786 \times P_{CO_2} \times 10^{(pH\ -6.1)} + 13.77 \times pH - 124.58$$

Positive base excess numbers indicate the presence of a metabolic alkalosis, whereas negative numbers indicate the presence of a metabolic acidosis. The base deficit can be used to calculate the amount of HCO_3^- (or other base) needed to normalize the pH. Because the volume of distribution of HCO_3^- is 0.4,[43,44] the formula to calculate the amount of base that is required to normalize the pH of the blood is as follows:

$$\text{Base required} = (\text{Base excess} \times -1) \times (\text{Weight in kg}) \times 0.4$$

Example: A 12-year-old boy with chronic renal failure (estimated GFR = 25.3 mL/min/1.73 m^2) aspirates after having a hypertension-induced seizure and is now intubated and on a ventilator. His blood gas shows a pH of 7.19, P_{CO_2} of 46 mm Hg, and HCO_3^- of 18 mmol/L. His hemoglobin is 10.1 g/dL. The base excess is −10.8 mEq/L. How much sodium bicarbonate per kilogram would be needed to normalize the HCO_3^-?

Solution: The amount of HCO_3^- per kilogram needed to correct the metabolic acidosis is determined by multiplying the negative base excess by the volume of distribution (0.4). The patient would need 4.3 mEq per kilogram of HCO_3^-.

As with the serum anion gap, serum albumin concentrations impact base excess calculations.[45] If the serum albumin is low, as often occurs in critical care settings, the base excess will be more positive than the reported value, as demonstrated in this equation:

$$\text{Base excess correction} = 0.25\ (4.2 - \text{Serum albumin in g/dL})$$

DELTA ANION GAP

This measurement assesses the change in the anion gap relative to HCO_3^- and is of use in patients who have an anion gap metabolic acidosis. The delta anion gap can be calculated using the following equation:

$$\text{Delta anion gap} = (\text{Anion gap} - 10) \div (24 - HCO_3^-)$$

The normal delta anion gap is 1 to 1.6. If the delta anion gap is less than 1, then the HCO_3^- has decreased more than the

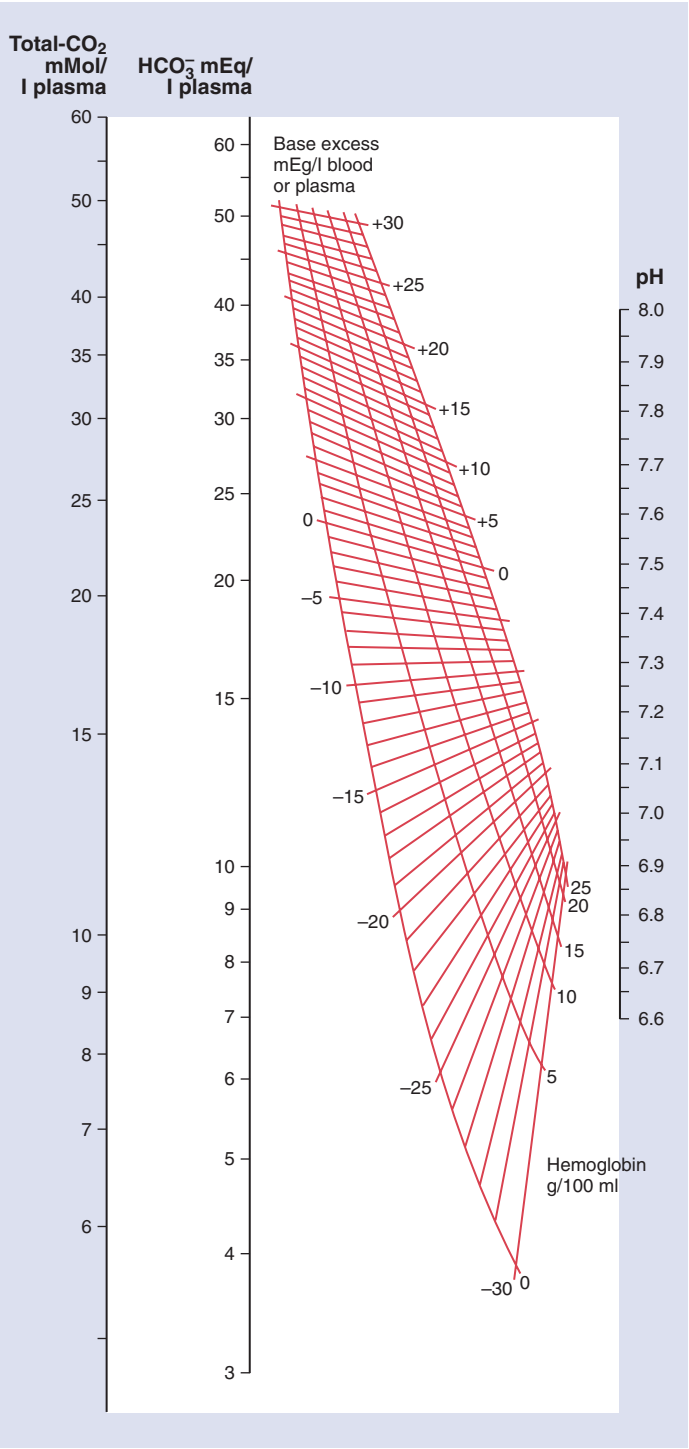

Figure 14-9 Siggaard-Andersen alignment nomogram. Scales for pH, P_{CO_2}, base excess of whole blood of different hemoglobin concentrations, plasma bicarbonate, and plasma CO_2. (Redrawn from Siggaard-Andersen O: The acid-base status of blood. Scand J Clin Lab Invest 15:211-217, 1963, by permission of Scandinavian University Press.)

amount that could be explained by the anion gap and therefore there is an additional metabolic acidosis. Conversely, if the delta anion gap is greater than 1.6, then the HCO_3^- is higher than one would expect given the anion gap, thus indicating that the patient has an undetected metabolic alkalosis.

Example: A 3-year-old boy was brought to the emergency department after ingesting an unknown quantity of aspirin. His blood gas shows a pH of 7.20, P_{CO_2} of 46 mm Hg, and HCO_3^- of 18 mmol/L. Other values are serum Na^+ of 132 mEq/L, Cl^- of 102 mEq/L, and serum total CO_2 of 8 mmol/L. Calculate the delta anion gap.

Solution: The anion gap is 22 mmol/L, 12 mmol/L higher than the 10 mmol/L given in the equation. The serum total CO_2 is 8 mmol/L, 16 mmol/L less than the normal 24 mmol/L. The delta anion gap is 0.75, indicating the patient has at least two causes for his metabolic acidosis. The respiratory compensation is appropriate given the severity of metabolic acidosis.

METABOLIC AND RESPIRATORY DERANGEMENTS

Metabolic Acidosis

There are three basic mechanisms that can cause serum HCO_3^- levels to fall, yielding a metabolic acidosis: (1) an acid is added to the body fluids, HCO_3^- buffers the acid, leaving less HCO_3^-, (2) HCO_3^- is lost through the gastrointestinal tract[46] or by the kidneys, or (3) serum HCO_3^- levels are decreased by dilution with a non–HCO_3^--containing solution.[47] The compensatory response to both acute and chronic metabolic acidosis is a respiratory alkalosis, where hyperventilation decreases P_{CO_2} values.

Any evaluation of any metabolic acidosis should include a determination of the serum anion gap. The limits of electrochemical neutrality (e.g., the sum of all the positively charged ions equals the sum of the negatively charged ions [anions]) ensure that there are equal numbers of positive and negative ions in body fluids. The anion gap can be determined by the use of the following equations:

$$\frac{Na^+ + \text{Unmeasured cations} = (Cl^- + HCO_3^-) + \text{Unmeasured anions}}{}$$

$$\frac{\text{Anion gap} = Na^+ - (Cl^- + HCO_3^-) = \text{Unmeasured anions} - \text{Unmeasured cations}}{}$$

Unmeasured cations include K^+, Ca^{2+}, and Mg^{2+}. Unmeasured anions include albumin and phosphate. Note that serum K^+ in this formula is considered as an unmeasured cation and should not be added to the Na^+ in the calculation of the anion gap. The normal anion gap is 12±4 mmol/L.[48] Under normal conditions, the anion gap is predominantly composed of negative charges on serum proteins including albumin[48,49] (Fig. 14-10). The anion gap falls by 2.5 mmol/L for every 1-g/L reduction in serum albumin.[50] The anion gap is clinically useful because it can be used to determine the cause of the metabolic acidosis.[51]

Most patients with a metabolic acidosis have either an increased or a normal anion gap. If, hypothetically, hydrochloric acid is infused into the blood, then there is a milliequivalent per milliequivalent replacement of HCO_3^- for Cl^-, yielding a normal anion gap acidosis. The same is true for intestinal or renal loss of HCO_3^-. The determination of a urine anion gap can be particularly helpful in diagnosing renal tubular acidosis.[52] However, if HCO_3^- is replaced by an unmeasured anion, the anion gap will increase. Changes in the anion gap are linked to P_{CO_2}. For every 1-mmol/L rise in

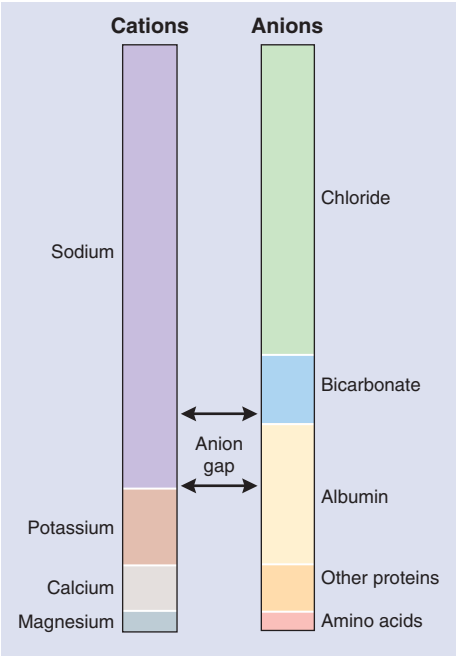

Figure 14-10 Serum anion gap. Due to the demands of electrochemical neutrality, the concentration of positive and negative ions in serum must be equal. The serum sodium value is greater than that of chloride and bicarbonate combined. The normal ion gap, 12 ± 4 mmol/L, is composed of albumin, phosphates, and amino acids. If the anion gap is elevated, bicarbonate has been replaced by other anions, making the anion gap greater than normal.

Table 14-5
Causes of an Anion Gap Acidosis

Cause	Unmeasured Anion
Toxins and drugs	
Ethanol	Lactic acid
Ethylene glycol	Oxalic acid
Isoniazid toxicity	Lactic acid
Methanol	Formic acid
Paraldehyde	Acetic acid
Salicylates	Lactic acid
Isopropyl alcohol	Oxalic acid
Lactic acidosis	Lactic acid
Uremia	Uric, oxalic, succinic, pimelic, and adipic acids
Amino acidopathies	
Maple syrup urine disease	α-Keto-isocaproic, α-keto-β-methylvaleric, α-ketoisovaleric, Indolacetic, acetoacetic, and β-hydroxybutyric acids
Isovaleric acidemia	Isovaleric acid
Glutaric acidemia	Glutaric, lactic, Isobutyric, isovaleric, and α-methylbutyric acids
Propionyl coenzyme A carboxylase deficiency	Propionic, methylcitric Propionylglycine, acetoacetic, β-hydroxypropionate, and β-hydroxybutyric acids
Methylmalonic acidurua	Methylmalonic acid
Defects in carbohydrate metabolism	
Diabetic ketoacidosis	Acetoacetic and β-hydroxybutyric acids
Fructose-1,6-diphosphatase deficiency	Lactic and pyruvic acids
Glucose-6-phosphatase deficiency	Lactic acid
Pyruvate carboxylase deficiency	Lactic and pyruvic acids
Succinyl-coenzyme A–transferase deficiency	Acetoacetic and β-hydroxybutyric acids

serum anion gap, the P_{CO_2} should decrease by 1 mm Hg. An increased anion gap can be caused by an increase in unmeasured anions and/or a decrease in unmeasured cations[48] (Table 14-5). A decreased anion gap is often due to hypoalbuminemia, hypercalcemia, hyperkalemia, hypermagnesemia, or lithium.

Most of the acute change in serum HCO_3^- is repaired by intracellular buffering processes.[53] Hemoglobin, phosphorus, protein, and bone[31,54] all contribute to buffering H^+. Serum Cl^- levels rise in response to the decrease in HCO_3^- levels.

There is increasing evidence that intravenous sodium bicarbonate infusions should not be used to treat critically ill patients with an anion gap metabolic acidosis.[7,55,56] There are also insufficient data to recommend sodium bicarbonate infusion in newborn resuscitation.[57-59] Thus, sodium bicarbonate treatment is typically reserved for the treatment of a hyperchloremic metabolic acidosis, including renal tubular acidosis, diarrhea, a ureterosigmoidostomy, and amino acid or cholestyramine infusions. In addition to sodium bicarbonate, sodium acetate (in intravenous solutions), oral sodium citrate, and potassium citrate may be used to correct a persistent hyperchloremic acidosis.

Because the injectable solution of sodium bicarbonate has a Na^+ content of 1000 mEq/L, large doses can cause significant hypernatremia.[56] Intravenous use of diluted sodium bicarbonate solution in concentrations of 140 mEq/L in patients with normal renal function rarely causes hypernatremia. In situations where a patient remains acidemic but is significantly hypernatremic, *tris*-hydroxymethyl aminomethane (THAM) can be used.[55] THAM can be used in patients with renal acidosis, salicylate or barbiturate intoxication, and increased intracranial pressure associated with cerebral trauma.[60] THAM dosing is based on the following formula:

$$\text{THAM (mL of 0.3 mol/L solution)} = \text{Lean body weight (kg)} \times \text{Base deficit (mmol/L)}$$

Serum K^+ values inversely correlate with serum HCO_3^- values. Serum K^+ concentrations fall with an infusion of HCO_3^- due to the movement of K^+ back into cells in exchange for H^+. A pH increase of 0.1 leads to a decrease in serum K^+ of 0.2 to 0.4 mEq/L. Conversely, for every decrease in blood pH of 0.1, the serum K^+ rises by 0.6 mEq/L.

Respiratory Acidosis

Any process that interferes with ventilation can cause a respiratory acidosis. The causes of ventilatory failure include chronic obstructive pulmonary disease, drugs, extreme ventilation-perfusion mismatch, extensive infiltrative process, exhaustion, neuromuscular disorders, and excessive CO_2 production.

The compensatory response to respiratory acidosis is a metabolic alkalosis. Hypercapnia stimulates the secretion of H^+ by the distal tubule (see Fig. 14-8), which lowers urine pH.[17,61,62] Serum HCO_3^- values also increase because HCO_3^- secretion in the distal tubule is inhibited.[63] The higher

HCO_3^- concentration is maintained by enhanced renal HCO_3^- reabsorption in both proximal and distal tubules. As serum HCO_3^- levels increase, the serum Cl^- levels must decrease. Hypercapnia leads to a decrease in proximal sodium chloride reabsorption and causes chloriuresis. The compensatory response of metabolic alkalosis, to chronic hypercarbia, usually takes 1 to 2 days.

Example: A 16-year-old boy with a pulmonary hemorrhage due to Wegener granulomatosis has a pH of 7.32, $PaCO_2$ of 52 mm Hg, and HCO_3^- of 26 mmol/L.

Diagnosis: The elevated HCO_3^- could not have caused the acidemia, so the principal cause of the acidemia is a respiratory acidosis. Yet, the renal compensatory process either is incomplete or has not had time to correct the pH to normal.

Occasionally, an overshoot in HCO_3^- generation occurs so that the blood is alkaline due to nighttime hypercapnia or a renal response geared to blood PCO_2 rather than pH. Therefore, the patient with a chronic respiratory acidosis may present with a modest alkalosis.

If there were no compensatory process, the recognition of the inciting problem would be quite easy. Formulas have been derived that describe the relationship between CO_2 and HCO_3^- in acute and chronic acid-base disorders (see Tables 14-2 and 14-4). These formulas can assist in the determination of the primary event and the subsequent compensatory process. In most cases, the direction of the pH deviation suggests the primary process.

Discriminating between Acute and Chronic Respiratory Acidosis

Acute respiratory acidosis is usually caused by an abrupt decline in ventilation that causes the PCO_2 to rise and pH to fall. A child with acute respiratory acidosis frequently is hypoxic and presents with tachypnea, dyspnea, and hyperpnea.

Example: An arterial blood gas sample obtained from a child with known severe asthma, now presenting to the emergency department with status asthmaticus, reveals a low pH (7.26) with a high PCO_2 (62 mm Hg) and a slightly elevated serum HCO_3^- (27 mmol/L).

Diagnosis: These results are consistent with a child who has impending respiratory failure. Most asthmatics have a mild respiratory alkalosis at the time of presentation. The elevated HCO_3^- is attributable to buffering by intracellular buffering mechanisms. The increase in serum HCO_3^- by 1 mmol/L for every 10–mm Hg increase in PCO_2[64] is immediate.

Renal buffering does not noticeably impact the pH until 12 to 24 hours after the respiratory acidosis begins.[65] Treatment of the patient with acute respiratory acidosis involves rapid recognition and correction of the inciting cause coupled with oxygen administration. Sodium bicarbonate, which can cause a rise in PCO_2, should be used only to preclude the serious cardiovascular affects of acidosis.

The basis for chronic respiratory acidosis is typically a decrease in alveolar ventilation. Plasma CO_2 values are elevated; however, unlike in the patient with acute respiratory acidosis, effective renal compensation has occurred. Therefore, serum pH values are only slightly below normal. For each increase in the PCO_2 of 1 mm Hg, the HCO_3^- value increases by 0.41 mmol/L.[66] Serum Cl^- values are decreased to reciprocate the increase in serum HCO_3^-.

Example: A 3-month-old infant with bronchopulmonary dysplasia on diuretic therapy has the following venous blood gas and laboratory results: pH 7.38, PCO_2 66 mm Hg, PO_2 43 mm Hg, HCO_3^- 37 mmol/L, serum Na^+ 136 mEq/L, serum K^+ 2.9 mEq/L, serum total CO_2 39 mmol/L, serum Cl^- 86 mEq/L.

Solution: This blood gas obtained from a child with stable bronchopulmonary dysplasia is remarkable for the normal to slightly low pH, a markedly elevated PCO_2, and the appropriately elevated HCO_3^- (i.e., an effective renal compensation for the chronic respiratory acidosis).

Loop and thiazide diuretics are helpful in the management of chronic pulmonary disease because excessive fluid causes pulmonary congestion. Yet, loop and thiazide diuretics can cause worsening of the metabolic alkalosis by causing a contraction alkalosis, as shown in the example above.

Metabolic Alkalosis

Metabolic alkalosis, an acid-base disorder characterized by an increased concentration of serum HCO_3^-, can be caused by three major mechanisms: (1) intravascular volume contraction where Cl^- is lost disproportionately to HCO_3^-, (2) loss of H^+, or (3) net addition of HCO_3^- to the extracellular space.

Chloride loss, without concurrent H^+ loss, most commonly occurs with gastrointestinal disease, chemical diuretic use,[67] cystic fibrosis,[68,69] Bartter syndrome,[70] or Gitelman syndrome.[71,72] With intractable Cl^- depletion, the kidney increases the reabsorption of HCO_3^- by increasing distal tubule H^+ secretion. A metabolic alkalosis can develop when Cl^- is lost in excess of Na^+ from the gastrointestinal tract of patients with acute diarrhea.[73] Chloride losses due to diarrhea may range from 10 to 110 mEq per liter of stool. There is a rare congenital form of chloride diarrhea in which there is a defect in bowel transport of Cl^-.[74,75] Chemical diuretics, including loop (furosemide, bumetanide, ethacrynic acid) and thiazide (including chlorothiazide, hydrochlorothiazide, and metolazone) diuretics, can cause a profound loss of Cl^- by the kidney. Loop diuretics such as furosemide, bumetanide, and ethacrynic acid block the symporter within the thick ascending limb of the loop of Henle[76] (Fig. 14-11). Owing to the large amount of Na^+ and Cl^- reabsorption attributable to the symporter, the diuresis seen with a loop diuretic is much greater than that seen with any other class of diuretic. The normally functioning symporter cotransports two Cl^- molecules, one K^+ molecule, and one Na^+ molecule from the tubule lumen into the cell.[77] Loop diuretics also increase the excretion of calcium and magnesium, thereby increasing the risk of urolithiasis.[78] Thiazide diuretics, including hydrochlorothiazide, metolazone, and chlorothiazide, inhibit the function of a sodium chloride pump found within the distal convoluted tubule and decrease calciuria.

Bicarbonate values rise acutely with the use of loop and thiazide diuretics due to at least four mechanisms. First, contraction of the intravascular volume, without net loss of HCO_3^- causes an increase in serum HCO_3^- levels.

Second, increased salt delivery to the distal tubule stimulates K^+ and H^+ secretion independent of an aldosterone effect,[79] thus contributing to higher serum HCO_3^- values.

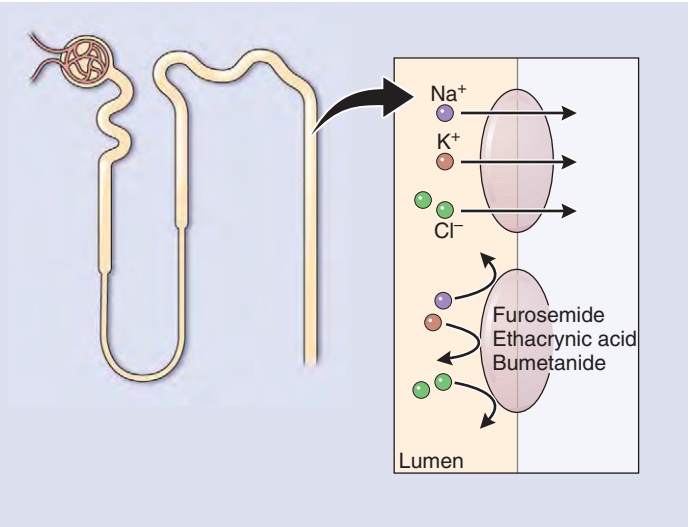

Figure 14-11 The thick ascending limb symporter reabsorbs two chloride molecules with one potassium and one sodium molecule. Dysfunction of the symporter causes Bartter syndrome. Loop diuretics inhibit symporter function, causing the loss of sodium, chloride, potassium, and water in the urine, and decrease the effectiveness of the countercurrent exchange.

Third, extravascular volume contraction causes the GFR to decrease. As a result, more Na^+ and water are reabsorbed in the proximal tubule. Because Na^+ delivery is decreased to the collecting duct, the juxtaglomerular apparatus secretes renin into the afferent arteriole. A renin-mediated increase in angiotensin II leads to an increase in aldosterone levels. Aldosterone binds to a cytoplasmic receptor found in distal renal tubular cells. The aldosterone–cytoplasmic receptor complex is translocated to the nucleus where the gene for the Na^+ pump is upregulated, transcribed, and translated. The Na^+ pump protein is transferred to the luminal surface, where it reabsorbs Na^+ in exchange for K^+. As K^+ depletion develops, luminal H^+,K^+,ATPase increases. Renal proton secretion decreases the H^+ concentration in serum, thereby increasing pH and HCO_3^-. As plasma K^+ levels begin to decrease due to diuretic-mediated K^+ depletion, aldosterone levels decrease. In the distal tubule, aldosterone promotes H^+ excretion in exchange for Na^+. As aldosterone levels decline, the amount of H^+ secreted by the tubule also declines. This represents an important feedback mechanism to prevent severe hypokalemia and metabolic alkalosis.

Finally, profound hypokalemia due to K^+ depletion causes K^+ to egress from somatic cells. Because all cells have a K^+-Na^+ pump that keeps intracellular levels of Na^+ low, Na^+ cannot move into the cell in exchange for the K^+ leaving the cell. Hydrogen ions; however, can move into the cell, thereby decreasing serum H^+ concentrations. Serum HCO_3^- levels rise in response.

Treatment of the hypokalemic, hypochloremic metabolic alkalosis caused by diuretics typically consists of KCl- or K^+-sparing diuretics. Potassium chloride therapy is advantageous in that both K^+ depletion and Cl^- deficiency are corrected.

Example: A 4-month-old girl with bronchopulmonary dysplasia has chronic CO_2 retention and is receiving furosemide and metolazone therapy. ABG results show pH 7.41, P_{CO_2} 58 mm Hg, P_{O_2} 53 mm Hg, and HCO_3^- 36 mmol/L. Her serum Na^+ is 137 mEq/L, serum K^+ 2.4 mEq/L, serum Cl^- 86 mEq/L, and serum total CO_2 36 mmol/L. How would one describe this acid-base problem?

Diagnosis: In this particular case, the child is slightly alkalemic due to (1) respiratory acidosis and (2) excessive metabolic alkalosis compensatory response because of the contraction alkalosis.

Patients with Bartter syndrome, which is caused by a malfunction or absence of the $2Cl^-$-Na^+-K^+ symporter in the thick ascending limb of the loop of Henle, also experience profound chloriduria and metabolic alkalosis.[71] The Cl^- depletion causes extracellular volume contraction and increases the serum HCO_3^-. Patients with cystic fibrosis can present with significant metabolic alkalosis due to the loss of Cl^- through sweating.[68,80]

Hydrogen ions can be lost through gastrointestinal or renal mechanisms. The secretion of HCl in the stomach leaves behind a cation and HCO_3^- in the serum. If the H^+ is lost from the body (e.g., vomiting), there will be a net increase in HCO_3^-. Renal H^+ losses can be accelerated by the presence of aldosterone,[81,82] angiotensin II,[82] and diuretics.

Hydrogen ion concentrations can decrease in response to changes in intracellular and extra cellular K^+ distribution. With significant K^+ depletion, K^+ moves out of the cell in order to maintain the ratio of intracellular and extracellular K^+ and a hydrogen ion moves in to maintain electrochemical neutrality. Sodium cannot be exchanged for K^+ because all cells have a Na^+-K^+ pump that pumps Na^+ out of the cell. Hydrogen ions move from the extracellular space into the intracellular space, thus causing a metabolic alkalosis.

The administration of HCO_3^- or substances that generate HCO_3^- such as citrate, acetate, or lactate will cause a rise in serum HCO_3^- levels. Because the kidney has the capacity to excrete HCO_3^- and decrease urinary acidification in response to an alkali load,[83] the alkalosis that develops in response to exogenous alkali is typically mild.

There are three mechanisms that act to return the pH toward 7.40 when a metabolic alkalosis develops. There are intracellular buffering mechanisms by which H^+, derived from intracellular proteins and phosphate, is released into the extracellular space. Lactic acid levels also increase and provide additional H^+ for buffering.[43] The kidney has the capacity to excrete HCO_3^- via beta intercalated cells in the distal tubule.[18] Compensatory respiratory acidosis is the third process by which the pH is returned toward normal. The degree of compensation via respiratory acidosis is somewhat limited because Pa_{O_2} also drops with hypoventilation and the body will not develop a compensatory respiratory acidosis to the point of hypoxemia. Nevertheless, ventilatory drive is decreased and Pa_{CO_2} values can increase to approximately 55 mm Hg. With respiratory compensation, the Pa_{CO_2} should increase by 0.25 to 1 times the HCO_3^- change.

There are factors such as volume depletion, aldosterone, and K^+ depletion that interfere with renal HCO_3^- wasting, thus maintaining the alkalosis.[84] Volume depletion decreases the amount of glomerular filtrate delivered to the proximal tubule; therefore, Na^+ and HCO_3^- reabsorption are increased. Aldosterone increases distal tubule H^+ secretion via the H^+,K^+-ATPase luminal pump.[81,82] Potassium depletion increases the rate of HCO_3^- reabsorption,[85] thus causing a metabolic alkalosis.

Occasionally, metabolic alkalosis can occur in patients who experience a rapid resolution of their chronic hypercapnia but cannot excrete HCO_3^- rapidly enough. Conversion of large amounts of lactic acid due to shock can also cause a metabolic acidosis.[86]

The effective treatment of a metabolic alkalosis depends on the recognition of Cl^-- responsive and -resistant processes. Sodium or potassium chloride replacement will lead to rapid resolution of the Cl^- depletion–induced metabolic alkalosis.[87] Blocking the reabsorption of HCO_3^- in the urine with acetazolamide can correct a metabolic alkalosis. The reabsorption of HCO_3^- is dependent on the presence of carbonic anhydrase, which is found in large amounts only in the convoluted proximal tubule.[88] Inhibition of carbonic anhydrase yields an inability of the tubule to reabsorb HCO_3^-. The use of even a single dose of acetazolamide, a carbonic anhydrase inhibitor, can lead to a rapid improvement of a metabolic alkalosis.[89,90]

Acetazolamide has also been effectively used to prevent altitude sickness.[91-93] Acetazolamide causes a metabolic acidosis by decreasing the reabsorption of HCO_3^- in the proximal tubule. In response to a metabolic acidosis, the respiratory drive increases, thereby increasing O_2 levels.

Individuals who have sodium chloride–resistant metabolic alkalosis typically have increased mineralocorticoid activity or pseudohyperaldosteronism (Liddle syndrome) or may be K^+ depleted.[94] Patients with apparent mineralocorticoid activity experience growth failure, hypertension, and a chronic hyokalemic metabolic alkalosis.[95] Mineralocorticoid activity can be blocked with spironolactone,[72,96,97] triamterene,[98] or amiloride.[97]

Although not commonly used, the intravenous infusion of hydrochloric acid has also been used to correct a severe metabolic alkalosis.[99-101]

Respiratory Alkalosis

Respiratory alkalosis is caused by a process whereby the pH rises in response to a decreasing P_{CO_2}. The P_{CO_2} falls when ventilatory losses of CO_2 exceed CO_2 production. Generally, ventilation can be increased due to central or peripheral neural stimulation, mechanical ventilation, or voluntary effort.

The renal compensatory mechanism is a metabolic acidosis. Buffering by H^+ release from intracellular sources constitutes the first defense against respiratory alkalosis.[10] Amazingly, buffering is complete in minutes and persists for at least 2 hours.[102] In response to acute respiratory alkalosis, the HCO_3^- decreases by 1 to 3 mmol/L for every 10–mm Hg decrease in Pa_{CO_2}.

The kidney compensates in response to respiratory alkalosis by reducing the amount of new HCO_3^- generated and by excreting HCO_3^-.[30] The process of renal compensation occurs within 24 to 48 hours.[28] The stimulus for the renal compensatory mechanism is not pH, but rather P_{CO_2}.[103,104] In chronic respiratory alkalosis, the plasma HCO_3^- is decreased 2 to 5 mmol/L for every 10–mm Hg decrease in P_{CO_2}. The only means to treat a respiratory alkalosis is to correct the underlying disorder responsible for causing the disorder.

Table 14-6
Simple Acid-Base Disorders

Type of Disorder	pH	$Paco_2$	HCO_3^-
Metabolic acidosis	↓	↓	↓
Metabolic alkalosis	↑	↑	↑
Acute respiratory acidosis	↓	↑	↑
Chronic respiratory acidosis	↓	↑	↑
Acute respiratory alkalosis	↑	↓	↓
Chronic respiratory alkalosis	↑	↓	↓

From Schrier RW: Renal and Electrolyte Disorders, 3rd ed. Boston, Little Brown and Company, 1986, p. 146.

Simple Acid-Base Disorders

Acid-base problems generally fall into two broad categories: those with a single primary disorder coupled with a compensatory response, a simple acid base disorder, or those in which two or more primary disorders occur together, a mixed acid-base disorder. The type of acid-base disorder can be determined by evaluating the pH, P_{CO_2}, and the HCO_3^-. In a simple acid-base problem, the P_{CO_2} and the HCO_3^- always move in the same direction (Table 14-6). Expected arterial CO_2 values in patients with metabolic acidosis can be calculated based on the serum HCO_3^- concentration according to the following simplified equation[105]:

$$Pa_{CO_2} = 1.5(HCO_3^-) + 8$$

Movement of the P_{CO_2} and HCO_3^- in opposite directions indicates a mixed acid-base disorder. Assessment of the appropriateness of the compensation using Tables 14-2 and 14-4 and Figure 14-12 can also be helpful in uncovering a mixed acid-base problem.

Example: A 2-year-old boy with hypochloremic metabolic alkalosis is diagnosed as having Bartter syndrome. His initial blood gas result was pH 7.42, P_{CO_2} 50 mm Hg, and HCO_3^- 32 mmol/L.

Diagnosis: This is an example of simple acid-base disorder with a metabolic alkalosis and a compensatory respiratory acidosis.

Mixed Acid-Base Disorders

A mixed acid-base disorder is a combination of two primary disorders.[49] Recognition of a mixed acid-base disorder is dependent on determining whether the compensatory process was adequate and appropriate. Frequently, the blood gas result will fall outside of the predictive bands found in an acid-base nomogram (see Fig. 14-12). Patients with mixed acid-base disorders may have a serious deviation of the pH, while others may have a normal pH. When there is a significant deviation of the pH, one of the two primary disorders blocked the compensation for the other.

Example 1: A 9-month-old boy with renal tubular acidosis is unable to take his medication due to the respiratory distress associated with respiratory syncytial virus. His admission arterial blood gas results are pH 7.19, Pa_{CO_2} 56 mm Hg, Pa_{O_2} 67 mm Hg, and HCO_3^- 17 mmol/L.

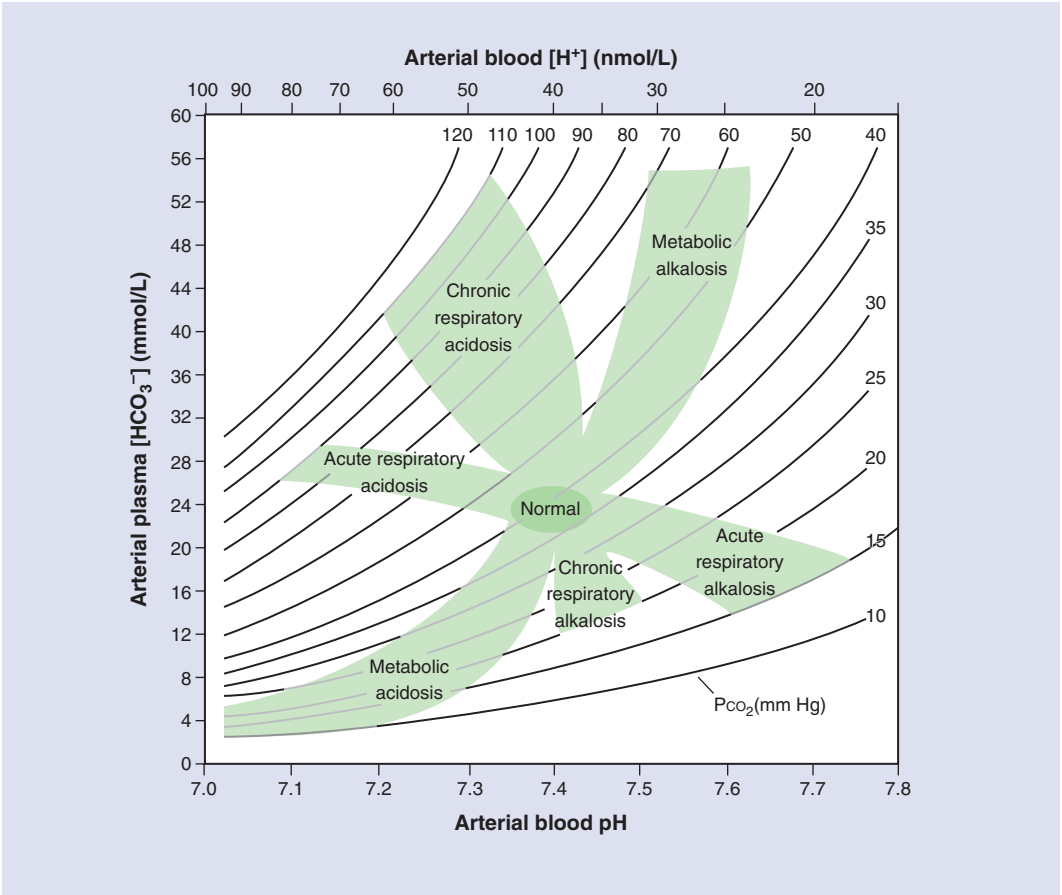

Figure 14-12 Acid-base nomogram. The nomogram bands represent 95% confidence limits for an acid-base disorder. (Redrawn from Brenner B, Rector FC: Acid-base disorders. In Brenner B, Rector FC [eds]: The Kidney, 7th ed. Philadelphia, WB Saunders, 2004, p. 938, with permission.)

Solution: This is an example of a mixed acid-base disorder with a metabolic acidosis and acute respiratory acidosis. Note that the P_{CO_2} and HCO_3^- do not move in the same direction.

Example 2: A 13-month-old girl presents with a 2-day history of nonbilious vomiting and diarrhea. The child has vomited 10 times over the past 36 to 48 hours. Initial laboratory tests show a serum HCO_3^- of 14 mmol/L.

Diagnosis: This is an example of a mixed acid-base disorder because the patient has a metabolic acidosis but also has metabolic alkalosis due to vomiting with loss of HCl. The metabolic alkalosis is not obvious due to the severity of the metabolic acidosis. Without the vomiting, the metabolic acidosis would have been worse.

Occasionally, the amount of compensation is excessive given the clinical situation. For example, children presenting with aspirin intoxication will typically have Pa_{CO_2} values lower than expected based on the acidosis caused by the aspirin alone.[106] The excessive respiratory alkalosis is attributable to the stimulatory effect that aspirin has on ventilation.

Patients with chronic lung disease typically have high P_{CO_2} values and an appropriate compensatory metabolic alkalosis. The addition of diuretics, which are frequently used to decrease alveolar interstitial edema, causes serum HCO_3^- values to increase to levels greater than expected on the basis of the respiratory acidosis alone. The blood gas results are frequently consistent with a simple metabolic alkalosis.[107] A patient's history may be the only means by which the mixed acid-base disorder may be suspected.

Example: A 15-month-old girl with bronchopulmonary dysplasia receives furosemide at a dosage of 1 mg/kg/day. Her typical blood gases on 0.5 L of nasal O_2 are as follows: pH 7.49, Pa_{CO_2} 55 mm Hg, Pa_{O_2} 87 mm Hg, and HCO_3^- 42 mmol/L.

Diagnosis: This patient has mixed acid-base disorder; chronic respiratory acidosis, compensatory metabolic alkalosis, and metabolic alkalosis due to a severe contraction alkalosis. The child develops a viral pneumonia. The arterial blood gas results are pH 7.33, Pa_{CO_2} 74 mm Hg, Pa_{O_2} 67 mm Hg, and HCO_3^- 39 mmol/L. If one were not familiar with the case, this would appear to be an acute respiratory acidosis with an incomplete compensatory metabolic alkalosis; however, with an increase of the $Paco_2$ value by 34 mm Hg (above 40 mm Hg), one would anticipate an acute HCO_3^- compensation of only 3 to 4 mmol/L. Moreover, the blood gas value falls into the chronic respiratory acidosis prediction band.

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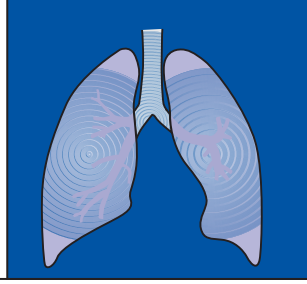

CHAPTER 15 Diagnostic and Therapeutic Procedures

Robert E. Wood

TEACHING POINTS

- The most serious complication of a diagnostic procedure, other than death of the patient, is to do the procedure and obtain the wrong answer.
- Patients (and their families) should be as comfortable and safe as possible during procedures. Sedation/anesthesia can be critical elements in achieving this goal, but so are more subtle factors such as body language and the words one uses.
- A diagnostic procedure is indicated when there is a critical lack of information necessary for the care of the patient, which is best obtained by that procedure.
- Every human activity has risk, even the lack of activity. We must balance risk and benefit in planning and performing diagnostic procedures. Not doing a diagnostic procedure may increase the patient's risk, by forcing the physician to treat by Levi's method (the seat of one's pants), rather than on the basis of firm knowledge.
- Cognitive errors (wrong procedure, wrong analysis, etc.) can be as serious as technical errors.
- A, B, C: Tend to airway, breathing, then anything else.

GENERAL PRINCIPLES

Invasive procedures should be performed only when less invasive or noninvasive or less expensive procedures cannot yield the same or equivalent information. They should be performed only with the proper equipment and with sufficient numbers of trained and skilled personnel (both operator and assistants). The procedure should be performed in an appropriate setting, such as a well-equipped and staffed procedure (or operating) room or an intensive care unit, rather than at the patient's bedside.

Careful attention should be given to the timing of procedures. In general, earlier diagnosis results in earlier selection of the most effective therapy and avoids the confounding influence of empirical therapy. This should in turn result in savings of more than just money. Elective procedures should, in general, not be performed at hours that will result in significant delays in the processing of diagnostic specimens. Finally, scheduling of elective procedures to avoid meal times and to possibly coincide with normal nap times may reduce stress and strain on patients as well as parents.

Careful and appropriate monitoring of the patient's vital signs (pulse, respiratory rate, and blood pressure) and physiologic status (mental status, oxygen saturation) before, during, and after the procedure is essential. In general, one person (not the operator) should be responsible for monitoring the patient and responding to changes in status.[1]

Patients should be comfortable during and after procedures and within the limits of safety, reasonable convenience, and cost. In many, if not all, cases, this means sedation, which must be carried out with skill and with appropriate agents. If adequate provision cannot be made for safe and effective sedation and monitoring of the patient, then general anesthesia should be used.

SEDATION AND ANESTHESIA FOR PROCEDURES

Optimal sedation or anesthesia of a patient in preparation for a procedure provides for relief of anxiety and pain and also ensures that the patient remains relatively still during the procedure. Although general anesthesia can achieve all these goals, sedation can be used safely and effectively in most children for most diagnostic procedures. On the other hand, physicians should not hesitate to use general anesthesia whenever it is in the patient's best interests, whether for safety or for comfort. Examples of situations in which general anesthesia may be appropriate for procedures normally done with sedation include patients with an unstable airway, patients who have been traumatized by numerous prior procedures, patients who are known to respond poorly to conventional sedation, and patients for whom a prolonged or difficult procedure is anticipated. Current anesthetic techniques have greatly reduced the risk traditionally associated with general anesthesia,[2,3] and patients should not be deprived of the benefits of general anesthesia when it is appropriate, even though it is more expensive.[4] With either general anesthesia or sedation, monitoring of the patient must not stop when the procedure is over, because respiratory depression may last longer than sedation, especially when the stimulation associated with the procedure is no longer a factor.

Sedation is a state of depressed awareness between the fully conscious state and surgical anesthesia. Responsiveness to pain and other stimuli is decreased, as are reflexes. As the depth of sedation increases, respiratory drive is depressed. Careful and continuous monitoring is necessary to ensure

patient safety. Current guidelines for sedation[1,5] require that vital signs, oxygenation, and the patency and adequacy of the airway be monitored continuously during sedation. C*onscious sedation* is a buzzword and refers to the level of sedation at which the patient maintains protective reflexes and response to verbal commands. Conscious sedation may be most appropriate for nonpainful procedures, such as radiographic imaging studies. In practice, many (especially younger) pediatric patients require a deeper level of sedation to safely and effectively tolerate potentially painful procedures. Therefore, extra care must be taken to provide effective monitoring, and sedative agents should be chosen with regard to duration of action.

The choice of medications for pediatric sedation is an important determinant of success. Children (and their parents) are anxious about impending medical procedures. Children who must undergo repeated procedures are particularly vulnerable to psychologic trauma and should be handled with extra care.[6] Agents that partially or totally block short-term recall (e.g., benzodiazepines) can be extremely valuable. However, these agents are not in themselves usually sufficient for effective sedation for invasive procedures except perhaps at high doses. In general, both an analgesic agent and an anxiolytic agent should be used for any procedure involving pain; analgesia and sedation are not necessarily the same. Both types of agents depress the respiratory drive, and their effects may be additive.

Because children often become upset before a procedure, some form of presedation is useful if there is no contraindication such as unstable upper airway obstruction. Chloral hydrate has traditionally been used for this purpose; some concerns have been raised about this agent (potential mutagenicity in bacterial studies), but it has been approved for use in children by the American Academy of Pediatrics.[7] Other medications can be used, including oral[8] or nasal midazolam or ketamine.[9] A child who is comfortably sleepy separates more easily from a parent and can then be given additional medications to achieve the degree of sedation needed for the procedure itself. If the child is upset and crying at the time that medications are being given for sedation, larger doses will be required. Some children become excited and disinhibited when given sedative agents; this is usually only a stage through which they pass on the way to sedation, but it is more likely to be a problem if inadequate initial doses are used.

Chemical sedation is more readily controlled if the agents are given by the intravenous (IV) route because there is less uncertainty regarding absorption and the time course of the medication's effect. It may be helpful to place a lidocaine and prilocaine cream (EMLA Cream)[10] on potential IV sites before presedation to facilitate IV placement after the child has become somewhat sedated. In general, fractional dosing should be used and the patient's response assessed before additional medications are given. The response to medications such as midazolam and narcotics should be maximal within 2 to 3 minutes. Rapid infusion leads to a high concentration in the brain, with hypotension and respiratory depression or even apnea; infusion over 60 to 90 seconds is equally efficacious and safer than bolus infusion.

There are many safe and effective techniques for chemical sedation (Table 15-1),[11] and the operator should choose one or two and develop expertise with these, including a thorough knowledge of the pharmacology of the drugs, their side effects, and interactions. When there is doubt about a technique, consultation should be obtained from a pediatric anesthesiologist.

Table 15-1
Drugs Commonly Used for Pediatric Sedation

Agent	Dose/Route	Comment
Diphenhydramine	1 mg/kg PO	This is a very mild sedative.
Chloral hydrate	75-100 mg/kg PO	Maximum dose is 2 g; this medication may cause gastric irritation.
Midazolam	0.75 mg/kg PO	Onset occurs in 10-20 min.
	0.4 mg/kg nasal	—
	0.05-0.2 mg/kg IV	Maximal effect occurs in 2-3 min.
Meperidine	1-4 mg/kg IV	—
Morphine sulfate	0.05-0.1 mg/kg IV	—
Fentanyl	1-3 µg/kg IV	This medication may cause rigid chest syndrome.
Ketamine*	2-10 mg/kg IM	This medication should be used with midazolam and atropine.
	1-3 mg/kg IV	—
Methohexital*	1-2 mg/kg IV	This medication provides 1-5 min of general anesthesia.
Pentobarbital	1-3 mg/kg IV	This medication is used primarily for imaging studies.
	2-6 mg/kg IM	—
	2-6 mg/kg PO	—
Reversal Agents†		
Naloxone	Neonates: 0.01-0.1 mg/kg IV	—
	Infants <20 kg: 0.1 mg/kg IV	—
	Children >20 kg: 2 mg IV	—
Flumazenil	Children <20 kg: 0.01 mg/kg IV	—
	Children >20 kg: 0.2 mg IV	—

PO, oral; IM, intramuscular.
*Agents that may require special (anesthesia) qualifications for use.
†The effect of such agents (especially reversal of respiratory depression) may not last as long as that of the primary agent; repeated doses may be required, and careful monitoring is always necessary.

Patients (and their parents) who are under stress are more open to suggestion than they ordinarily would be; that is, they behave as though they are in a light hypnotic trance. Physicians must be aware of this phenomenon and use it for the patient's benefit. Inadvertent negative suggestions can have a dramatic impact on the patient's (or parents') behavior. One should be careful to use positive suggestion, avoiding negatives, and to prepare the patient for an experience that will be as relaxed and comfortable as possible. Children in particular are quite suggestible, and operators skilled in the techniques of hypnosis or simple distraction can often perform minor procedures with no sedation at all.[12] Because many pediatric practitioners are not necessarily skilled in these techniques, it seems most practical to combine simple relaxation and positive suggestion with chemical sedation.

Sedation diminishes protective reflexes; one of the major risks of sedation is aspiration of gastric contents. Patients should have nothing by mouth for several hours before sedation. Clear fluids may be given up to 2 hours before sedation.[13,14] Young infants may become dehydrated or hypoglycemic if they have nothing by mouth for too long, so IV fluid may be necessary before a procedure.

After completion of the procedure, the patient must be carefully monitored to ensure safe emergence from sedation. Some practitioners reverse the effect of the sedation (e.g., using naloxone, flumazenil, or both agents).[15] However, this practice may have serious shortcomings. The effect of the reversing agent may not last as long as that of the primary agent; therefore, patients treated with reversing agents must be monitored longer and more carefully. Furthermore, extremely rapid reversal of sedation can be frightening and disorienting; it is kinder and gentler to allow the patient to awaken naturally as long as vital signs are stable. On the other hand, reversal agents should be available for use in an emergency when IV sedation is performed.

There are only semantic differences between deep sedation and light general anesthesia. In many cases, it is extremely advantageous to utilize the services of a pediatric anesthesiologist for children undergoing invasive procedures. The agents used by anesthesiologists have more rapid onset, and recovery is usually much faster, than with the agents traditionally used by pediatricians for sedation. An anesthesiologist can take full responsibility for monitoring the child, as well as for recovery afterwards. The result can be a safer and more comfortable experience for the child.

BRONCHOSCOPY

Indications

Bronchoscopy affords direct visual inspection of the upper and lower airways and allows collection of diagnostic specimens such as washings, brushings, or biopsies. The most common indications for diagnostic bronchoscopy in pediatric patients include stridor, atelectasis, recurrent or persistent pneumonia, suspected foreign body aspiration, persistent wheezing unresponsive to medical therapy, hemoptysis, persistent cough, suspected congenital anomalies, upper airway obstruction, and suspected vocal cord paralysis. Because upper airway lesions are frequently associated with lower airway lesions,[16,17] it is usually appropriate to examine both the upper and lower airways even when the primary indication for the procedure involves the upper airway (e.g., stridor, suspected vocal cord paralysis).

Bronchoscopy can be used for therapeutic purposes as well. Extraction of foreign bodies from the airways, removal of tissue masses or other forms of airway obstructions such as mucus plugs, and therapeutic bronchopulmonary lavage are primary examples of therapeutic bronchoscopy.

Contraindications

Bronchoscopy is contraindicated when other, less invasive or less risky procedures can yield the same diagnostic information or therapeutic benefit. Relative contraindications (some of which may in themselves be indications) include massive hemoptysis, severe airway obstruction, severe hypoxemia, severe bronchospasm, and bleeding diatheses such as thrombocytopenia. All these conditions require additional care with sedation and anesthesia, instrumentation, airway management, preparation of the patient, and monitoring before, during, and after the procedure. None, however, is an absolute contraindication to bronchoscopy if the potential benefit of the procedure exceeds the potential risk. In some circumstances in which the potential benefit to the patient is marginal and the risk to medical personnel is significant (such as patients with cavitary tuberculosis), bronchoscopy may be contraindicated.

Instrumentation

Bronchoscopy may be performed with either rigid or flexible (fiberoptic) instruments. In general, depending on the training and preference of the operator and the availability of suitable instruments, either type of bronchoscope can be used for most purposes. However, there are some specific situations in which a flexible instrument has special advantages. These include examination of the lower airways in a patient who is intubated with an endotracheal or tracheostomy tube (the flexible bronchoscope can be passed through the tube without having to extubate the patient) and a patient in whom there is an unstable cervical fracture, cervical ankylosis, or mandibular hypoplasia (these conditions all make it difficult or impossible to pass a rigid bronchoscope into the trachea through the mouth). A flexible bronchoscope has a much smaller diameter than a rigid instrument and thus can be passed farther into the distal airways. Because it is flexible, it can also reach the upper lobes more easily than a rigid instrument.

There are situations in which the use of a rigid bronchoscope is necessary or more advantageous. These include the extraction of tracheal or bronchial foreign bodies and the evaluation of patients with suspected H-type tracheoesophageal fistula, laryngoesophageal cleft, and bilateral abductor paralysis of the vocal cords. Because the rigid bronchoscope is passed through the mouth, it yields a better view of the posterior aspect of the larynx and trachea than a flexible bronchoscope, which is usually passed through the nose and thus approaches the larynx from the posterior aspect, giving a better view of the anterior part of the larynx and upper trachea.

FLEXIBLE BRONCHOSCOPES

Flexible bronchoscopes are constructed of thousands of glass fibers that carry the image (some instruments have a video chip at the tip to generate the image) and illumination, and their distal tips can be angulated to direct the instrument into the desired anatomic location. Most of these instruments have a small but functional suction channel, which allows the instillation and retrieval of liquids such as saline (for diagnostic lavage or clearing secretions from the lens) and medications such as topical anesthetics or antibiotics. The most important aspect of a flexible bronchoscope is that it must be small enough to allow the patient to ventilate around it; the standard "pediatric" instruments have a diameter of 2.8 or 3.7 mm. An ultrathin instrument with a diameter of 2.2 mm (but no suction channel) is also available. The standard pediatric flexible bronchoscope can be used in patients of virtually any age, but may result in total airway obstruction in children who weigh less than 2.5 kg. The smallest "adult" flexible bronchoscope is 4.9 mm in diameter and can be used (if necessary) in children as young as about 4 years. Although the potential for airway obstruction is higher with this larger instrument, it has a larger suction channel, and the image quality is higher.

The image seen through a flexible bronchoscope is composed of several thousand points of light and color, each representing the light transmitted by a single glass fiber. Although the resolution of the flexible instrument is necessarily lower than that of a rigid bronchoscopic telescope, it is nevertheless quite adequate for diagnostic purposes. The glass fibers are fragile. Flexible bronchoscopes should be handled only by responsible, well-trained persons. A flexible bronchoscope should never be passed through a patient's mouth (even under general anesthesia and even through an endotracheal tube) without a suitable bite block in place; the cost in dollars per millisecond can be astronomical.

RIGID BRONCHOSCOPES

Rigid bronchoscopes are essentially metal tubes; it is difficult to see well through a rigid bronchoscope unless a telescope is used. The glass rod (Hopkins) telescope[20] gives infinite resolution and good illumination. Telescopes are available with distal prisms to facilitate views of the upper lobes. The greatest advantage of a rigid bronchoscope is its relatively large inner diameter, through which one can ventilate the patient's lungs and pass a wide variety of instruments.

Techniques for Bronchoscopy

Bronchoscopy is usually performed with the patient supine and the bronchoscopist standing (or sitting) behind the patient's head. A flexible bronchoscope allows other positions for both the patient and bronchoscopist.

Care should be taken to achieve effective topical anesthesia of the larynx before the tip of the bronchoscope is passed through the glottis. Although some bronchoscopists use transtracheal injection of lidocaine in adults, this is a dangerous practice in children and is unnecessary. For flexible bronchoscopy, simple instillation of lidocaine into one nostril (0.5 to 1 mL of 2% lidocaine) usually results in effective anesthesia of the nose and larynx. Additional lidocaine (0.5 to 1 mL of 2% lidocaine) is sprayed onto the larynx through the suction channel of the bronchoscope. For rigid bronchoscopy, the larynx can be directly sprayed with lidocaine after exposure with a laryngoscope. A 1% solution is used below the glottis to reduce the amount of lidocaine absorbed by the patient. The total dose should not exceed approximately 7 mg/kg.[21]

FLEXIBLE BRONCHOSCOPY

After adequate sedation or anesthesia, the upper airway is anesthetized with topical lidocaine. The flexible bronchoscope is passed through one nostril. In some circumstances, the bronchoscope may be passed through the mouth, but this is more difficult than transnasal passage, is less informative, and risks damage to the instrument if an effective bite block is not used. Other approaches include passage through an endotracheal tube (oral or nasal), a nasopharyngeal tube, or a tracheostomy tube or stoma.

As the bronchoscope is passed into the trachea, the patient must be assessed for adequacy of ventilation and topical anesthetic effect. If necessary, supplemental oxygen can be given through the suction channel of the flexible bronchoscope, but care must be taken not to wedge the tip of the instrument into a bronchus while oxygen is being passed through the channel; this will prevent the development of a pneumothorax. The tip of the bronchoscope is then directed to systematically inspect all the airways.

RIGID BRONCHOSCOPY

Rigid bronchoscopy is almost always performed with general anesthesia. Ventilation must be interrupted while a laryngoscope is inserted to allow the bronchoscope to reach the larynx. The tip of the bronchoscope is gently passed through the glottis and into the trachea under direct vision. When the shaft of the bronchoscope has been advanced far enough that the ventilating side holes are below the glottis, the anesthesia circuit is attached to the bronchoscope, and ventilation can be resumed. When forceps or other instruments are passed through the bronchoscope, ventilation must be interrupted unless a Venturi jet ventilation system is being used or flexible instruments are being passed through a side port. Some operators use the glass rod telescope alone, with the patient breathing spontaneously. This technique requires careful attention to anesthetic technique.

The patient's neck must be somewhat extended and the mandible brought forward to pass a rigid bronchoscope into the trachea. This allows good visualization of the laryngeal anatomy, but distorts the airway dynamics. For evaluation of airway dynamics, flexible instruments are superior.

In many patients, a combination of both rigid and flexible instrumentation provides optimal diagnostic and therapeutic results.

BRONCHIAL BRUSHING

Small-diameter brushes can be passed through the suction channel of flexible bronchoscopes (or through a rigid bronchoscope) to obtain specimens containing large numbers of epithelial cells. In adults, this is often done in the evaluation of suspected malignancy (which is rare in pediatric patients). A more common use for bronchial brushing is to obtain microbiologic specimens that are (supposedly) uncontaminated by secretions from the upper airways. Microbiology

specimen brushes are protected by plastic sheaths, which in turn are protected by outer sheaths plugged with wax.[22,23] As the catheter/brush assembly traverses the bronchoscope, the wax plug and outer catheter prevent contamination of the brush with material inside the suction channel of the bronchoscope. The assembly is passed under direct vision to near the desired location, and the inner catheter is advanced out the end of the outer catheter, dislodging the wax plug (which melts or is coughed out later). The brush is then advanced into position, and the specimen is obtained by repeatedly moving the brush against the bronchial wall; it is then withdrawn into the inner catheter. The inner catheter is withdrawn into the outer catheter, and the entire assembly is then removed from the bronchoscope. The outer catheter may then be wiped with alcohol; the inner catheter and then the brush are extended, and with sterile wire cutters, the brush is cut off into a suitable specimen container.

This technique can be used to obtain a lower airway specimen uncontaminated by secretions previously suctioned through the bronchoscope. Unfortunately, many patients aspirate oral secretions during topical anesthesia and passage of the bronchoscope, so a specimen obtained with a microbiology specimen brush is clearly not guaranteed to be uncontaminated by upper airway flora.

However, the smallest specimen brush is too large to pass through the suction channel of the pediatric flexible bronchoscope, so in most pediatric patients, the clinician must be content with direct aspirates or specimens from bronchoalveolar lavage (BAL) for microbiologic studies (see later section). If the child is large enough for a small adult bronchoscope (4.9-mm diameter; 2.0-mm suction channel), then a microbiology brush may be used.

Complications of Bronchoscopy

The complications of bronchoscopy[24-30] depend on the technique and instruments used, the underlying risk factors of the patient, the skill, experience, and diligence of the bronchoscopy team, and, of course, luck. The bronchoscopist should identify risk factors in advance, reduce the risk when possible, and carefully balance risk against benefit when choosing instruments and techniques.

In general, complications may be classified as mechanical, physiologic, infectious, and cognitive. Mechanical complications include trauma to the airway and airway obstruction and are best prevented by the careful selection and use of instruments. If a bronchoscope is passed through an area of compressed or stenosed airway, mucosal edema or accumulation of mucus may occlude that airway after the procedure. Judicious use of systemic steroids may be indicated when the risk of edema after the procedure is high. Epistaxis or bronchial hemorrhage can result from trauma from the bronchoscope itself or from instruments passed through the bronchoscope. Perforation of the tracheobronchial mucosa may lead to air leaks (which may require the insertion of a chest tube) or hemorrhage; perforation is most common when transbronchial biopsy is performed. Hemorrhage usually is transient, and no intervention is needed except suctioning or perhaps local lavage with ice-cold saline or 1:10,000 epinephrine. Severe hemorrhage may require selective intubation of the contralateral mainstem bronchus, packing of the bronchus, or the use of a bronchial-blocking balloon catheter. Clots remaining in the airways after hemorrhage may require removal by extensive suctioning or even rigid bronchoscopy.

Physiologic complications result from alterations in gas exchange or vagal tone. Hypoxemia may develop when the airway is obstructed by the bronchoscope, when ventilation is interrupted (as during the extraction of a foreign body), or as a result of respiratory depression induced by sedation. Flooding of the airways with saline (or blood) also may lead to hypoxemia. Hypercarbia is usually the result of excessive sedation or anesthesia but may also occur in the setting of high-grade airway obstruction. Brief hypercarbia is usually of little consequence, however, and the administration of supplemental oxygen during the procedure can usually prevent or reduce the magnitude of hypoxemia.

Changes in vagal tone (usually because of insufficient topical anesthesia) can lead to bradycardia. Other cardiac dysrhythmias may occur, especially in patients with hypoxemia or preexisting cardiac problems. Laryngospasm and bronchospasm may also occur; both can be prevented or minimized by effective topical anesthesia. Similarly, ineffective topical anesthesia in the distal airways can result in severe coughing, which may then lead to mechanical trauma. On the other hand, excessive use of topical agents (usually lidocaine) can result in hypotension, seizures, and other effects. Bronchoscopy can also result in increased intracranial pressure.[31]

Infectious complications of bronchoscopy may affect either the patient or the bronchoscopy personnel; care must be taken to ensure that instruments are not contaminated from the previous patient and that proper technique is used to protect patient and personnel alike.[32-35] Although children are less likely than adults to aerosolize *Mycobacterium tuberculosis* during coughing, bronchoscopists have been infected in this way by pediatric patients; of course, other infectious agents can also be spread in this fashion. Patients may aspirate oropharyngeal secretions, thus contaminating their lower airways, and infection can be spread from one area of the lungs to another during bronchoscopy. Finally, pseudoinfections can occur when the specimens, but not the patient, are contaminated; this can result in considerable diagnostic and therapeutic confusion.[36,37]

Cognitive complications include the failure to recognize pathology, the failure to perform a procedure when it is indicated, the performance of procedures when they are not indicated, and the use of inappropriate instruments or technique. The most serious complication of a diagnostic procedure, other than death of the patient, is to fail to gain the desired information (or to reach the wrong diagnostic conclusion) while placing the patient at all the risk, cost, and discomfort of the procedure.

BRONCHOALVEOLAR LAVAGE

One of the more important aspects of diagnostic bronchoscopy is the retrieval of specimens from the distal airways. Although direct aspiration of secretions from the proximal airways can be useful, a more representative and informative specimen can be obtained by washing a relatively large area of the distal airways and alveolar spaces with sterile saline. Strictly speaking, in bronchoalveocan lavage (BAL),[38,39] a

sufficient volume of saline is used to ensure that the fluid subsequently aspirated contains some of the fluid lining of the alveolar surface. When relatively small volumes of saline are used, the term *bronchial lavage* is often used. In practice, especially in pediatric patients, it may be difficult to ascertain the minimum volume necessary to achieve BAL.[40] On the other hand, for the most common clinical indications in pediatric patients, it may make very little difference to the interpretation of the data whether a bronchial lavage or BAL is performed. This is especially true in the diagnosis of pulmonary infections.

Indications

BAL is performed in pediatric patients primarily to obtain a representative sample from the distal airways for microbiologic studies.[40] For example, patients with pulmonary infiltrates and presumed pulmonary infection who do not produce sputum are candidates for diagnostic BAL. On the other hand, most pediatric patients with pneumonia have a viral infection and do not require bronchoscopy or BAL; immunosuppressed patients, those who have recurrent or persistent pneumonia (including those in whom therapy has failed), or those with unusual clinical circumstances may benefit from the procedure, however. Young patients with cystic fibrosis, in whom it may be difficult to ascertain the flora of the lower respiratory tract, may also benefit.[41,42]

BAL is indicated in the investigation of interstitial pulmonary disease. Although such use in adults has been relatively disappointing in terms of the ability to make specific diagnoses of noninfectious entities, it is nevertheless reasonable to use BAL to exclude infection before the decision to perform an open lung biopsy is made.[43,44]

In addition to microbiologic studies, the content of proteins, cells, and other constituents of the airway surface fluid may be determined.[45] The cellular component may be of particular interest.[46-48]

Contraindications

There are no absolute contraindications to BAL if it is skillfully performed with suitable technique. Only about half the saline used for BAL is recovered, leaving the rest in the alveolar spaces and distal airways. Although this is absorbed over several hours, significant impairment of gas exchange may result from flooding of the alveolar spaces with saline or from the airway occlusion required during the procedure.[49] Patients who are profoundly hypoxic may suffer further respiratory embarrassment as a result of BAL; the relative effect can be minimized by the use of a smaller instrument (which would wedge into a more distal airway, thus washing a smaller volume of lung). Patients with severe pulmonary hypertension may be at high risk for complications.[28]

Instrumentation

Successful and safe BAL requires that the saline be delivered to a discrete portion of the lungs. Therefore the delivery system, a flexible bronchoscope or a catheter, should be gently wedged into a bronchus. Merely instilling saline into a endotracheal tube, for example, may be unsafe or ineffective because large volumes produce respiratory distress and small volumes do not reliably reach the alveoli. In either case, the amount of saline recovered by suction is relatively small.

Techniques

BAL is most readily performed with a flexible bronchoscope,[39] which can be directed to the area of primary interest. The bronchoscope is advanced into the selected bronchus until its tip is gently wedged in place. Sterile saline is instilled through the suction channel; this may be done with a syringe, or if large volumes will be used, tubing from a reservoir may be connected to the suction adapter. When the desired volume has been instilled, the fluid is withdrawn using gentle suction.

When a rigid bronchoscope is used, a catheter must be passed through the bronchoscope and wedged into position. Such catheters are small relative to a flexible bronchoscope and therefore sample a more limited region of the lung than BAL performed with a flexible bronchoscope. It may also be more difficult to direct the catheter into a specific bronchus.

Nonbronchoscopic BAL may be performed by passing a catheter through an endotracheal or tracheostomy tube.[50,51] In special circumstances, this might be done with fluoroscopic guidance, but nonbronchoscopic BAL is usually done in the setting of diffuse lung disease, when there is relatively little need to direct the catheter to a specific site. As with rigid bronchoscopes, nonbronchoscopic BAL samples a smaller site than flexible bronchoscopic BAL. Nevertheless, significant diagnostic information can often be obtained with relatively little cost and risk.

For achieving some measure of reproducibility and standardization of BAL technique in adults, the same volumes and aliquot numbers are used for each procedure. Typically, these may be three 100-mL aliquots or five 50-mL aliquots.[38] Cells migrate more slowly than soluble constituents, and the total yield of cells approaches a limit as the number of aliquots increases.[52] Various markers have been used to determine the dilution of the epithelial lining fluid (ELF); urea is used most commonly. It is assumed that urea exists in the ELF at the same concentration as in plasma; therefore the ratio of urea in BAL fluid to urea in plasma gives a measure of the dilution of ELF in the BAL fluid.[53] However, BAL does not sample a static space or volume of airway surface liquid. There is a constant exchange of fluid, electrolytes, and other soluble constituents across the airway and alveolar epithelium.[54-56] Thus the concentration of any material or cell type in the BAL specimen depends on the volume of fluid used for the lavage, the efficiency of mixing and recovery, the initial concentration in the ELF, the time during which the fluid resides in the alveolar space, and the rate of flux of the material or fluid into the BAL fluid during the procedure.

In pediatric subjects, there is no agreement regarding standard technique. Wedging the same size bronchoscope into an airway in children of various ages and sizes (or using a different size bronchoscope) results in washing a greatly varying proportion of total lung volume. For example, in a newborn, a 3.5-mm flexible bronchoscope may wedge into a lobar bronchus, whereas in a 4-year-old child, it may wedge into a subsubsegmental bronchus. It is unclear whether using the

same volume of saline in these two situations results in washing similar surface areas. Reported techniques include volumes of 0.5 to 3 mL/kg or the use of a fixed volume (usually two aliquots of 10 mL each) for each patient almost regardless of age.

In general, it is useful to perform BAL with more than one aliquot of saline. Some authorities discard the return from the first aliquot, suggesting that it represents "bronchial" rather than "alveolar" washings.[57] The composition of the first aliquot is indeed somewhat different from subsequent aliquots, but there is no practical way to obtain a pure bronchial or alveolar fraction. In pediatric practice, there is little rationale or justification for discarding the first aliquot or processing it differently because material from the proximal airways is washed distally and therefore contaminates the subsequent aliquots.

If BAL is being performed to evaluate a specific radiologic lesion, then the bronchoscope should be positioned in the appropriate bronchus. On the other hand, if there is no localized area of disease, it is advantageous to choose the lingula or right middle lobe for lavage. These bronchi are relatively long and relatively horizontal, and the tip of the bronchoscope is more likely to remain comfortably wedged in the bronchus (even with coughing) than if it is wedged into a basal segment of one of the lower lobes.

The amount of fluid returned is usually between 40% and 60% of that instilled. In patients whose bronchi collapse around the tip of the bronchoscope, there may be more difficulty achieving return of the saline. Patients under general anesthesia or on mechanical ventilation also have low returned volumes.

Complications

A significant percentage of patients who undergo BAL experience transient fever and even chills, usually beginning 4 to 6 hours after the procedure. This phenomenon is almost always self-limiting, should be anticipated, and is readily treated with antipyretics. It most likely results from absorption of toxins or inflammatory mediators from the alveolar surface and is more common in patients whose airways are inflamed.[58,59]

BAL can result in hypoxemia because residual saline in the lavaged area interferes with gas exchange until the saline has been absorbed. It may also stimulate mucus production and cough. Wedging of the bronchoscope into an airway may result in localized bleeding. If the bronchoscope is not wedged snugly, saline spills into adjacent bronchi and stimulates cough and respiratory distress.

Specimen Handling

The purpose of BAL is to obtain a specimen for analysis; the care with which the specimen is handled is as important to the success of the procedure as the techniques used to obtain the specimen. Prompt processing reduces the loss of labile substances (or organisms) or the overgrowth of microbial species. Cells adhere to glass surfaces, and specimens collected or transported in glass containers may be depleted of their cellular content in relatively nonpredictable ways.

The analyses performed on BAL specimens should be determined by the indications for the procedure, although it makes sense to perform bacterial cultures (preferably, a quantitative culture) in almost all cases. At least a simple cytologic preparation should also be made. Other cultures and diagnostic tests (e.g., antigen detection, polymerase chain reaction) can be performed according to the clinical indications. BAL can be used for research applications,[60] and a wide variety of substances have been measured in BAL specimens from pediatric patients.

INTERPRETATION OF FINDINGS

There are many difficulties inherent in the interpretation of findings from BAL fluid; these relate to the area of lung sampled, the (variable and usually unknown) dilution of the fluid, and the expected normal values.[38,61,62] In some cases, interpretation is simple. For example, identification of material or organisms that should not be present in normal lungs, such as the cysts of *Pneumocystis jiroveci*, should give a relatively unequivocal diagnosis. In the case of substances that may be found in the lungs under normal conditions, interpretation is more challenging and may depend on relative quantitation. An example is the presence of lipid in alveolar macrophages. A large amount of lipid (large intracytoplasmic droplets in a substantial percentage of cells) strongly suggests aspiration.[63] However, chronic and sometimes acute inflammation can result in the accumulation of lipid in macrophages, presumably as a result of the phagocytosis of dead neutrophils and debris. There is some suggestion that such "endogenous" lipid may be discriminated by the size of the intracytoplasmic lipid droplets and by the number of cells containing such droplets, but there is no gold standard by which such identification can be proved. If aspiration is suspected, lipid stains should be performed, but the unequivocal identification of exogenous substances (perhaps by chemical means) would be more definitive proof of aspiration.

Microbiologic diagnosis is complicated,[64] especially by the relative difficulty of ensuring that the specimen is not contaminated with oral secretions. Bacteria may contaminate the bronchoscope during passage through the nose or mouth, or they may be aspirated into the trachea as a result of topical anesthesia. Although the risk of orotracheal aspiration can be reduced by placement of the patient into a head-down position before the application of the topical anesthetic and by being careful not to suction through the instrument channel until the tip of the bronchoscope is at least at the level of the carina, the clinician can never be certain that there is no contamination (this is also true when a microbiology specimen brush is used, as discussed previously). Quantitative culture can be helpful in this regard. Clearly, there is a difference between 2000 and 2,000,000 colonies in each milliliter of BAL fluid, the latter being more consistent with pulmonary infection and the former with oral contamination. Furthermore, except in patients who have neutropenia, pulmonary infection should be accompanied by significant numbers of neutrophils in the BAL fluid. Therefore BAL specimens should be examined microscopically to ascertain the relative distribution and number of cell types. (Gram's stains are not optimal for this purpose.) The absence of inflammatory cells should make the clinician very suspicious that the bacteria in the BAL specimen are from the mouth

and not the lungs. The presence of intracytoplasmic bacteria is also strong evidence of infection.[48] Care must be taken to avoid overinterpretation.[61]

The total number of cells in the BAL fluid depends on the technique used for BAL as well as the concentration of cells in the ELF. The significance of cell counts is subject to considerable uncertainty, although if the same technique is always used, the clinician may have more confidence in relative numbers. In the author's experience, the fluid from BAL performed using two 10-ml aliquots of saline in pediatric patients in whom no infection or inflammation is suspected (and in whom cultures are sterile) contains 100,000 to 300,000 cells/milliliter, 95% of which are alveolar macrophages and 1% to 2% are neutrophils. In patients with infection, the cell numbers and the percentage of neutrophils are much higher (ranging up to 99% neutrophils). Other authors have reported similar findings.[45,47,65]

Eosinophils are rarely seen in BAL fluid from subjects free of lung disease but are seen in the BAL fluid of patients with allergic states, foreign body reactions, and parasitic diseases. Increased percentages of lymphocytes may be seen in the BAL fluid of patients with sarcoidosis and other interstitial diseases.[66,67]

INTUBATION

Indications

An artificial airway is established to bypass airway obstruction, to facilitate mechanical ventilation, or to achieve repeated access to the lower airways for suctioning. The choice of tube type depends on the indications for and the anticipated length of intubation.

Contraindications

There are no absolute contraindications to the establishment of an artificial airway. Certain factors make the procedure more difficult or risky and may mandate one or another alternative technique (including tracheostomy). Risk factors include bleeding diatheses, severe hypoxemia, cardiovascular instability, and severe airway obstruction. However, some of these are also indications for intubation. Unstable cervical fractures mandate endoscopic rather than conventional intubation because the neck must be kept immobilized. Great care must be taken if a patient requires intubation with a full stomach because the risk of aspiration is great.

Instrumentation

The essential requirements for intubation include a suitable artificial airway and a method for visualizing the larynx (i.e., a laryngoscope). In some situations, an endotracheal tube may be passed via the nose and into the trachea without exposing the larynx for direct visualization; in others, a flexible bronchoscope may be used to direct the endotracheal tube.

Intubation must be performed in an appropriate setting, with appropriate measures for monitoring the patient and for altering the approach if warranted. Rarely must a patient be intubated immediately; in most circumstances, bag and mask ventilation is sufficient until suitable preparations can be completed. Alternative methods for ventilating the patient's lung must always be available before elective intubation is attempted; these include (at least) a mask, a self-inflating resuscitation bag or an anesthesia bag with a source of compressed oxygen, and an oral airway of appropriate size.

Table 15-2
Suggested Endotracheal Tube Sizes*

Age	Internal Diameter	Length	
		Oral	Nasal
Premature	2.5-3.0 mm	8 cm	11 cm
Newborn	3.0-3.5 mm	9 cm	12 cm
6 mo	3.0-3.5 mm	10 cm	14 cm
1 yr	4.0-4.5 mm	12 cm	16 cm
2 yr	5.0-5.5 mm	14 cm	17 cm
2-4 yr	5.5-6.0 mm	15 cm	18 cm
4-7 yr	6.0-6.5 mm	16 cm	19 cm
7-10 yr	6.5-7.0 mm	17 cm	21 cm
10-12 yr	7.0-7.5 mm	20 cm	23 cm
12-16 yr	7.5-8.0 mm	21 cm	24 cm

From Chatburn RL, Lough MD: Pediatric respiratory therapy, 3rd ed. St Louis, Mosby, 1985, pp 148-191.
*Note: Tube size should allow an air leak at a pressure not exceeding 25 cm H_2O.

The endotracheal tube must be the appropriate diameter for the patient's airway. Table 15-2 lists the customary tube sizes.[68] Useful approximations for the appropriate endotracheal tube size include the diameter of the fifth digit of the patient's hand or the following formula:

$$\text{Diameter in millimeters} = (\text{Age}/4) + 4$$

Tubes of this size and at least one size larger and smaller should be available before the clinician attempts intubation. In general, there should be a leak of air around the endotracheal tube at no greater than 25 cm H_2O pressure to reduce the potential for trauma to the subglottic space and development of subglottic stenosis.[69] Depending on the indication for intubation, an endotracheal tube may have a cuff near its distal end to seal the trachea, a monitoring lumen through which gas may be sampled, both, or neither. Although cuffed tubes are less often used in pediatric patients because the cricoid diameter is relatively small and thus there is relatively little leak around the endotracheal tube, they may be warranted if relatively high airway pressures are required to maintain ventilation. In adolescents or adults, the diameter of the endotracheal tube is relatively smaller in relation to the tracheal or cricoid diameter, and a cuff may be necessary for conventional ventilation.

Techniques for Intubation

PREPARATION OF THE PATIENT

For elective intubation, the patient should have an empty stomach[14,70] and should be given appropriate medications to reduce anxiety and relieve pain. Topical anesthesia of the larynx improves patient comfort and reduces the risk of adverse reactions such as laryngospasm and severe vagal reactions. In an emergency, it is probably even more important to have effective laryngeal anesthesia to reduce the probability of gagging and emesis, which could lead to aspiration. This

may be accomplished by instilling 1 to 2 mL of 2% lidocaine through the mouth or nose; effective topical anesthesia is achieved within 30 to 60 seconds. It is not necessary to apply the lidocaine directly to the glottis; the superior laryngeal nerve crosses the floor of the pyriform sinuses and is very superficial; pooling of lidocaine in the pyriform sinuses results in effective laryngeal anesthesia. Atropine may be administered to reduce salivary secretions and to reduce the potential for vagal stimulation. Patients may have severe vagal reactions when the larynx is manipulated without effective laryngeal anesthesia, even under what appears to be a surgical level of general anesthesia.

ORAL INTUBATION

With oral intubation the patient's neck is slightly extended, and a laryngoscope is gently inserted into the mouth. The laryngoscope should be held in the left hand and passed along the right side of the tongue. The tongue is then moved toward the left, exposing a path for visualization and passage of the endotracheal tube along the right side of the mouth. The laryngoscope blade is used to elevate the tongue; the tip of the blade is placed into the vallecula. In some circumstances, it may be necessary to elevate the epiglottis with the tip of the laryngoscope blade, but this may traumatize the epiglottis or vocal cords and is usually not necessary. The laryngoscope is lifted straight up to expose the larynx. Under direct vision, the endotracheal tube is inserted into the mouth and is guided through the glottis. It may help to stiffen the endotracheal tube with a soft-metal stylet, but the tip of the stylet should never extend beyond the end of the endotracheal tube; the use of stylets increases the risk of laryngeal trauma during intubation. Alternatively, the endotracheal tube can be stiffened by cooling it in ice for a few minutes. The tube is passed into the trachea to the desired distance, and the laryngoscope is withdrawn from the mouth.

The position of the endotracheal tube is then verified. Definitive proof that the tube is in the trachea involves demonstration of carbon dioxide in the exhaled gases. In the operating room, a capnometer is often used for this purpose; disposable indicators are also available that demonstrate a color change when exposed to carbon dioxide.[71] The more traditional and common method is to observe for chest rise and to listen for breath sounds while the patient is ventilated with an anesthesia bag; the breath sounds should be symmetric bilaterally (assuming that the patient had symmetric breath sounds before intubation). Observation of condensation of moisture in the tube during exhalation is not definitive because it can be seen with esophageal intubation as well. Success is clinically verified when the patient's condition stabilizes or improves. The tube is secured in position, and its location is definitively verified via a chest radiograph (or a flexible bronchoscope [see later section]).

In newborns, an endotracheal tube can be guided into the larynx with the index finger without using a laryngoscope. Although this method is useful in an emergency, its disadvantage is that the larynx is not visualized.

NASAL INTUBATION

Passage of the endotracheal tube through the nose has some advantages over oral intubation. A nasal tube leaves the mouth free so that infants can carry on nonnutritive sucking. A nasal tube is more easily secured in position and moves less than an oral tube. Because it passes behind the tongue, a nasal tube may be more comfortable than an oral tube. On the other hand, nasal intubation may be more difficult, and sometimes there may be nasal trauma. There is a small but significant incidence of sinusitis complicating nasal intubation. Some (especially inexperienced) operators may find nasal intubation more difficult; it may be useful to initially intubate orally and then to switch to a nasal tube when the patient is more stable.

Passage of a nasotracheal tube is performed in much the same fashion as oral intubation, except that the tube is first passed through one nostril to a depth such that its tip can be expected to be just above the larynx. The tube should be lubricated with a sterile, water-soluble jelly, and the nose anesthetized with topical lidocaine before insertion of the tube. When the larynx is exposed with a laryngoscope, the tip of the tube is grasped with McGill forceps and advanced into the glottis. Alternatively, the tube can be advanced while the neck is flexed or extended to guide the tip of the tube into the glottis. An assistant advances the tube or controls the patient's head and neck. Some operators prefer to perform blind nasal intubation without laryngoscopy; in this technique the tube is inserted through the nose and advanced to a position estimated to be near the larynx. By listening to the breath sounds through the tube and observing for condensation of moisture in the tube, the clinician can estimate the location of the tip of the tube. The tube is advanced while the patient's neck is flexed or extended to, it is hoped, advance the tube into the trachea. Although this technique sounds awkward, it can be surprisingly successful when performed by experienced operators, and it may be necessary in a patient whose mouth cannot be opened. (However, see the section on endoscopic intubation for a more effective technique.)

ENDOSCOPIC INTUBATION

Although the standard methods for oral and nasal intubation are successful in most cases, there are clearly circumstances in which these techniques are difficult or inappropriate. These situations include patients with mandibular hypoplasia, cervical or mandibular ankylosis, masses in the mouth or neck, and severe contractures of the neck. A flexible bronchoscope provides a nearly foolproof method for accomplishing the intubation and a diagnostic evaluation of the airway.[72,73]

A flexible bronchoscope of appropriate size is passed through the endotracheal tube. The flexible bronchoscope is then passed through the nose or mouth and into the trachea. When the tip of the bronchoscope reaches the carina, the endotracheal tube is advanced over the bronchoscope until the tip of the tube is seen just above the carina. The bronchoscope is then withdrawn. Experienced operators should be able to accomplish this maneuver in 1 minute or less. Not only is the airway anatomy visualized, but the location of the tip of the endotracheal tube is also immediately verified. When the tube has been positioned and the patient's lung has been ventilated for at least 1 minute, the lower airways should be examined to ensure that there is no anatomic abnormality and that the lobar and segmental airways are patent.

Virtually any patient can undergo endoscopic intubation; intubation can be performed on a premature infant when a 2.5- or 3.0-mm endotracheal tube is used with a 2.2-mm ultrathin flexible bronchoscope. The standard 2.8-mm pediatric flexible bronchoscope can be used with endotracheal tubes ranging in size from 3.0 to 4.5 mm; with larger tubes, a larger flexible bronchoscope should be used.

Although bronchoscopic intubation is simple in principle and is almost always successful, it requires a skilled and experienced operator. The procedure may be difficult in patients in whom there is a mass lesion or pharyngeal collapse. Insufflation with oxygen through the suction port of the bronchoscope (or through a nasopharyngeal tube) can be very helpful; occasionally the clinician may need to use a rigid laryngoscope to lift the mandible and tongue so that the glottis can be visualized.

During bronchoscopic intubation, there is a risk of damage to the flexible bronchoscope; it is likely that more bronchoscopes are damaged in the process of intubation than with any other procedure. This is especially true of the ultrathin instruments.

CARE OF THE INTUBATED CHILD

The endotracheal tube must be secured in place, with reasonable provision for comfort, so that it cannot easily be dislodged. Tubing attached to the endotracheal tube should be supported in a way that reduces tension on the tube. Inspired gases must be adequately humidified to prevent inspissation of secretions, and secretions should be removed from the tube by suctioning at regular intervals. Suction catheters should not routinely be passed beyond the tip of the endotracheal tube.

In a patient whose respiratory tract has been intubated for more than a few hours, additional factors must be taken into account. Phonation is impossible, and if the patient is awake and alert, some provision for effective communication may be necessary. Sedation may be appropriate for the duration of intubation because many children are frightened and uncomfortable. Chest physiotherapy should be routinely performed to help mobilize secretions to the tip of the tube. Nutritional needs must be met by routes other than the oral route.

When the patient requires intubation over a period of several days to weeks, secretions may accumulate in the tube despite regular suctioning and saline irrigation. This may require that the tube be changed. In general, however, the number of tube changes should be kept to a minimum because each change introduces the potential for trauma to the subglottic space. When prolonged intubation is contemplated, serious consideration should be given to tracheostomy.

LARYNGEAL MASK AIRWAY

An alternative to endotracheal intubation that may be useful in selected circumstances is the laryngeal mask airway.[74,75] This device consists of a triangular mask (with an inflatable cuff around the perimeter) attached to a large-bore airway. The mask is inserted into the posterior pharynx; the apex of the triangle enters the proximal esophagus. The cuff is inflated to seal the mask around the larynx and the base of the tongue. The laryngeal mask airway may be used for short-term anesthesia or for endoscopic procedures performed under general anesthesia when the supraglottic airway does not need to be examined.

TRACHEOSTOMY

A tracheostomy is an artificial airway inserted surgically into the cervical trachea. The terms tracheostomy and tracheotomy (the latter referring to the surgical placement of the tracheostomy tube) are used interchangeably in practice. Tracheostomy tubes may be maintained indefinitely and are generally comfortable (once the postoperative period is over). They may be removed and replaced with relative ease and allow the patient to swallow and to phonate.

Indications

The primary indication for tracheostomy is the maintenance of a long-term artificial airway. Although endotracheal tubes may be maintained in infants and young children for weeks to several months, placement of a tracheostomy tube reduces the risk of laryngeal damage. In patients with large pharyngeal tumors or severe subglottic obstructions, tracheostomy may be the only method of establishing a safe and secure airway. Finally, in some patients with chronic laryngeal incompetence, a tracheostomy may be performed to facilitate pulmonary cleansing.

Contraindications

There are few absolute contraindications to the placement of a tracheostomy except perhaps the presence of tumor or infection in the surgical field. Coagulation defects and unusual anatomic conditions (including significant tracheal obstruction by the innominate artery) make tracheostomy more difficult and may warrant delay until the underlying condition is corrected.

Instrumentation

Tracheostomy tubes may be constructed of metal or plastic; the plastic tubes are much more common today. Metal tubes and large plastic tubes used in adults typically have a removable inner cannula, which must be removed and cleaned several times each day. Because of the small diameter of the tubes used in infants and young children, most nonmetallic pediatric tracheostomy tubes do not have inner cannulas. The tube size (diameter and length) must be matched to the airway dimensions of the patient. There is a bewildering array of tube types on the market, and virtually all can be customized for the particular needs of the patient.

Technique

Tracheotomy is a surgical procedure; details of technique may be found in standard surgical texts. In brief, an incision is made over the cervical trachea, avoiding the thyroid isthmus and associated vessels. The incision is extended by blunt dissection to the anterior tracheal wall. The trachea is usually entered between the second and third (or third and fourth) tracheal rings; in children, one ring often must be divided. A suitable tube is inserted through the tracheal incision and secured in place.[76,77]

It may be difficult to reinsert the tracheostomy tube if it becomes dislodged before healing of the incision and establishment of a mature stoma, especially if the ends of the cartilage ring that was cut in the operation resume their normal position. Therefore it is customary to place retraction sutures around the ends of the cut cartilage ring; these are left in place until the tube is successfully changed (usually after 5 to 7 days) and it is verified that the stoma is stable. In an emergency recannulation, these retraction sutures can be used to pull the ends of the cartilage ring laterally, thus dilating the stoma so that the tube can be reinserted.

Alternative techniques exist for placing a tracheostomy tube, although they are not readily applicable in infants and young children. In brief, these involve transtracheal needle puncture followed by passage of a guidewire and a dilator; the tracheostomy tube is placed in much the same fashion as an over-the-wire vascular catheter.[78,79]

In an emergency, cricothyroidotomy[80] may be used to place an artificial airway into the trachea below the larynx. A horizontal incision is made directly over the cricothyroid membrane (identified by feel just at the inferior margin of the thyroid cartilage). After dilation with a suitable instrument, a tube is passed into the trachea. Because cricothyroidotomy risks laryngeal damage, the patient should undergo formal surgical revision and placement of a conventional tracheostomy as soon as it is feasible if there is a continuing need for the tracheostomy tube.

Complications

Immediate complications of tracheotomy include hemorrhage, air leak (pneumothorax, pneumomediastinum, or subcutaneous emphysema), and possibly damage to the recurrent laryngeal nerves. Displacement of the tube before the stoma has healed may have disastrous consequences if the patient does not have a functional airway.

Long-term complications include the development of granulation tissue, which may completely obstruct the suprastomal trachea; bleeding from the stoma, which is usually minimal but may be massive from the creation of a tracheoinnominate fistulas; respiratory distress resulting from obstruction or dislodgment of the tube; and trauma to the lower airways from suction catheter use. Infection is a constant risk because the normal defenses of the upper airway are bypassed.

Care of the Child with a Tracheostomy

A tracheostomy tube interferes with the normal humidification of inspired air. The inspired air should be humidified to reduce the risk of inspissation of secretions in the airways or the tracheostomy tube; a mist collar should be used in infants most of the time. After some months, many patients can tolerate nonhumidified air more easily, but some provision should still be made for adding humidification at least part of the time. "Artificial noses" are small devices that attach to the tracheostomy tube, condense some moisture during exhalation, and evaporate it on inspiration to partially humidify the inspired air; these may be useful,[81] and they also filter the inspired air.

Patients with tracheostomies require assistance clearing secretions from the airways and in keeping the tube patent. Dry mucus has the consistency of dry rubber cement and can occlude a tracheostomy tube, with lethal consequences. Therefore suctioning of the tube on a regular basis is essential. Suction catheters can traumatize the airway; this leads to increased mucus production, mucus stasis, and sometimes bronchial stenosis.[82] Suctioning should be performed only deeply enough to clear the tracheostomy tube; chest physiotherapy and cough should clear the bronchi of secretions.

Tracheostomy tubes should be changed at regular intervals (typically once a week). Caregivers must learn the techniques involved.[83] Metal tracheostomy tubes have very thin walls, and an obturator must be used during insertion to prevent the tube from cutting the tissue. However, obturators are not necessary with plastic tubes to prevent tissue damage and they obstruct the airway during insertion. If difficulty is encountered during attempted insertion of the tube (sterile, water-soluble lubricant should always be used), a suction catheter passed through the tube can be used as a guidewire in the same fashion as a guidewire with a vascular catheter. It is a good practice to have a spare tube one size smaller than the usual tube because in an emergency, it may be necessary to use a smaller tube to reestablish an airway.

The tracheostomy tube must be secured to the patient's neck with an appropriate strap. Various materials are used, ranging from adjustable Velcro straps to simple twill tape. The strap must be tight enough to prevent accidental decannulation but not so tight that it is uncomfortable. Materials must always be kept close at hand to cut or remove the strap and replace the tracheostomy tube quickly in case of emergency. An emergency kit should contain a clean tube of the appropriate size with straps already in place and ready to be secured, another tube one size smaller, a suction catheter, lubricating jelly, and scissors.

Because of the risk of catastrophic airway obstruction if the tracheostomy tube becomes dislodged or obstructed, infants and young children with tracheostomies must be monitored carefully. Unfortunately, there is no entirely satisfactory way to do this. Cardiorespiratory monitors may respond to airway occlusion only after the child has become sufficiently hypoxic to become apneic, whereas pulse oximeters have a very high rate of false alarms. Nevertheless, caregivers must be well trained to detect and respond quickly and appropriately to emergencies by suctioning, giving positive-pressure breathing, changing the tracheostomy tube on an emergency basis, and providing the basic elements of resuscitation. The preparation of a child and family for home care with a tracheostomy is complex and demanding.[84]

Tracheostomy tubes should be sized to fit the needs of the patient. In very young infants, the internal diameter of the tube should be large enough to minimize airway resistance, with relatively little concern for the child's ability to vocalize around the tube. Most full-term newborns do well with a tube with an internal diameter of 3 to 3.5 mm. The end of the tube must not touch the carina, but the tube must be long enough that it lies parallel to the tracheal axis. A short tube often pushes into the posterior membranous portion of the trachea, producing partial expiratory obstruction; this

also places the child at risk of developing granulation tissue at the tip of the tube. The tube size must be increased to keep pace with the child's growth. It also becomes more important to allow for some air movement around the outside of the tube to facilitate phonation.

At some point, it may become feasible to provide the patient with a one-way ("speaking") valve on the tracheostomy tube. This allows the child to breathe in through the tube but forces expired air through the glottis, thus facilitating both phonation and improved clearance of secretions.[85] There must be sufficient airway around the tube for effective airflow; expiratory pressures during quiet breathing greater than 10 cm H_2O are not well tolerated. On the other hand, some children with severe tracheomalacia or bronchomalacia benefit greatly from the enhanced expiratory resistance provided by the speaking valve.

Most patients with tracheostomies develop some granulation tissue at the superior margin of the stoma[86]; this may progress to complete obstruction of the suprastomal trachea with potentially lethal consequences. It is prudent to examine the airway with a bronchoscope at regular intervals[17,87] to assess for this complication as well as to evaluate the patient's readiness for possible decannulation.[88] Although there is controversy about how aggressively to remove small to medium suprastomal granulations, it is clear that near-total obstruction places the child at risk of serious complications.

Specific criteria for decannulation include the ability to breathe adequately without support and an anatomic and functionally patent airway.[87] Endoscopic examination of the airway before decannulation is virtually mandatory, and the airway should be examined with the tracheostomy tube removed. Some authors prefer to place a series of increasingly smaller tracheostomy tubes in preparation for decannulation, culminating in a small, plugged tube. In this author's experience, however, endoscopic evaluation followed if necessary by degranulation and immediate decannulation is almost always successful. If the airway is obstructed by granulation tissue or the collapse of the anterior tracheal wall,[89] then smaller tracheostomy tubes will not solve the problem. If the airway structure and dynamics appear adequate, the child should be observed in the hospital for 48 hours; the stoma usually closes very rapidly (often within hours), and a true emergency may arise if the child needs recannulation. In a small percentage of children, a persistent tracheocutaneous fistula requires surgical closure at a later date. Some children require laryngeal or tracheal reconstruction before successful decannulation.

THORACENTESIS

Indications

The accumulation of fluid in the pleural space often poses diagnostic problems that may be directly addressed by analysis of the fluid. Pleural effusions that are very small or that on clinical grounds are clearly the result of simple mechanical processes may not require thoracentesis. Examples of the latter include patients with congestive heart failure or severe hypoproteinemia. On the other hand, if infectious or malignant disease is suspected, then analysis of the fluid is warranted.[90]

Contraindications

If the diagnostic importance is sufficiently high, there are no absolute contraindications to thoracentesis. However, certain situations (i.e., thrombocytopenia) make the procedure more risky. Because children need sedation for thoracentesis, hypoxic patients are at greater risk from respiratory depression during the procedure. Careful attention to the patient's physiologic condition, continuous monitoring, and correction of risk factors amenable to correction (e.g., platelet transfusion) reduce the risk. It may not always be possible to determine the location of the diaphragm from simple radiographs, so there is some risk of puncturing the liver or spleen if the needle is placed too low.

Instrumentation

In brief, thoracentesis involves inserting a needle through the intercostal space and into the pleural space. If the goal is merely to obtain a specimen for diagnostic purposes, especially if the fluid is not loculated, then a simple needle of suitable length and diameter can be used. If the goal is to withdraw a substantial volume of pleural fluid, then use of a plastic catheter (passed over a small needle or through a larger needle) is more suitable. If an IV catheter (catheter over the needle) is used, it must be long enough to reach the pleural space and should be large enough that even highly viscous fluid can be withdrawn through it. Generally, a 16- or 18-gauge catheter should be used.

Radiographic or ultrasound evaluation before attempted thoracentesis is needed to determine the relative volume of fluid and its mobility or lack thereof. If the entire hemithorax is opacified, it may sometimes be difficult to ascertain the amount of fluid present and the position of the diaphragm; a computed tomographic or ultrasound scan can be very helpful. Small or loculated fluid collections are best located with ultrasound; the most appropriate site can be marked before skin preparation so that the needle can be inserted directly into the fluid.

Technique

The patient should be prepared with appropriate sedation and monitored carefully. Because fluid moves with gravity, it is usually most effective to perform the procedure with the patient sitting erect (usually leaning slightly forward and supported on pillows or an overbed table). Alternatively, in a supine patient the needle can be placed in the posterior axillary line with the patient very near the edge of the procedure table. The level of fluid is determined by percussion. The most common site for the insertion of the needle is the seventh intercostal space in the midaxillary or posterior axillary line; this may be modified according to the clinical situation (with ultrasound guidance if necessary).

After appropriate skin cleansing, disinfection, and sterile draping, a small-gauge needle is used to infiltrate lidocaine into the track intended for the larger needle. The needle, which is attached to a syringe containing 1 to 2 mL of lidocaine, is inserted perpendicularly to the skin and advanced to the rib and then up and over the top of the rib, thus avoiding the neurovascular bundle, which follows the inferior margin of the rib. The needle should be held with the fingers against

the skin so that if the patient moves, the operator's hand and the needle move in the same direction at the same time. The needle is carefully advanced with the other hand, which may be used to alternately gently withdraw and inject lidocaine. As soon as pleural fluid appears in the syringe, the depth of the needle is marked, and the needle is withdrawn. Then the larger needle/catheter is inserted in the same track, and gentle suction is applied as the needle reaches the marked depth. When fluid is obtained, the needle/catheter is advanced slightly into the pleural space, and the needle is withdrawn, leaving the catheter in the pleural space. A three-way stopcock is then attached to facilitate repeated aspiration with a syringe or drainage into a reservoir. When the desired amount of fluid has been withdrawn, the catheter is removed, and the site is dressed with a simple dressing; pressure dressings are seldom necessary. If fluid is not obtained with the probing needle, it may be because the fluid is loculated and the needle has been placed in the wrong position (the clinician should consider ultrasound guidance or try one interspace higher) or because what appears to be pleural fluid may in fact be pleural thickening.

An alternative technique is to use a large-bore needle (after the probing needle has been used to provide local anesthesia and locate the pleural fluid) through which a plastic catheter is passed. Once the needle enters the pleural space, the catheter is advanced and the needle withdrawn. Yet another technique is to use a catheter advanced over a guidewire that has in turn been passed into the pleural space through a needle[90,91] (see the section on the placement of chest tubes).

Complications

The complications of thoracentesis include bleeding, pneumothorax, and infection. Although the absolute risk of bleeding is small, it may be prudent to ensure that clotting mechanisms are normal before thoracentesis. Pneumothorax may occur if the needle is advanced too far, especially if the patient moves or coughs. An upright chest radiograph should be obtained after the procedure to evaluate for air leak. In patients with massive accumulations of pleural fluid, removal of large volumes can lead to unilateral pulmonary edema or hypotension. (As the pulmonary vascular bed in the previously collapsed or compressed lung fills with blood, the blood pressure may fall.) These complications seem to be more likely when the fluid has been present for a long time; there are no specific guidelines as to how much fluid may be safely withdrawn in a given patient.[92,93] Clearly, if the volume of fluid in the pleural space is sufficient to cause respiratory distress, then at least enough should be removed to relieve the distress. Purulent fluid should be drained as completely as possible; if the fluid is highly purulent it will also be highly viscous, and it may be necessary to insert a large-bore chest tube to achieve adequate drainage.

Specimen Handling

Specimens of pleural fluid should be sent for total and differential cell count, appropriate cultures, and determination of total protein content. Because pleural fluid often contains considerable amounts of fibrin, it is useful to collect some of the fluid into a tube containing an anticoagulant and to use this tube for cell counts and other determinations. Other analyses may be performed, including (but not limited to) amylase, glucose, and pH, depending on the clinical setting.

Interpretation of Findings

See Chapter 68.

TUBE THORACOSTOMY

Indications

A chest tube[90,91] is placed to remove air or fluid from the pleural space. In contrast to simple thoracentesis, which may also be used to treat pleural effusion or pneumothorax, a chest tube is left in place to enable drainage over a period of time. The size and type of tube are determined by the quantity and nature of the material to be drained; small tubes are suitable for the treatment of a pneumothorax, whereas much larger tubes may be required to drain an empyema. In rare circumstances, a chest tube may be placed prophylactically in anticipation of life-threatening pneumothorax or pleural fluid accumulation.

Contraindications

If the accumulation of pleural fluid or air is immediately life threatening, there are no contraindications to chest tube placement. Factors that make the procedure more risky include uncorrected thrombocytopenia, clotting factor deficiencies, extensive infections or tumors involving the chest wall, and severe scoliosis or other anatomic deformities.

Instrumentation

The essential instruments for chest tube placement include a suitable tube, the equipment with which the chest wall is penetrated, and a closed drainage system to which the tube is connected. Chest tubes, depending on their intended purpose, range in size from a 20-gauge IV catheter to 30-French (9.5-mm diameter) or larger. The tip of the tube is smooth to prevent trauma to the lung, and the proximal end must be capable of attaching to a drainage system. For a simple pneumothorax, a through-the-needle plastic catheter may be suitable, although such relatively thin-walled catheters may kink. Another disadvantage of such simple tubes is that there is only one hole (at the end); if the single hole becomes occluded, the tube becomes nonfunctional. In most cases, it will be more appropriate to use a tube designed to be passed over a guidewire because such tubes not only are stronger but also have more than one hole through which air or fluid may drain. When fluid is to be drained, a larger-diameter tube is more appropriate, depending on the viscosity of the fluid.

Drainage systems consist of tubing and a reservoir along with some mechanism to maintain a negative intrathoracic pressure. The most common (and simplest) system includes a chamber into which fluid drains; this chamber is connected to another reservoir containing sterile water, and the tubing from the first chamber extends some distance below the surface of the water in the second chamber. This arrangement allows fluid and air to escape, but prevents flow of air back

into the pleural space. The second chamber can be attached to a vacuum line to maintain a continuous negative pressure; this may be important in the management of pleural air leaks.

For emergency treatment of a pneumothorax when a closed, water-sealed drainage system is unavailable or inappropriate, a simple one-way valve may be attached to the chest tube.[94] When intrathoracic pressure increases, air escapes through the valve, but it cannot reenter the chest. Such systems can be lifesaving but should in most situations be converted to appropriate water-seal drainage as soon as feasible.

Technique

There are two general techniques for chest tube insertion: percutaneous placement and surgical placement.

PERCUTANEOUS INSERTION

Catheters may be inserted either through a large-bore needle or over a guidewire; in either case, the technique is very similar to that for simple thoracentesis. After suitable skin preparation and local anesthesia, the needle is inserted through the intercostal space along the superior margin of the rib. When the pleural space is reached, the catheter (or guidewire) is advanced and the needle withdrawn. The needle may be directed initially to guide the catheter or wire into the desired location (generally posteriorly for drainage of fluid and anteriorly for drainage of air).

The technique for placement of an over-the-wire catheter is analogous to that for a similar vascular catheter. After insertion of the guidewire through the probing needle, the needle is removed. A sharp scalpel (No. 11 blade) is used to make a small incision at the point of insertion, and a dilator is passed over the wire. Because the dilator is quite stiff, it should not be passed deeply into the thorax, but its tip must penetrate the parietal pleura. The dilator is removed, and the selected catheter is then threaded over the guidewire and advanced into the chest. The catheter should be grasped very close to the chest wall as it is advanced to prevent kinking of the guidewire. When the tube has been advanced to the desired depth, the guidewire is removed, and the tube is connected to a closed sterile drainage system.

SURGICAL INSERTION

The chosen site is prepared as for thoracentesis. After instillation of local anesthetic, a skin incision just long enough to accommodate the chest tube is made approximately 2 cm below the intended insertion site. The skin is pulled upward so that the incision overlies the intended puncture site. A surgical clamp is used to penetrate the intercostal space just above the rib and to dilate the wound so that the tube can be passed. The tip of the tube is grasped with the clamp, inserted through the track, and advanced into position after the clamp is removed. Alternatively, a chest tube with an internal trocar may be used instead of the surgical clamp. The trocar has a sharp point and may be used to penetrate the intercostal space as well as to facilitate the passage of the tube itself. Great care must be taken, however, when a trocar is used in this fashion so that penetration of the lung is avoided. The tube or trocar must be held with the gloved hand very close to the chest wall so that it cannot advance farther than intended once the pleura is penetrated. The tube is advanced over the trocar, which is then removed.

When the tube is in place, the tension on the skin overlying the insertion site is released, creating a subcutaneous track for the tube. This reduces the risk of air leakage around the insertion site and allows the tube to exit the chest on an oblique angle rather than perpendicularly. A purse-string suture should be placed around the tube, and the tube should be anchored to the chest wall with another suture or suitable taping. The tube should be secured so that accidental traction on the tube neither pulls the tube from the patient's chest nor moves the tube within the chest (which is painful).

Removal of Chest Tubes

A chest tube placed to drain a pleural effusion is usually left in place until the daily volume of drainage is minimal, whereas that placed for treatment of a pneumothorax is left until there has been no air leak for at least 24 hours. If the tube does not drain the pleural space adequately, it may require repositioning or replacement.

It is prudent to clamp a chest tube for some period of time before its removal. If fluid or air then reaccumulates within the pleural space, it is only necessary to unclamp the tube. When the tube is to be removed, any sutures attached to the tube are removed, the entrance site is covered with sterile gauze impregnated with petroleum jelly, and the tube is withdrawn. Before the tube is pulled, it should be rotated to break up adhesions between the tube and the lung. Gentle pressure is maintained over the insertion site during and after withdrawal. The tube should be withdrawn promptly to prevent entrance of air into the pleural space through the proximal side holes in the tube once they exit the chest. The purse-string suture, if used, is pulled tight and tied, and a pressure dressing is applied. A chest film with the patient sitting erect is obtained after removal of the tube to ensure that there is no residual pneumothorax.

Complications

The complications of chest tube insertion are essentially the same as those of thoracentesis, and include bleeding, damage to the neurovascular bundle, perforation or laceration of the lung, and infection. If the drainage system to which the tube is connected is mishandled, ascending infection may contaminate the pleural cavity. Likewise, disconnection of the tube from its underwater seal may result in a large pneumothorax.

PERCUTANEOUS NEEDLE ASPIRATION OF THE LUNG

Before the advent of flexible bronchoscopy and BAL, the only way to obtain a specimen from the distal airways involved rigid bronchoscopy, open lung biopsy, or percutaneous needle aspiration.[95-97] Although needle aspirations are seldom performed today, this is the only way except open biopsy to guarantee that there is no chance of contamination of the specimen by upper respiratory tract flora.

Indications

Percutaneous needle aspiration may be indicated when it is necessary to obtain a specimen from the distal airways and alternative methods, such as flexible bronchoscopy, are not available or for some reason are contraindicated. Patients with pulmonary consolidation or lesions located close to the pleura are the most appropriate candidates. Very small volumes of specimen are obtained and may be examined by microscope or a variety of microbiologic techniques. Percutaneous needle aspiration of lung lesions may be desirable in the investigation of possible malignancy or granulomatous disease. The site for the puncture can be guided by findings on radiographic studies.

Contraindications

Patients with noncorrectable bleeding disorders should not undergo percutaneous needle aspiration. Other factors that increase risk include pulmonary hypertension and positive-pressure ventilation. Percutaneous needle aspiration should not be performed through a pleural effusion.

Technique

The technique for percutaneous needle aspiration is very similar to that for thoracentesis. However, the object is for the needle to traverse the visceral pleura in the area of the parenchymal lesion. Sedation and local anesthesia are used as for thoracentesis. A needle of suitable size and length is attached to a syringe containing 1 to 2 mL of sterile, nonbacteriostatic saline. The needle is advanced to a position just short of the pleura. Cooperative patients are requested to hold their breath (most children will not do so, of course), and then the needle is rapidly advanced across the pleura. As quickly as possible, the contents of the syringe are injected, and then the plunger of the syringe is withdrawn to aspirate as much material as possible into the syringe (usually this amounts to only a few drops). The needle and syringe are then rapidly withdrawn. This entire process should take only 2 to 3 seconds; a longer time increases the risk of laceration of the pleura and pneumothorax.

Transtracheal aspiration[98] is a related procedure that has been performed for similar indications. This procedure, which is rarely performed since the advent of flexible bronchoscopy, involves passage of a catheter through a needle that has been inserted through the cricothyroid membrane, and then aspirating secretions from the airway. Fatal complications have been reported,[99] and the procedure does not guarantee that the specimen is not contaminated with oral secretions. Transtracheal aspiration should not be performed in infants and young children.

In the investigation of deeper parenchymal lesions for suspected malignancy, especially in older patients, a very thin, flexible needle can be used to reduce the risk of laceration of the lung. Fluoroscopy (preferably biplane fluoroscopy) or computed tomography should be used to guide the needle into the lesion. If warranted, a cutting needle may be used to obtain a small specimen of lung parenchyma for histologic examination. This procedure increases the risk of bleeding and air leak.

Complications

Pneumothorax is an obvious risk of percutaneous needle aspiration. Usually, the air leak is small and requires no therapy, but insertion of a chest tube is sometimes required. The risk of bleeding is somewhat higher than that for thoracentesis.

PLEURAL BIOPSY

Indications

Biopsy of the parietal pleura is indicated in the evaluation of pleural disease not diagnosed by thoracentesis or other methods. Most commonly, malignancy or mycobacterial disease is suspected. Pleural fluid is usually present when a pleural biopsy is considered.

Contraindications

Patients with uncorrectable bleeding disorders should not undergo pleural biopsy.

Instrumentation

A pleural biopsy needle (Cope or Abrams) consists of an outer cannula that is perforated near its tip, a cutting trocar, and a stylet. The Abrams needle is generally preferred.[90]

Technique

The patient is prepared as for thoracentesis. Because the biopsy needle is relatively large, a small skin incision is made with a scalpel (No. 11 blade). The needle with the cutting trocar and stylet in place is then passed through the parietal pleura. The stylet is withdrawn; a syringe can be attached to withdraw pleural fluid and confirm the position of the needle tip. The cutting trocar is rotated (Abrams) or withdrawn (Cope) to the open position, and the needle is withdrawn so that the opening in the outer cannula engages pleural tissue. The cutting trocar is then rotated (or advanced) to the closed position so that the biopsy specimen is held within the core of the trocar (it may be recovered by aspiration into the syringe or by removal of the cannula). Several specimens can be obtained in the same site by rotating the outer cannula and repeating the biopsy process. The operator should consider the orientation of the cutting port and avoid taking a biopsy toward the inferior aspect of the rib above the puncture site (to avoid cutting the neurovascular bundle).[100]

Complications

Pneumothorax and bleeding are the two most common complications. Care must be taken to avoid the neurovascular bundle by inserting the biopsy needle through the inferior part of the intercostal space and to avoid taking a biopsy in the superior aspect of the site.

THORACOSCOPY

There have been rapid advances in endoscopic instrumentation and technique in recent years. Many thoracic procedures that previously required open surgical approaches can now be performed with endoscopic visualization and manipulation. Continued miniaturization of instruments will ensure that

pediatric patients are not deprived of the benefits of such minimally invasive diagnoses and surgery.[101]

One potential limitation of thoracoscopy is that the patient must be able to tolerate one-lung anesthesia. The lung must be at least partially deflated to visualize the pleural surfaces. In pediatric patients, this may present technical problems in airway management. Patients with respiratory failure or insufficiency may be poor candidates for thoracoscopy. However, they are also poor candidates for thoracotomy, and in some cases, thoracoscopy can be informative even if the lung cannot be deflated.

Indications

Diagnostic thoracoscopy[102] is indicated in the evaluation of complicated pleural effusions (especially if malignancy is suspected), persistent pneumothorax, subpleural lung nodules, and mediastinal or pleural nodes or masses. In addition, thoracoscopic techniques may be indicated for lung biopsy or for the achievement of pleurodesis.[103,104]

Contraindications

As previously noted, the inability of the patient to tolerate one-lung anesthesia may make thoracoscopy inappropriate, and obliteration of the pleural space may make it impossible. As with other invasive procedures, uncorrected bleeding disorders increase the risk of hemorrhage.

Instrumentation

Thoracoscopy involves direct visualization of the intrathoracic contents through a rigid telescope inserted through the intercostal space. The telescopes are similar to those used for rigid bronchoscopy. A variety of ancillary instruments are available to manipulate the lung and intrathoracic contents. The telescopes and other instruments are passed through trocars, which allow an instrument to be removed and reinserted as necessary.

Technique

Thoracoscopy is a surgical procedure requiring general anesthesia. In general, more than one trocar (often three) is inserted into the thoracic cavity; one is used for a telescope, and others are used to manipulate the lung. Placement of the trocars depends on the area of interest. The lung is at least partially deflated, grasped with forceps, and pulled or pushed aside to achieve adequate visualization. The presence of pleural adhesions may complicate the inspection.

In addition to visual inspection, specimens of lung, pleura, or lymph nodes may be obtained with a variety of biopsy instruments. Hemostasis can be achieved by electrocautery, staples, sutures, or laser. Because the entire pleural surface can be visualized, thoracoscopy may be more versatile than limited thoracotomy when a lung biopsy is required.

LUNG BIOPSY

When other diagnostic methods have failed, histologic examination of lung tissue may be required. There are two techniques for obtaining such a specimen: transbronchial biopsy and open lung biopsy. Because of its technical limitations, transbronchial biopsy should rarely be used in pediatric patients, although it plays a critical role in the management of patients after lung transplant. Transbronchial biopsy specimens are very small, and histologic diagnosis is not as easily made as with an open biopsy.

Indications

Lung biopsy may be indicated in the evaluation of interstitial or other diffuse infiltrative diseases, nodular disease, and sometimes, suspected infection. Lung biopsy is indicated in the evaluation of suspected malignancy and suspected rejection after lung transplantation.[105,106] In general, bronchoscopy with BAL should be performed before open lung biopsy. In most cases, the pertinent diagnostic information from bronchoscopy and BAL is available within 24 hours, and the more invasive procedure (if it is necessary) is not delayed long. If the information is urgently required (as in a lung transplant) or if only a transbronchial biopsy is desired, then biopsy and BAL are performed at the same time.

Contraindications

If lung biopsy is the only way to achieve the necessary diagnosis, then there are no absolute contraindications to biopsy, but the technique may be dictated by the clinical circumstances. The risk of pneumothorax after transbronchial biopsy is much higher, for example, in patients on positive-pressure ventilation.

Instrumentation

Transbronchial biopsy is performed with flexible forceps passed through a bronchoscope.[107] These devices induce a substantial amount of crush artifact in the specimen obtained. The smallest available forceps are approximately 1 mm in diameter and can be used with the standard (2.8-mm) pediatric flexible bronchoscope. Unfortunately, the small size of the specimens obtained with this instrument severely limit the practical applications of the technique. The largest forceps available are approximately 2.5 mm in diameter and require the use of a flexible bronchoscope 6 mm in diameter.

Technique

Lung biopsy may be performed surgically or by thoracoscopy. An advantage of these techniques is that the lung surface can be examined and the specimen is much larger than that obtained by transbronchial biopsy. Automatic stapling devices are used to detach the specimen and seal the cut edges of the lung.

Transbronchial biopsy should be performed with fluoroscopic guidance, both to ensure that the selected area of the lung is being sampled and to reduce the risk of pleural perforation. The flexible bronchoscope is advanced to the desired bronchus, and the forceps are passed through the suction channel. The closed forceps are advanced to the desired depth, retracted slightly, opened, and then advanced to meet gentle resistance before closing. A slight tug should be felt and may be viewed on the fluoroscope if tissue is obtained. The specimen is placed immediately into either fixative or saline; if the specimen floats, it is more likely to contain

alveolar tissue. Multiple specimens are usually obtained to ensure that an adequate amount of tissue is available for analysis.

Complications

Lung biopsy always carries the risk of hemorrhage, air leak, or both, and the overall risks are higher in patients with respiratory failure or multiorgan failure. The incidence of pneumothorax after transbronchial biopsy is relatively small and depends somewhat on the technique used and the nature of the lung disease (the risk is higher in patients with poor pulmonary compliance). Deaths from massive hemorrhage have occurred after transbronchial biopsy. Infectious complications of transbronchial biopsy are those associated with bronchoscopy, and the incidence of complications may be increased if atelectasis results from bronchial obstruction caused by blood clots due to bleeding from the biopsy sites. Good pulmonary cleansing to clear the airways of clots after transbronchial biopsy reduces the incidence of complications.

NASAL MUCOSAL BIOPSY AND BRUSHING

The nasal mucosa consists of ciliated epithelium nearly identical to that of the trachea and bronchi. Therefore the nose is an important site for diagnostic evaluation of generalized mucosal abnormalities.

Indications

Patients suspected of having primary ciliary dyskinesia may undergo nasal mucosal biopsy for functional and ultrastructural evaluation of ciliary function.

Contraindications

There are essentially no contraindications to nasal biopsy. However, a biopsy taken during the course of a viral infection may reveal abnormalities that would not be present otherwise and that are not relevant to the patient's underlying condition.[108,109]

Instrumentation

Ciliated cells can be obtained with a small brush about 1 to 2 mm in diameter or with a small curette. The latter is more likely to yield intact pieces of epithelium.

Technique

Under normal circumstances, the anterior third of the nasal epithelium is squamous, whereas the more posterior two thirds is ciliated. The biopsy should be obtained from an area of ciliated epithelium; the most appropriate area is at least halfway along the inferior turbinate, preferably under this structure. The specimen is placed into tissue culture medium for examination by light microscopy for ciliary beat frequency and pattern or by electron microscopy. Functional analysis should take place as soon as possible because ciliary activity may decrease rapidly in traumatized cells; in general, ciliary activity is less likely to be demonstrable in individual cells than along the border of a patch of epithelial surface where the cells are more intact. Patients with primary ciliary dyskinesia have cilia that beat very slowly and incoordinately or not at all; the cilia may appear rigid. Specimens that appear to be abnormal should be processed for electron microscopy. A diagnosis of ciliary dysfunction should not be made in the absence of ultrastructural confirmation and may be complicated by environmental or infectious influences.

SPUTUM EXAMINATION

The examination of sputum is an important aspect of pulmonary diagnosis, at least in patients who produce sputum.[110] Invasive procedures to obtain specimens from the lower respiratory tract should usually be deferred until sputum has been evaluated. Unfortunately, sputum specimens may be difficult to obtain from children.

Indications

Sputum should be examined whenever productive cough is part of the complex of symptoms. A productive cough implies the presence of an abnormal quantity of respiratory secretions (or inadequate clearance). Induced sputum specimens may be useful in the diagnosis of diffuse lung diseases and certain infectious diseases such as tuberculosis. Sputum may be examined microscopically as well as by microbiologic methods.

Technique

There are two problems associated with sputum examination: obtaining a specimen and ensuring that the specimen comes from the lower respiratory tract. Even though they may have copious tracheal secretions and a cough that sounds productive, young children are usually unable to expectorate the specimen. A common practice therefore is to obtain a swab from the posterior pharynx while attempting to induce a cough. Although this may be successful (the swab will obviously have a sample of mucus, which may be green or yellow), it is not always certain that such a specimen comes from the lungs and not from the nasopharynx. There is a relatively poor correlation, at least in young children, between the results of such "gag sputum" specimens and specimens obtained by bronchoscopy and BAL. Microscopic examination of the specimen for the presence of alveolar macrophages can help determine whether the specimen is indeed from the lower respiratory tract.

In older patients who do not have a productive cough, it may still be possible to induce sputum by the inhalation of an aerosol (especially an ultrasonic aerosol) of saline (hypertonic or isotonic).[111] This procedure may place medical personnel at some risk, and they should be protected by appropriate procedures from the aerosol generated by the patient's cough.

To reduce the probability of contamination of the sputum specimen with oral secretions, the specimen should ideally be collected after the mouth is rinsed with water and not within an hour or so of a meal. The patient should be instructed to provide sputum rather than saliva, although it may be possible to separate material that appears to be sputum from saliva after expectoration. It is standard in many

microbiology laboratories to remove saliva by washing the sputum specimen with sterile saline before processing it.

Sputum may be examined microscopically as a wet mount by placing it under a coverslip on a microscope slide, or it may be smeared and stained with a variety of stains, depending on the purpose of the examination. Although Gram's stain is usually used in the microbiology laboratory, this is not an effective stain for study of cell types. Wright's or Giemsa stains are useful for evaluating inflammatory cells and eosinophils and identifying alveolar macrophages (the absence of which suggests that the specimen may not have come from the lower respiratory tract). The presence of numerous neutrophils does not in itself prove that the specimen came from the lungs, but the presence of large numbers of squamous epithelial cells does suggest heavy contamination with oral secretions.

SUGGESTED READINGS

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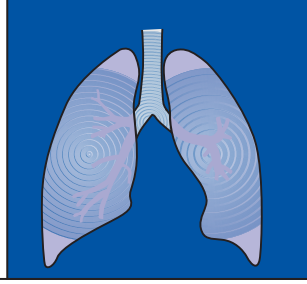

CHAPTER 16 Pharmacology of the Lung and Drug Therapy

Joseph D. Spahn and Stanley J. Szefler

TEACHING POINTS

- Medication effect is determined by pharmacokinetic and pharmacodynamic properties.
- Effect of inhaled medications such as glucocorticoids is directly related to the delivery device, potency of the drug, and distribution and elimination.
- Variability in medication response should be anticipated and potentially related to medication adherence, pharmacogenetics, and the interaction of pharmacokinetics and pharmacodynamics.

Lung pharmacology is a diverse topic. Not only are a number of pharmacologic properties involved in the administration of drugs to the lung, but the lung itself is a complex site for drug delivery and metabolism. Simple factors such as the timing of doses can have a profound effect on the pharmacologic response to selected medications. In pediatric practice, age- and size-related patient variables must also be considered.

This chapter reviews basic principles of pharmacology that pertain to the lung and therapeutic dosing strategies in pediatric patients. Asthma, one of the most common chronic diseases in children, serves as the focus. Pharmacologic treatments of specific disease entities are covered in the relevant chapters.

THE LUNG AS A SITE FOR DRUG DELIVERY

The lung is a complex site for the administration of medications. The lung can be divided into four basic anatomic components—airways, vasculature, innervation, and interstitium—each of which has its own subcomponents. Successful delivery to these sites depends on a number of different variables that are directly affected by the relevant anatomic structures. The choice of target site is important in achieving the goal of therapy (e.g., eradicating infection, attaining bronchodilation, reducing inflammation).

Airways

The airways, simply thought of as a series of narrowing and branching tubes, consist of cartilaginous bronchi, membranous bronchioles, and terminal gas-exchanging ducts or alveoli.[1] These can be subdivided into their various cross-sectional components, which include the epithelium, lamina propria, smooth muscle, and submucosal connective tissue. The β-adrenergic receptors of smooth muscle serve as the target for the β-adrenergic agonist bronchodilators. Inflammatory cells or other cells such as epithelial lining cells or infectious organisms may also be the actual target cells for drug delivery. For example, lymphocytes, thought to play an important role in the pathogenesis and severity of asthma, are the target cells of glucocorticoid therapy. The bifurcations resulting from the branching of the airways and the reductions in airway caliber with each branching provide unique challenges to drug delivery by the inhaled route of administration.

Vasculature

The blood supply of the lungs and airways, the bronchial arteries, originates from either the aorta or the intercostal arteries. The functional pulmonary circulation is a complex network of arteries, arterioles, capillaries, venules, and veins. Blood flows from the pulmonary artery to the arteries of the lung and then to the capillaries, where gas exchange occurs in the alveoli. From there, the oxygenated blood returns via the venules, veins, and pulmonary vein and then to the circulation of the body. In general, the vasculature follows adjacent to the branching airways; however, at the periphery of the lung the veins branch away to pass between the lobules, whereas the arteries and bronchi continue down the centers of the lobules.[2] Because of the vast numbers of alveoli present, the majority of the total blood volume and surface area are present in the capillaries in the walls of the alveoli.[1] This has implications not only for drug therapy with regard to therapeutic effects but also for drug-induced toxicities because the entire blood volume circulates through the lungs and comes into contact with this vast surface area.

Innervation

Innervation of the lung has been well described with regard to the adrenergic and cholinergic pathways. Although abnormalities of these pathways have been described in asthma, such as enhanced α-adrenoreceptor function, impaired β-receptor function, and enhanced cholinergic responses, all of which ultimately result in bronchoconstriction, there is increasing evidence that neural mechanisms may contribute

to the airway inflammation associated with the disease.[3,4] In addition to the classic cholinergic and adrenergic pathways, the nonadrenergic, noncholinergic (NANC) pathway is also involved in regulating the tone and secretions of the airways and vasculature.[3,4] NANC nerves can either be excitatory (eNANC) or inhibitory (iNANC). Our knowledge of the neural regulation of the airways has greatly expanded over the past decade by applying molecular biology techniques, by using knockout and transgenic mice, and by the development of several neurotransmitter antagonists. It has also become increasingly clear that there is significant interaction between the neural and immune systems. Cholinergic nerves form the predominant bronchoconstrictors of neural pathway in humans. Excessive activity of cholinergic nerves may play an important role in asthma, particularly during acute exacerbations. The eNANC pathway also contributes to asthma with substance P and neurokinin A, the neurotransmitters involved in the eNANC system. These tachykinins are potent vasodilators and bronchoconstrictors. In addition, they are proinflammatory because they are involved in the stimulation of T and B lymphocytes, mast cells, and macrophages. They are also chemotactic agents for eosinophils and neutrophils. The iNANC pathway is the only neural-mediated system involved in bronchodilation with vasoactive intestinal peptide (VIP) and nitric oxide (NO)—the implicated neurotransmitters.[4,5]

Interstitium

Pulmonary interstitium, which surrounds the blood vessels, consists of loose connective tissue (primarily collagen and elastic fibers[6]) and is generally sparse under normal conditions. Although comprising a small volume, changes in vascular permeability may result in a dramatic expansion of the perivascular interstitium, which is a major storage compartment for excess extravascular fluid in the initial stages of pulmonary edema.[7] Thus, although it is not normally a target site for drug therapy, the interstitium can clearly be important in the pathogenesis of lung disorders.

ROUTES OF DRUG DELIVERY

Before any medication can be effective, it must be delivered to its site of action in the target tissues. A number of methods can be used to effectively deliver medication. These can be broadly divided into the topical and systemic routes of administration. Topical administration includes the inhalation of aerosols delivered by the commonly used metered dose inhalers, dry powder inhalers, and nebulized solutions. Systemic delivery consists of vascular distribution after oral and parenteral administration. Each of these routes has advantages and disadvantages. The inhaled route of administration is discussed in greater detail in Chapter 17.

Inhaled Administration

The inhaled route of administration is generally preferred over systemic routes because medications are delivered directly to the site of action, bypassing the need for absorption as with orally administered medications. Smaller doses are required, and a more rapid onset of action can be obtained.[8] Any potential systemic adverse effects can also be minimized or avoided, provided that the drug has a low degree of systemic activity and absorption. Thus, the inhaled route of administration appears to be advantageous over systemic delivery (Table 16-1).

The inhaled route for drug delivery is affected by a variety of physiologic and physicochemical factors. Not only must the inhaled medication be contained within particles small enough to be aerosolized, but the particles within the aerosol must also be of proper diameter to be inhaled, avoid impaction with the pharynx, and travel down through the bifurcations of the bronchi to the smaller airways, which is the target site for most inhaled medications.[9,10] Because infants and young children have smaller lungs and airways, the delivery of medications via inhalation can be considered more difficult in this population than in adults. Diseased airways, which have reduced conductance and airflow, may cause further difficulties in achieving adequate drug delivery.

Deposition of particles in the airways occurs via basic physical mechanisms. Large particles (those >5 μm in diameter) affect the pharynx and wall of the larger airways because of the inertia of the inhaled particle (inertial impaction), and small particles (those <5 μm in diameter) deposit in the small airways as a result of gravitational sedimentation.[9,10] Other factors, such as brownian movement and electrostatic forces, play lesser roles in the deposition of particles in the respira-

Table 16-1
Topical and Systemic Routes of Drug Delivery

Route	Advantages	Disadvantages
Topical: inhaled	Drug is delivered directly to site of action. Drug bypasses absorption. Route provides reduced incidence of adverse effects.	Coordination is often required for optimal use and delivery. Route may be inconvenient. Administration may be inconsistent.
Systemic: oral	Drug is easy to administer. Route is convenient. Drug can be inexpensive.	There are potential problems with absorption. There is potential for first-pass metabolism. Drug interactions can occur. There is increased incidence of adverse effects. There is limited exposure at site of action.
Intravenous	Drug has 100% bioavailability. Route provides rapid onset of action.	Route is inconvenient. Administration is costly. Aseptic technique is required. There is potential for drug interactions. There is increased incidence of adverse effects. There is limited exposure at site of action.

tory tract. Even smaller particles (those generally <1 μm in diameter) are often too small to be deposited and retained in the airways and are exhaled. Thus the "respirable range" of aerosol particles consists of those larger than 1 μm and smaller than 5 μm in diameter.

Drugs for inhalation must first be solubilized in a delivery vehicle which should not have adverse effects of its own.[11] Some highly desirable medications for inhaled administration are not water soluble and thus require unique and innovative delivery vehicles. Liposomes have been proposed as delivery vehicles for targeting various water-insoluble medications, such as glucocorticoids and cyclosporin, to the lung.[12,13]

The delivery device itself must produce aerosols containing particles of an appropriate size, between 1 and 5 μm in diameter, as previously mentioned. Several studies have demonstrated that the different brands of metered dose inhalers and nebulizers can produce varying aerosol characteristics, rates of output, output, and residual volumes[14-17] and that some single lots of nebulizers may even demonstrate widely variable characterstics.[18,19] This can have profound implications when the optimal delivery device is selected for critical medications, such as pentamidine.[20,21]

Each type of delivery device has advantages and disadvantages (Table 16-2). With drug delivery from metered dose inhalers, the potential for local or systemic adverse effects can be minimized with proper technique and spacer devices. The benefits of spacer devices include less need for coordinating inhalation and actuation for proper use (as with breath-actuated devices), the time needed for the propellant to evaporate, retention of the larger nonrespirable particles, and reduction of particle velocity.[22] If a drug has a poor topical-to-systemic potency ratio, however, an increase of systemic adverse effects can be observed because of better pulmonary deposition.

Metered dose inhalers that use chlorofluorocarbons (CFC) as the propellant are being replaced by metered dose inhalers that use hydrofluoroalkanes (HFA) because of the increasing concern over the effect of CFCs on the earth's ozone layer.[23] Although the CFC propellants used in metered dose inhalers represent a minute fraction of the total worldwide production and use, the Montreal Protocol has spurred the development of new methods for drug delivery.

Several such examples are the dry powder inhalers, which include the Turbuhaler (AstraZeneca LP, Wilmington, Del), and newer devices such as Diskus (GlaxoSmithKline, Research Triangle Park, NC), and Twisthaler (Schering-Plough, Kenilworth, NJ). All are similar in that they are breath-actuated devices that deliver a dry, micronized powder of medication to the lungs. Because they require some degree of coordination, these devices cannot be used in young children. A benefit of newer dry powder inhalers may be better lung deposition[24] with similar or even improved total bioavailability compared with metered dose inhalers[24,25]; however, some have suggested that these devices can provoke coughing and that increased bioavailability may alter the risk for systemic adverse effects. All of the aforementioned devices contain multiple doses.

The drug must be delivered to the site of action in concentrations sufficient to produce therapeutic effects. As mentioned previously, delivery of medications to the lung of pediatric patients can be considered more difficult because of the smaller airways. Complicating this issue further is the inability of young children to cooperate, as all of the delivery systems require good effort to be effective. Other topical delivery systems, such as the sublingual and transdermal routes, are available; however, these do not yet have applications in pediatric pulmonary practice.

Oral Administration

The oral route of drug administration requires absorption from the gastrointestinal tract as an initial step. Although this route may often be more convenient than the inhaled route, especially for younger children, a number of factors can adversely influence its use.

First, a drug given orally must be bioavailable from the gastrointestinal tract. Epinephrine, for example, is not administered orally because of rapid metabolism in the gastrointestinal mucosa and liver, making the drug ineffective. If a drug can be administered orally, other drugs or food can affect the gastric emptying time or the drug absorption itself. For

Table 16-2
Inhaled Drug Delivery Devices

Delivery Device	Advantages	Disadvantages
Metered dose inhaler	Standard of therapy	Need for coordination Phase-out of fluorocarbon propellants
Metered dose inhaler with spacer device	Reduced topical effects Reduced systemic drug absorption Need to clean spacer Increased pulmonary drug deposition	Cost of spacer Possible provocation of cough
Dry powder inhaler	Actuation by breath Possible increased pulmonary drug deposition	Possible requirement for high flow rates compared with metered dose inhaler Some single-dose units only
Nebulizer	Ease of use Efficient delivery	Inconvenience for some patients Need for water-soluble drug Need to clean nebulizer High cost (air compressors and ultrasonic) Possible inconsistent drug delivery (jet) Possibility of chemical breakdown of drug (ultrasonic) Potential mechanical difficulties (ultrasonic)

example, the bioavailability of theophylline can be affected by the specific sustained-release formulation, administration with meals, and patient variables such as gastric motility and absorption from the gastrointestinal tract.[26] Although sustained-release formulations are designed to affect the rate but not the extent of absorption, differences have been observed.[26] Patient factors that can affect gastrointestinal motility and absorption (e.g., dumping syndromes or ostomies, which greatly shorten gastrointestinal transit time) can also adversely affect the bioavailability of medications.

The second factor that influences oral administration is the incidence of adverse effects. The stimulatory effects of β-adrenergic agonists are greater after systemic compared with inhaled administration. For both terbutaline and oral albuterol, studies have shown significantly more adverse effects and increased heart rate and tremor but similar efficacy when intravenous administration is compared with inhaled administration.[27,28] Another example is the chronic administration of oral glucocorticoids. Although very effective in the long-term management of asthma, the adverse effects of chronically administered oral glucocorticoids preclude its use in all but the most severe asthmatic patients. A medication given orally must, therefore, not only be active, but it must also have a low degree of adverse effects.

Parenteral Administration

Parenteral routes of administration include the subcutaneous, intramuscular, and intravenous routes. For these routes to be viable, a medication must be water-soluble or in suspension. The intravenous route of administration bypasses the absorption step, resulting in 100% bioavailability. Another advantage is the rapid onset of action. These routes of drug administration may not always be viable because of inconvenience and cost. Also, the drug's adverse effects are not reduced compared with the effects after oral administration. Other disadvantages with parenteral routes are patient discomfort, the need for sterile conditions, and potential risks to health care practitioners from blood-borne pathogens. In some cases, however, these routes of administration may be the only way to achieve therapeutic concentrations at the target tissues, such as with some anti-infective agents and in emergency situations with asthmatic patients.

PHARMACOKINETICS

Drug Distribution

The following sections provide a brief overview of pharmacology. The first section deals with the various pharmacokinetic parameters such as volume of distribution and clearance (Box 16-1) whereas the second section deals with pharmacodynamics. *Pharmacokinetics* describe the relationship between the concentration of the drug at its site of action to time, whereas *pharmacodynamics* describe the relationship between the concentration of the drug to its clinical effects (Fig. 16-1). The distribution of systemically administered medications is important in that the drugs must be available to the target tissues. The *volume of distribution (Vd)* relates a drug's plasma concentration *(C)* to the concentration in the tissues and is defined by the following equation:

BOX 16-1 Definitions of Pharmacokinetic Parameters and Their Relevance to Inhaled Glucocorticoids in Asthma

Bioavailability. Bioavailability refers to the amount of drug systemically absorbed. In the case of inhaled glucocorticoid (GC) therapy, two routes of absorption are available. The drug can be absorbed via the oral route or via the lung. Both routes of absorption contribute to the systemic bioavailability.

Clearance. Clearance refers to the volume of blood that is cleared of the drug per unit of time. The clearance rates for all of the inhaled GC preparations are quite rapid and approach that of hepatic blood flow. This property contributes significantly to the high topical to systemic potency because these drugs are cleared quickly from the systemic circulation.

Volume of distribution. Volume of distribution refers to the distribution of the drug in the tissues of the body. Largely, this property is dependent on the lipophilicity of the drug: the greater the lipophilicity, the greater the apparent volume of distribution. The volumes of distribution among the available inhaled GCs vary greatly, but this parameter affects the topical-to-systemic potencies to a much lesser extent than that of systemic clearance.

Elimination half-life. The elimination half-life refers to the rate at which a drug is removed from the systemic circulation. It is derived from both the clearance and volume of distribution of the drug in question.

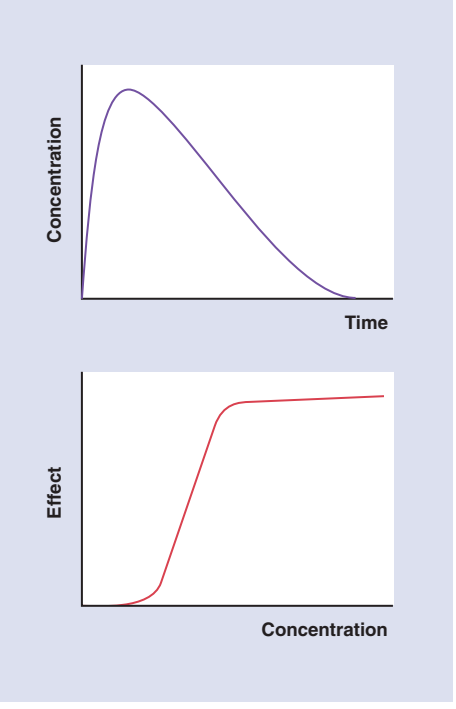

Figure 16-1 Graphic representations of the distinction between the pharmacokinetic and pharmacodynamic properties of a drug. The pharmacokinetics describe the concentration of a drug at the site of action over time, whereas the pharmacodynamics tries to relate the concentration of the drug to its clinical effects.

Eq 16.1

$$Vd = \frac{Dose}{C}$$

However, this does not provide insight into the drug's concentration at the relevant target tissue sites. A drug's volume of distribution, known from population values, allows calculation of the loading dose *(LD)* required to give a specified peak plasma drug concentration (C_p), as follows:

Eq 16.2

$$LD = Vd\ C_p$$

With oral dosing, the bioavailability of the particular drug and dosage form must also be considered. For some medications, such as theophylline, a "therapeutic range," which balances the desired therapeutic effects with the unwanted toxic effects, has been developed.[29,30] In the case of theophylline, the traditionally regarded therapeutic range (10 to 20 μg/mL) has been reassessed, and new guidelines recommend lower concentrations (5 to 15 μg/mL).[31,32]

The volume of distribution is related to the drug's lipophilicity, plasma protein binding, and route of elimination. A highly lipophilic medication, which tends to distribute and bind more widely to body tissues, generally has a larger volume of distribution and is metabolized in the liver.[33] Drugs that are highly protein bound or that have large molecules and thus remain primarily in the plasma, tend to have smaller volumes of distribution and are excreted unchanged by the kidney.[33] Factors affecting these parameters, such as competitive protein binding by other medications or metabolic changes that can affect protein binding (pH, serum albumin concentration, disease states that affect affinity of binding to albumin), can influence the drug's volume of distribution and can result in changes in therapeutic effect or toxicity.

For drugs that distribute to highly perfused tissues (versus adipose tissue), dosing is often based on ideal body weight. Examples of such drugs are aminoglycoside antibiotics and, on occasion, theophylline. Finally, differences among drugs themselves can manifest as differences in distribution to specific tissues. It has been demonstrated in an animal model that methylprednisolone achieves higher concentrations in the lung and persists for a longer period of time than prednisolone.[34,35] This may result in a therapeutic benefit of methylprednisolone over prednisolone during treatment of inflammatory conditions of the lung.

Drug Elimination

Drugs are eliminated from the body via two general pathways. They are either metabolized in the liver or excreted in the urine. As alluded to previously, the route of elimination is affected to some degree by the lipophilicity and size of the drug molecule. Drug metabolism can occur in body tissues other than the liver; however, this is usually to such a small extent that the effect on the total body clearance is minimal. A notable exception are glucocorticoids, which are thought to be metabolized in all body tissues.[36] In most instances, the total body clearance of a drug is the sum of both the hepatic and renal clearances. If a steady-state serum drug concentration *(Css)* is desired, the clearance *(Cl)* must be known so that the maintenance dose *(MD)* can be calculated, as follows:

$$MD = Cl \bullet C_{ss} \bullet t \qquad \text{Eq 16.3}$$

where *t* is the dosing interval. Clearance can also be calculated directly with detailed pharmacokinetics studies. After the serum concentration versus time curve is plotted after a dose of a given drug, the clearance is calculated as follows:

$$Cl = \frac{Dose}{AUC} \qquad \text{Eq 16.4}$$

where *AUC* is the area under the serum concentration versus the time curve. The AUC is most commonly calculated using the trapezoidal rule, which involves dividing the serum concentration versus the time curve into a series of trapezoids and calculating their areas (Fig. 16-2). The AUC is the sum of the areas of these trapezoids, and is approximated by the following equation[37]:

$$AUC = {}^1/_2(C_1 + C_2)(t_2 - t_1) + {}^1/_2(C_2 + C_3)(t_3 - t_2) + {}^1/_2(C_3 + C_4)(t_4 - t_3) + {}^1/_2(C_{n-1} + C_n)(t_n - t_{n-1}) \qquad \text{Eq 16.5}$$

Hepatic Clearance

Hepatic elimination of medications often occurs via the cytochrome P-450 pathway. There are approximately 50 active cytochrome P-450s of which 8 to 10 are involved in the majority of drug metabolism reactions. These isoforms are abbreviated using the term CYP. The following describes the medication used to treat asthma followed by the CYP isoenzymes involved in their elimination: glucocorticoids (CYP3A4), the long-acting beta agonist formoterol (CYP2A6, 2C9, 2D6), the leukotriene-modifying agents montelukast (CYP2C9, 3A4), zafirlukast (CYP2C9), and zileuton

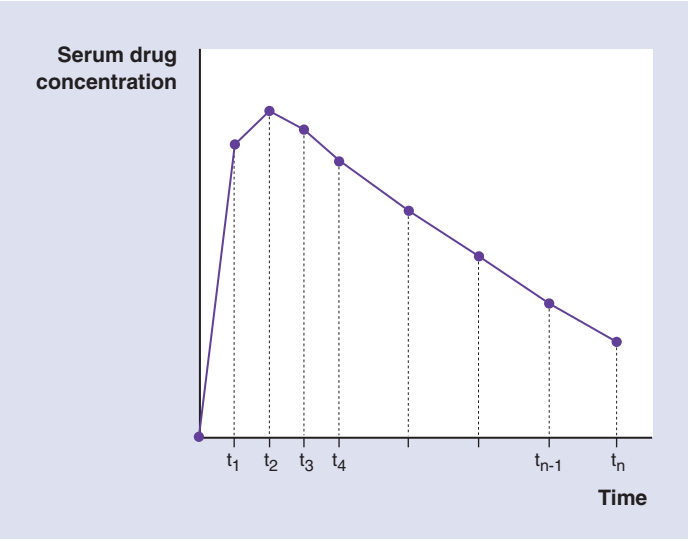

Figure 16-2 Division of a serum drug concentration versus time curve into a series of trapezoids for calculation of its AUC using the trapezoidal rule. AUC, area under the curve.

(CYP2C9, 1A2), and theophylline (CYP1A2, 2E1, 3A3).[33] This metabolic pathway is of importance because drugs metabolized by the P-450 system are susceptible to a number of drug interactions, resulting in either acceleration or reduction in metabolism based on whether the drug interaction results in inhibition or acceleration of the involved isoenzymes.

Theophylline is a good example of a medication significantly affected by drugs that either accelerate or inhibit the cytochrome-P-450 system. For example, the dose of theophylline must be reduced by ~50% in subjects receiving theophylline who are to be treated with a macrolide antibiotic such as erythromycin. Erythromycin is a potent inhibitor of the cytochrome P-450 system, and concomitant use with theophylline will substantially reduce theophylline metabolism, resulting in elevated serum concentrations and the potential for cardiac arrhythmias, seizures, and possible death. Theophylline has a narrow therapeutic index; concentrations below 5 μg/mL are ineffective whereas concentrations above 20 μg/mL can be associated with substantial toxicity. As a result, patients treated with theophylline require close monitoring and appropriate dosage adjustment to maintain levels within the therapeutic range. Of special consideration are the anticonvulsant agents phenytoin, phenobarbital, and carbamazepine, which enhance the metabolism of theophylline and glucocorticoids.[38-40] The macrolide antibiotics, troleandomycin, erythromycin, and clarithromycin, have also been shown to reduce methylprednisolone (but not prednisolone) clearance.[39-43]

Clearance and inactivation of drugs occur via other metabolic pathways. The short-acting β-adrenergic agonist albuterol, for example, undergoes conjugation in humans and glucuronidation in other species.[45] Drug clearance via these metabolic pathways is influenced by hepatic blood flow and the intrinsic capacity of liver enzymes to metabolize drugs.[44] Disease states that affect these factors can result in changes in drug metabolism. The most common disease state affecting the hepatic elimination of drugs is liver disease, which invariably results in reduced drug elimination. For example, theophylline elimination can be significantly altered by liver cirrhosis, acute hepatitis, cholestasis, and cor pulmonale.[25,46] Glucocorticoids, however, are extensively metabolized throughout the body.[36] Thus, liver disease has a minor impact on total body elimination, and dosage adjustments are not necessary. Other disease states can affect a drug's metabolism. Prednisolone elimination is enhanced in children with cystic fibrosis compared with children without the disease.[47] Elimination of other drugs metabolized via hepatic glucuronosyltransferase and biliary secretion are thought to be enhanced in cystic fibrosis as well, with oxidative metabolism unaffected.[48]

Renal Clearance

Renal drug clearance is a function of three mechanisms: glomerular filtration, tubular secretion, and tubular reabsorption. These mechanisms are influenced by plasma drug concentration and protein binding, urine flow and pH, and the general degree of kidney function and thus can affect the renal elimination of drugs.[45] For some drugs such as aminoglycoside antibiotics, estimates of creatinine clearance based on serum creatinine concentrations allow for a relatively accurate estimation of drug clearance and required dosing regimens.

First- and Zero-Order Elimination

Most drugs are metabolized by first-order elimination; that is, the rate of metabolism is proportional to the amount of drug in the body. A constant fraction of the drug in the body is metabolized per unit time. This constant is known as the *elimination rate constant* (k_e). The amount of drug removed *(R)* depends on the amount of drug present in the body *(A)* and is defined by the following equation:

$$R = k_e \bullet A \qquad \text{Eq 16.6}$$

The elimination rate constant can be calculated from a drug's clearance *(Cl)* and volume of distribution *(Vd)*, as follows:

$$k_e = \frac{Cl}{Vd} \qquad \text{Eq 16.7}$$

For some drugs, elimination pathways may become saturated. Thus, metabolism occurs at a fixed rate (k_m) or demonstrates zero-order elimination. With zero-order elimination, the amount of drug removed depends not on the amount of drug in the body but on the amount of time involved and can be described as follows:

$$R = k_m \bullet \text{Time} \qquad \text{Eq 16.8}$$

Most drugs demonstrate first-order elimination, with zero-order elimination observed in some patients as the dose is increased. A small fraction of the population may demonstrate zero-order theophylline metabolism even with therapeutic doses, and a number of instances of this phenomenon have been reported.[49] In such cases, changes in dosage do not correspond to proportional changes in serum concentration as they would if the drug demonstrated first-order elimination. Rather, small dosage increases can result in large increases in serum concentrations and possibly toxicity. Patients who demonstrate zero-order theophylline metabolism at concentrations within or close to the therapeutic range must be identified and then followed by close monitoring and careful dosage titration to maintain safe concentrations and prevent toxicities.

PHARMACOKINETICS AND PHARMACODYNAMICS OF INHALED MEDICATIONS

Glucocorticoids

By effectively delivering small quantities directly into the airway, inhaled glucocorticoids (GCs) maximize the beneficial effects while minimizing the unwanted systemic effects. In this way, one achieves a more favorable topical-to-systemic potency ratio or therapeutic index (Fig. 16-3). There are currently six inhaled GCs available for use in the United States: beclomethasone dipropionate (Qvar 40, 80 μg/inhalation), triamcinolone acetonide (Azmacort 100 μg/inhalation), flunisolide (Aerobid 250 μg/inhalation), budesonide (Pulmi-

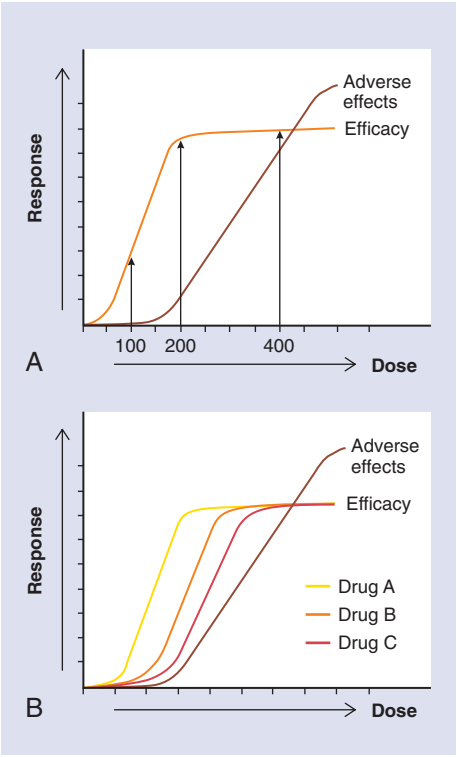

Figure 16-3 Graphic representation of the therapeutic index. The therapeutic index describes the relation between the wanted and unwanted effects of a drug. **A** demonstrates the point that the therapeutic index is dependent on the dose of the drug administered. The ideal dose is one that results in the greatest clinical effect with the smallest unwanted effect. **B** demonstrates the second important point—that the therapeutic index varies between members of a class of drugs. Drug A has the best therapeutic index; Drug B has a fair therapeutic index; Drug C has the poorest therapeutic index.

cort 200 µg/inhalation and 0.25 and 0.5 mg/2 mL solution), fluticasone propionate (Flovent 44, 110, 220), and mometasone furoate (Asmanex 220 µg/inhalation). A seventh product, ciclesonide, is currently undergoing phase III clinical studies. The pharmacokinetic and pharmacodynamic properties of inhaled GCs have received increasing attention as greater scrutiny has been placed on their potential adverse effects. The following discussion will provide an overview of how the pharmacokinetic and pharmacodynamic properties of inhaled GCs influence their effectiveness and potential for adverse effects.

DRUG DELIVERY

The delivery device and the propellant used to deliver inhaled glucocorticoids affect not only the amount of drug delivered to the lung, but also their deposition pattern within the lung.[50,51] Inhaled glucocorticoids can be delivered using three different devices. The most commonly used device is the pressurized metered dose inhaler (PMDI) that uses as a propellant either chlorofluorocarbon (CFC) or the "ozone friendly" hydrofluoroalkane (HFA). More recently, dry powder breath-actuated inhalers (DPIs), such as the Pulmicort Turbuhaler, Asmanex Twisthaler and the Advair Diskus, have been developed. The third type of device uses budesonide in a suspension for nebulization (Pulmicort Respules) for treatment in children 1 to 8 years of age.

The delivery device contributes significantly to the delivery of the inhaled GC to the lower airway. For example, budesonide delivered via the DPI Turbuhaler results in twice the lower airway deposition than that of the MDI.[24] The use of a holding chamber with MDIs can also significantly enhance the delivery of the drug into the lower airways while decreasing the amount of drug deposited on the oropharynx.[52,53] The mechanisms by which a holding chamber enhances drug delivery to the lungs are numerous. First, the holding chamber allows for a reduction in velocity of the ejected mass so that the majority of medication does not negatively affect the posterior oropharynx. Second, the aerosol has time to evaporate, thereby allowing for the generation of smaller particles from larger aggregate particles. Third, larger particles will deposit onto the chamber walls instead of the oropharynx.

In contrast to budesonide, where the DPI is a more efficient delivery device than the MDI, the opposite appears to be the case with fluticasone propionate. In a study published by the Asthma Clinical Research Network (ACRN), 111 µg/d of fluticasone propionate, delivered via a pMDI, resulted in a 10% suppression of plasma cortisol concentration area under the curve (AUC), whereas a fourfold greater amount (445 µg/d) was required when fluticasone propionate was delivered from a DPI device (Rotodisk).[51] The reason for discrepancy can be explained by differences in the fine particle dose (FPD) generated by the two devices. The FPD is considered to be the dose delivered to the lung. Fluticasone MDI provided an FPD of 52%, whereas DPI provided an FPD of only 11%.

The type of propellant used to power an MDI can have a profound effect on the amount of drug delivered and its deposition pattern within the airway. Glucocorticoids such as beclomethasone dipropionate, flunisolide, and ciclesonide dissolve into solution when HFA is the propellant, whereas all other inhaled glucocorticoids remain in a suspension, regardless of the propellant used. In solution, the average particle size is much smaller (1.1 µm), compared to an average particle size of 3.5 to 4.0 µm for glucocorticoids in suspension.[54] This is of clinical importance because smaller particles provide for greater drug delivery to the lung and greater delivery to the distal airways.[55] As a result, smaller concentrations of beclomethasone dipropionate–HFA have been shown to provide equivalent or superior efficacy compared to beclomethasone dipropionate–CFC.[56]

BIOAVAILABILITY

The systemic bioavailability of inhaled GCs is the sum of the absorption from both the oral and pulmonary routes (Fig. 16-4). The amount of drug swallowed is eventually absorbed from the gastrointestinal tract and is responsible for the oral bioavailability. Depending on the inhaled GC, oral bioavailability ranges from <1% for fluticasone propionate and mometasone furoate to 23% for triamcinolone acetonide.[57,58] Pulmonary bioavailability results from absorption of the inhaled GC that reaches the lung—with the amount of drug delivered determining the pulmonary contribution to systemic bioavailability. Thus, for fluticasone propionate, all of its systemic bioavailability comes from the pulmonary route, whereas for drugs such as triamcinolone acetonide and flunisolide, both oral and pulmonary bioavailability account for their systemic bioavailability (Table 16-3).

Table 16-3
Pharmacodynamic and Pharmacokinetic Parameters of Inhaled Glucocorticoids

Drug	RRA (L/hr)	Clearance (L)	Vd_{ss} (hr)	$t_{1/2}$ (%)	F_{oral} (%)	F_{inh} (%)
Mometasone furoate	2200	53.5	332	5.8	>1	NA
**Des-ciclesonide (active metabolite of ciclesonide)	1200	228	900	5.5	>1	52*
Fluticasone propionate	1800	69	318	7.8	>1	16
Beclomethasone monopropionate (active metabolite of BDP)	1345	120	400	2.7	26	55-60*
Budesonide	935	84	183	2.8	11	28
Triamcinolone acetonide	233	37	103	2.0	23	22
Flunisolide	180	58	96	1.6	20	39

*Delivered via hydrofluoralkanes-metered dose inhaler (HFA-MDI).
**Undergoing phase III clinical studies in the United States.
BDP, beclomethasone dipropionate; F_{inh}, inhalational bioavailability; F_{oral}, oral bioavailability; NA, not available; RRA, relative receptor affinity compared to dexamethasone (RRA = 100); $t_{1/2}$, plasma elimination half-life; Vd_{ss}, volume of distribution at steady state.

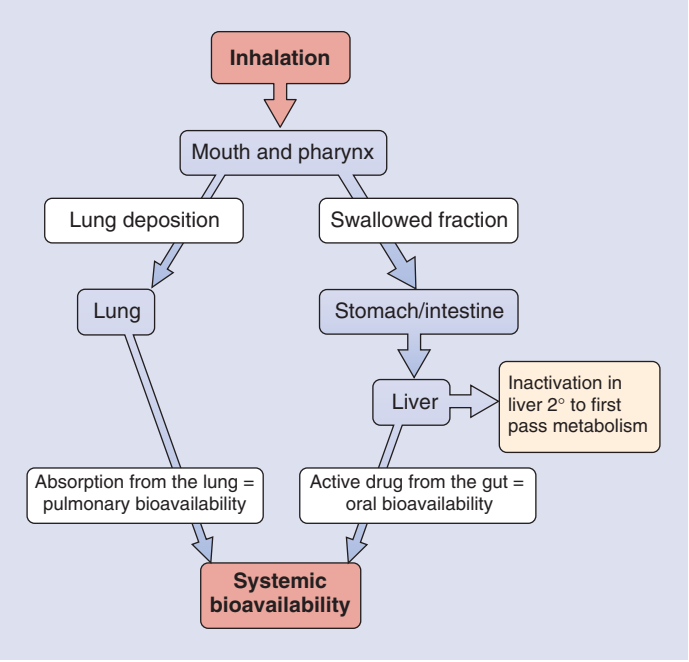

Figure 16-4 Flow diagram depicting the factors influencing the bioavailability of topically administered glucocorticoids. See text for details.

Airway diameter can also impact the bioavailability of an inhaled glucocorticoid. This point was demonstrated by Brutsche and colleagues,[59] who compared the pharmacokinetics of fluticasone propionate administered via MDI and spacer in asthmatics with significant airflow limitation (FEV_1 54% of predicted) to nonasthmatic controls (FEV_1 108% of predicted). The asthmatics, compared to the controls, had a significantly lower plasma fluticasone AUC (1082 versus 2815 pg/mL/hr), lower peak plasma fluticasone propionate levels (117 versus 383 pg/mL), and lower systemic bioavailability (10.1 versus 21.4%) following inhalation of fluticasone propionate.

Airway obstruction can also negatively influence efficacy. High-dose inhaled GC therapy administered over 1 to 2 weeks is often used to treat exacerbations of asthma.[60,61] Although inadequately studied, this form of therapy is thought to be efficacious in patients with mild to moderate exacerbations. Whether this practice is appropriate for severe exacerbations was recently examined.[62] In this study, 100 children with an acute severe asthma exacerbation (mean FEV_1 44% of predicted) who presented to the emergency department were randomized to receive high-dose fluticasone propionate (2000 μg) or prednisone (2 mg/kg) in addition to standard care, which included frequently administered albuterol and ipratropium. After 4 hours, the prednisone-treated subjects had a greater improvement in FEV_1 (18.9%) compared to those treated with fluticasone (9.4%). In addition, all subjects who received prednisone had stable or improved lung function, whereas 25% of the children treated with fluticasone actually had a decline in lung function. Of greatest importance, 31% of the children who received fluticasone required hospitalization compared to only 10% treated with prednisone. The authors concluded that fluticasone propionate was ineffective because of poor drug delivery as a result of significant airflow limitation. In this scenario, prednisone, although much less potent than fluticasone propionate on a microgram to microgram basis, was more effective because it reached sites of inflammation, perhaps the peripheral airways or deeper tissue layers, that were inaccessible via the inhaled route.

RECEPTOR AFFINITY

The affinity with which a GC binds to its receptor is an important pharmacodynamic parameter as receptor-binding affinity is closely linked to anti-inflammatory potency. Inhaled GCs with the highest receptor binding affinity have the greatest anti-inflammatory effects in vitro. Mometasone furoate has the greatest affinity, followed closely by fluticasone propionate and beclomethasone monopropionate (the active metabolite of beclomethasone dipropionate). The affinity of the remaining inhaled GCs in descending order is ciclesonide, budesonide, triamcinolone acetonide, and flunisolide (see Table 16-3).[63] Spahn and coworkers,[64] using an in vitro functional assay in which the concentration of GC required to inhibit lymphocyte activation by 50% was the pharmacodynamic parameter evaluated, found a similar hierarchy of potency. This pharmacodynamic assay has also been used clinically to assess GC responsiveness or resistance in adults and children with severe asthma.[65,66]

PULMONARY RETENTION TIME

Pulmonary retention is another important parameter to consider. Drugs with prolonged lung retention times have a

longer time within the lung to exert their anti-inflammatory effects and at the same time their absorption into the systemic circulation is delayed. Both of these factors are likely to contribute to a more favorable therapeutic index. Pulmonary retention is related to several factors including lipophilicity. The more lipophilic the GC, the greater the pulmonary retention time. FP is the most lipophilic GC; it also has a prolonged pulmonary retention time.[67] This finding was demonstrated by Esmailpour and coworkers,[68] who sought to investigate both the pulmonary retention and distribution of FP in vivo by having 17 subjects undergoing pneumonectomy or lobectomy for bronchial carcinomas inhale a single dose of fluticasone propionate (1000 μg) prior to surgery. The investigators were able to measure fluticasone propionate in the resected lung tissue for up to 16 hours. Of little surprise, central lung tissue had concentrations of fluticasone three to four times that of peripheral lung tissue, which in turn was approximately 100 times greater than that found in the serum.

Another method used to increase pulmonary retention time is to develop an inhaled GC that undergoes intracellular esterification with fatty acids. Fatty acid esterification within the lung has been demonstrated with both budesonide and ciclesonide. By creating fatty acid conjugates, a slow-release depot is produced which allows for a prolonged topical effect while minimizing systemic effects. In vitro studies have shown budesonide's pulmonary retention time to be as long or longer than FP owing to long-chain fatty acid conjugation within the airway epithelial cells.[69-71] This property likely explains why budesonide, although being less lipophilic and having a shorter half-life compared to fluticasone, has a once-daily indication, whereas fluticasone is administered twice daily.[72]

CLEARANCE AND VOLUME OF DISTRIBUTION

All of the available inhaled GCs display rapid systemic clearance with values approximating that of hepatic blood flow, which is the maximal rate at which hepatically metabolized drugs can be cleared.[63] As previously alluded to, the volume of distribution (Vd) is a measure of tissue distribution and is related to the lipophilicity of the drug (see Table 16-3).[73] Highly lipophilic drugs enter the tissues easily, resulting in a high Vd. The retention time in the various tissues of the body is dependent on the equilibrium that develops between the tissues and the systemic circulation. As a result, the volume of distribution is calculated by the ratio of the fraction unbound in the plasma (f_u) and in the tissue compartment (f_{uT}) and the volume of the plasma. Desisobutyryl-(des-)ciclesonide, the active metabolite of ciclesonide, has the highest Vd at 900 L, followed by beclomethasone monopropionate (the active metabolite of beclomethasone dipropionate) at 400 L, and fluticasone propionate at 318 L. The Vds of the other inhaled GCs are smaller with values ranging from 58 L for flunisolide to 84 L for budesonide (see Table 16-3).[75] It remains to be determined whether clinically significant correlations exist between Vd and measures of clinical efficacy and systemic adverse effects.

ELIMINATION HALF-LIFE

The elimination half-life varies substantially among the inhaled GCs and is dependent on both the systemic clearance rate and the volume of distribution (see Table 16-3). Given fluticasone propionate's large Vd, it is not surprising that it has the longest elimination half-life of 7.8 hours.[74] Desciclesonide has a larger Vd but its clearance is greater than that for fluticasone propionate. As a result, its half-life is shorter at 5.5 hours. The other inhaled GCs have values ranging from 0.1 to 0.2 hour for BDP to 5.8 hours for mometasone furoate (see Table 16-3).[24,57,76-78] Because fluticasone propionate has a long elimination half-life, it will take the drug longer to reach steady-state levels compared to the other inhaled GCs. This finding was supported by a recent study by Whelan and associates, who measured plasma fluticasone propionate concentrations following 1 and 6 weeks of fluticasone propionate 352 μg twice daily delivered via a CFC-containing MDI. The investigators found increasing fluticasone AUC from week 1 to week 6, suggesting that the time required to reach steady-state concentrations likely exceeds 1 week of treatment.[79]

Because FP is highly lipophilic, it has a larger volume of distribution and a longer elimination half-life. These properties have been used to explain fluticasone propionate's greater ability to suppress the HPA axis[80-82] compared to budesonide.[73] Although the greater Vd and longer terminal half-life of fluticasone propionate may contribute to its greater propensity to suppress the HPA axis, it should be noted that a large volume of distribution does not necessarily imply a greater potential for systemic effects. This is because GCs circulate primarily in an inactive protein-bound form. The active unbound form is independent of the Vd, with clearance and extent of protein binding the most important variables. Another potential explanation for fluticasone propionate's ability to suppress cortisol production especially at higher doses comes from the observation that fluticasone propionate binds to the GC receptor with greater affinity than the other inhaled GCs—with the exception of mometasone furoate. With increased receptor binding comes enhanced anti-inflammatory activity but also greater metabolic effects because all cells except red blood cells share the same GC receptor.

CICLESONIDE—A "THIRD GENERATION" INHALED GLUCOCORTICOID

Ciclesonide is currently undergoing phase III studies in the United States. It is considered a third generation inhaled GC because it has a number of unique features that distinguish it from other members of the class. First, it is a pro-drug. As it exists in the canister, ciclesonide is in an inactive form. Once it enters the lung, it is metabolized by lung esterases to its active form, des-ciclesonide. Des-ciclesonide has high GC receptor binding affinity, and as such, is likely to display significant anti-inflammatory effects. Second, because ciclesonide is inactive until it reaches the lung, there is less potential for local adverse effects such as oral candidiasis or dysphonia.[83] Third, ciclesonide undergoes lipid conjugation within the lung.[84] As previously discussed, inhaled GCs that undergo lipid conjugation have longer pulmonary retention times[69-71] and a greater potential to exert local anti-inflammatory effects. Fourth, once des-ciclesonide enters the systemic circulation, the majority (99%) is protein bound.[83] Because only the unbound or free fraction of a GC can bind to the GC receptor, drugs with extensive protein binding have little potential to exert systemic adverse effects. Des-

ciclesonide is 99% protein bound, whereas only 90% of fluticasone propionate is bound. This represents a 10-fold difference in protein binding (1% versus 10%) and a 10-fold difference in the concentration of drug available to exert systemic effects.[85] As a result, ciclesonide has fewer potential adverse effects than the other available inhaled GCs on a microgram-per-microgram basis. Ciclesonide has a relatively short half-life compared to the second-generation inhaled GC fluticasone (3.4 hours versus 8 to 10 hours).[83,86] The reason for its short half-life is its extremely rapid clearance from the systemic circulation. Ciclesonide is cleared from the circulation two to three times more rapidly than all the other inhaled GCs. This finding suggests that nonhepatic tissues must also contribute to its clearance. It should be stressed that much of the potential advantages of ciclesonide are yet to be proved in a clinical setting. These data will become available only when the drug is introduced for widespread use.

Inhaled Antibiotics for Cystic Fibrosis

Cystic fibrosis is the most common lethal inherited disease of whites—affecting 1 : 2000 to 1 : 2600 live births. It is a disorder of exocrine function involving multiple organs, but pulmonary disease is responsible for >90% of the morbidity and mortality in patients past the neonatal period. The defective gene has been identified and is located on chromosome 7q31.[87] The gene codes for a membrane-bound chloride channel called the cystic fibrosis transport regulator or CFTR. Patients with CF display increased viscosity of secretions from mucous glands and have undue susceptibility to chronic endobronchial colonization by *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Burkholderia cepacia*.

Chronic bronchopulmonary infection is thought to result in airway inflammation, which in turn leads to progressive loss of lung function.[88] Endobronchial colonization with *P. aeruginosa* occurs early in life (2 to 3 years), and once present it is difficult, if not impossible, to eradicate.[89] Thus, the mainstay of treatment in this disease is aggressive antibiotic therapy. Antibiotics are currently used in three distinct clinical situations: (1) antibiotics are used early in the course of the disease in an attempt to delay the onset of chronic colonization with *P. aeruginosa;* (2) intravenous antibiotics are used in combination with aggressive chest physiotherapy in a hospital setting to treat acute exacerbations; (3) once a child is colonized with *P. aeruginosa*, chronic antibiotics are administered in an attempt to slow the progressive decline in lung function associated with CF. Historically, the most frequent routes of delivery have been oral or intravenous, but over the past decade, inhaled antibiotic therapy has become increasingly utilized in an attempt to eradicate—or at least decrease the density of—*P. aeruginosa* in children who have become colonized.

Delivery of inhaled antibiotics such as tobramycin to patients with CF offers several potential advantages.[90] First, the drug is delivered directly to the site of infection. Second, much higher sputum concentrations can be achieved via the inhaled versus the oral or parenteral routes. Third, only a small fraction of the drug is absorbed from the lung and as a result, there is less potential for systemic toxicity. In addition, by delivering the antibiotic topically, there is less disturbance of the host's microorganisms. The following discussion will provide a brief overview of the pharmacokinetics and pharmacodynamics of inhaled tobramycin because it is the only inhaled antibiotic that is approved by the U.S. Federal Drug Administration (FDA) for use in children with CF.

INHALED TOBRAMYCIN (TOBI)

In 1997, TOBI (tobramycin solution for inhalation) was approved for use in children with CF 6 years of age and older. The recommended dose is 300 mg twice daily to be administered intermittently in 28-day cycles (28 days of therapy followed by 28 days off therapy). TOBI is dissolved in 5 mL of sterile preservative-free sodium chloride solution with an osmolality of 158 to 183 mOsm/kg and a pH of 6.0.[91] The manufacturer recommends TOBI to be administered using the PARI LC PLUS jet nebulizer with a DeVilbiss Pulmo-Aide compressor because this is the system that was used in the phase III studies designed to assess safety and efficacy.

As is the case with most inhaled medications, only a fraction of aerosolized tobramycin reaches the lower respiratory tract. Approximately 10% to 15% of the starting dose actually reaches the lung. As a result, the systemic bioavailability is also low with values ranging from 9% to 17.5%.[92,93] Ten minutes following administration of 300 mg of TOBI, the mean sputum tobramycin concentration was 1371 ± 1180 μg/g.[94] This value is much higher than the concentration thought to kill *P. aeruginosa* in sputum (100 μg/g).[95] Of importance, tobramycin concentrations 10 times the MIC may be required to suppress the growth and up to 25 times the MIC may be required to kill *P. aeruginosa* in sputum based on in vitro studies. In the two phase III placebo-controlled studies performed to gain FDA approval of TOBI, 464 patients received placebo or aerosolized TOBI 300 mg twice daily for 28 days (1 cycle) followed by 28 days off for a total of six cycles.[96] The mean sputum concentration 10 minutes after the initial dose was 1529 ± 1382 μg/g of sputum. TOBI was found to be more effective than placebo in improving lung function and decreasing the sputum density of *P aeruginosa.* Those who received tobramycin had a mean improvement in FEV_1 of 10%, whereas those who received placebo had a decrease in FEV_1 of 2% during the course of the study. The greatest improvement in FEV_1 came in the first 2 weeks, although improvement over placebo was maintained during the 20 weeks of the study. In addition, there was a significant decrease in sputum *P. aeruginosa* density in those who received tobramycin versus placebo at week 20. The mean serum tobramycin concentration 1 hour following the initial dose of TOBI was 0.94 μg/mL and unchanged 20 weeks later with a value of 0.98 μg/mL. Of note, sputum and serum concentrations were not related to age, gender, or baseline lung function. TOBI was well tolerated, although there was a trend toward increase in MIC in the *P. aeruginosa* isolates in the tobramycin-treated patients.

At present, there is some debate as to whether serum tobramycin concentrations should be monitored in children on chronic aerosol therapy. Most studies have shown serum concentrations to remain <2 μg/mL with no evidence for accumulation over time.[97] Nevertheless, nephrotoxicity should be assessed by obtaining serum creatinine, BUN, and urinalysis following 180 days of aerosolized tobramycin therapy.[98] Audiometric evaluation in the 500 to 8000 Hz

range has also been recommended after 180 cumulative days of therapy. Efficacy should be assessed by performing pulmonary function tests 2 to 4 weeks after institution of therapy. A lack of initial response does not preclude response later in the course because 30% of patients who did not have an immediate response were noted to have responded by 3 months of therapy.[96]

RECEPTOR PHARMACOLOGY

Receptors are biological units, specific protein recognition sites that bind or interact with molecules and determine the cellular response to such molecules at target tissues. These molecules commonly include drugs but also consist of endogenous hormones, neurotransmitters, mediators, and peptides. Receptor types include cell surface receptors and intracellular receptors. An example of each receptor site particularly relevant to respiratory diseases is the β-adrenergic receptor (cell surface) and the glucocorticoid receptor (intracellular).

Surface Receptors

Cell surface receptors, structurally consisting of polypeptide chains folded and crossing back through cell surface membranes several times, are known as *G-protein coupled receptors* because they interact with a guanine nucleotide regulatory protein.[99] Among these are the β-adrenergic receptors, adenosine receptor subtypes, and muscarinic receptor subtypes. The human β-adrenoceptor gene is located on chromosome 5 and codes for an intronless gene product of 1200 base pairs. The β-adrenoceptor family consists of at least three distinct groups, β_1, β_2, and β_3, which have been classically identified in heart, airway smooth muscle, and adipose tissue, respectively.[100]

Stimulation of β-adrenergic receptors results in a variety of effects. These include β_1 or chronotropic effects, and β_2 or smooth muscle relaxation effects. This stimulation of β_2-adrenergic receptors of the respiratory smooth muscle makes β-adrenergic agonist agents useful in the treatment of asthma. The mechanisms by which β-adrenergic agonists result in bronchodilation are well understood. Stimulation of the receptors activates adenylate cyclase and increases the level of intracellular cyclic adenosine monophosphate (cAMP). This is followed by activation of protein kinase A (PKA), inhibition of myosin phosphorylation, and lowering of intracellular calcium concentrations, which ultimately results in relaxation of airway smooth muscle.

Selectivity of an adrenergic agonist agent between β_1- and β_2-adrenergic effects results in a lesser incidence of the undesirable β_1 or chronotropic effects. Although it was once popular belief that β_1-adrenergic receptors existed only in heart tissue and β_2-adrenergic receptors were found only in lung tissue, radioligand-binding studies have demonstrated that each receptor subtype exists in both cardiac and lung tissue in almost equal proportions.[101] Stimulation of β_3-receptors, which are found in adipose tissue, is thought to result in the metabolic responses of adipocytes, muscle, and the gastrointestinal tract.[102]

The assessment of the pharmacodynamics of short-acting β-adrenergic agents is influenced by the development of tolerance (also referred to as *tachyphylaxis* or *desensitization*). Continuous exposure to a β_2-adrenergic agonist leads to reduced efficacy associated with diminished receptor density on the cell surface.[103] This is due to several intracellular mechanisms. Repeated receptor activation by agonist results in phosphorylation of serine and threonine amino acid residues on the intracellular carboxy terminus by serine-threonine kinase (also termed *β_2AR kinase*, *GPCR kinase*, or *GRK2*). This action, in combination with β-arrestin enzyme and cAMP protein kinase, results in internalization of the receptor into endosomes. The receptor in the endosomes may, in time, be recycled to the membrane surface, or may be degraded. With desensitization, decreased gene transcription (due to mRNA destabilization) of the β_2-adrenergic receptor also occurs.[104] Decreased response with the same or greater concentration of albuterol is consistent with tolerance to the drug, and may be characterized as a pharmacodynamic property termed *clockwise hysteresis*.[105]

Although receptor downregulation may play a role in tachyphylaxis to β-adrenergic agonists and perhaps the widely publicized potential for detrimental effects after regular use of these agents in treating asthma,[106,107] the clinical importance of such effects remains to be elucidated. Other factors, such as the inflammatory mediators phospholipase A_2, platelet activating factor, leukotrienes B_4 and C_4, 15-lipoxygenase products, oxygen metabolites, and cytokines, may also affect β-adrenergic receptor expression and function and, ultimately, control of severe asthma.[108]

Conversely, the upregulation of β-adrenergic receptors by GCs and thyroid hormones has been described.[103] Functionally, GCs, which are necessary for normal β-adrenergic receptor function, reduce the threshold for receptor stimulation and potentiate the bronchodilatory effects of agonist agents.[109-112] A twofold to threefold increase in the number of lung β-adrenergic receptors has been observed after the administration of GCs.[113-115] This is thought to result from increases in the rate of transcription- and receptor-specific messenger ribonucleic acid in cells.[116,117] GCs can also increase the responsiveness of desensitized cells to β-adrenergic agonists.[103,118,119]

Intracellular Receptors

The glucocorticoid receptor is an example of an intracellular receptor (Fig. 16-5). This receptor is located in both the cytoplasm and the nucleus of the cell. Because glucocorticoids are lipophilic molecules, they easily diffuse across the plasma membrane and enter the cytoplasm, where they interact with the glucocorticoid receptor and begin the chain of events that results in their biological effects. Once in the cell, binding of the glucocorticoid molecule to the receptor is preceded by a number of processes.

The first step involved in the binding of free glucocorticoid within the cell to the glucocorticoid receptor appears to be phosphorylation of the soluble receptor.[120-122] The next step is the binding of two 90-kD proteins,[123] which are from the family of heat-shock proteins elicited by stressors,[124,125] to the receptor, with binding of one hsp56 protein to the two hsp90 proteins.[126,127] Once it is bound to these proteins, the receptor complex can bind to the GC. It is thought that the receptor, when bound to hsp90, is stabilized in a high-affinity

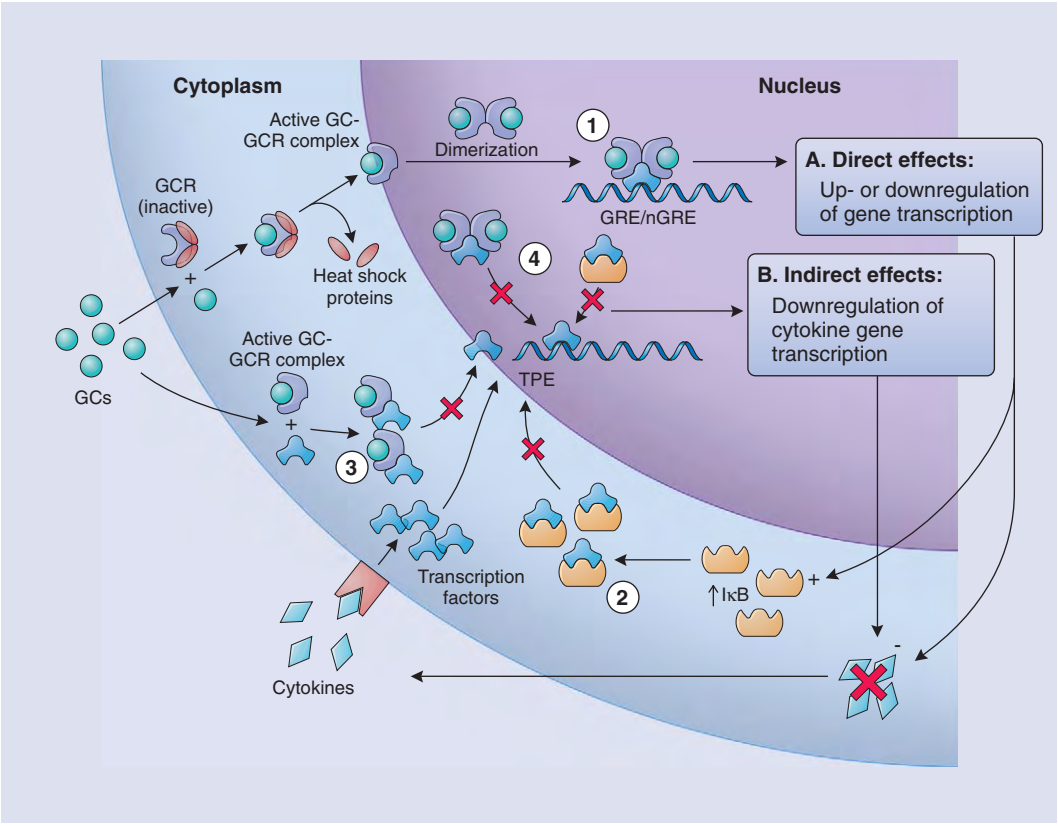

Figure 16-5 Model of glucocorticoid action. Glucocorticoids (GCs) easily diffuse across the plasma membrane of inflammatory cells where they bind to a cytoplasmic receptor, termed the *glucocorticoid receptor* (GCR). The GC-GCR complex is then transported to the nucleus where it dimerizes. GCs exert their anti-inflammatory effects in two major ways. By a process termed *trans*-activation, the GC-GCR complex binds to specific sites on the DNA called *glucocorticoid response elements* (GRE) and either up- or downregulates gene transcription (1). Second, in a process termed *trans*-repression, GCs inhibit transcription factor function. GCs can also inhibit the transcription of proinflammatory cytokines indirectly by either stimulating the production of Iκb, which then interferes with the ability of transcription factor function (2), or by binding to transcription factors directly (3). Transcription factors are essential in the transcription of proinflammatory cytokine genes. By interfering with the ability of transcription factors to bind to their binding sites, termed *transcription factor response elements* or TREs, GCs prevent transcription factor–induced gene transcription from occurring (4). *Trans*-repression is thought to be responsible for the majority of the anti-inflammatory effects of GCs, whereas *trans*-activation is thought to mediate many of the adverse effects associated with chronic GC use.

state for GCs.[128] Activation or transformation, the next step, is thought to result from a conformational change in the receptor that may result from dissociation of the receptor-hormone from the heat-shock proteins. Dimerization of two receptor-hormone complexes may also occur before nuclear translocation.[129]

When translocated into the nucleus, the GC receptor hormone complex can now exert its biological effects. We now know that two distinct processes account for the anti-inflammatory actions of GCs. By a process termed *trans*-activation, the GC-glucocorticoid receptor (GCR) complex binds to specific sites on the DNA called *glucocorticoid response elements* (GREs) and either up- or downregulates gene transcription. Once inside the nucleus, the "active" GC-GCR complex binds to specific DNA sites upstream from promoter regions, the GRE.[130] Binding of the GC-GCR to the GRE results either in upregulation or downregulation of gene products.[131] In this way, GCs inhibit the transcription of proinflammatory cytokines and inflammatory mediators. Alternatively, and more importantly, GCs, in a process termed *trans*-repression, inhibit transcription factor function.[132,133] Transcription factors such as AP-1 and NFκb are essential molecules in the upregulation of the inflammatory response. It is through this pathway that GCs exert the majority of their anti-inflammatory effects. In contrast, many of the adverse effects associated with chronic oral GC use likely come from *trans*-activation. Insight into the dichotomous effects of GCs has led many investigators to believe that the adverse effects of GCs could some day be separated from their anti-inflammatory effects.[134]

PHARMACODYNAMICS

Pharmacodynamics relates to the chemical and biochemical effects of a drug as they pertain to its mechanism of action. A drug's pharmacodynamics can be measured with regard to its onset of action, peak effect, duration of effects, and offset of action. For example, a number of factors alter the pharmacodynamics of GCs. Changes in the basic glucocorticoid structure, which result in differences in absorption, distribu-

tion, receptor affinity, and elimination, can affect the magnitude and duration of the drug's effects.[135] Thus, a drug's pharmacokinetics influences its pharmacodynamics, although this relationship is not always well understood. One might assume that changes in a drug's concentration or the dose administered would result in proportional changes in its clinical effect.

In a study investigating GC response as tyrosine aminotransferase activity in an animal model, a 10-fold increase in dose resulted in only a 50% increase in peak effect and a doubling of the duration of effect.[135] Further study using a similar model demonstrated that frequent smaller doses were more effective than larger single doses in prolonging the duration of effect.[136] Other studies have demonstrated a similar disproportion between changes in dosage and response. A study using lymphocytopenic effect as a measure of GC response showed a 33% increase in peak effect and a 20% increase in duration of effect after a sixfold increase in prednisolone dose.[137] In a model of methylprednisolone pharmacodynamics measured by whole blood histamine suppression, similar durations of effect were observed with a single 40 mg dose and a 20 mg dose followed by a 5 mg dose 8 hours later.[138] Therefore, it is not entirely surprising that low doses of GCs can achieve similar therapeutic effects compared with higher doses.[139,140] This may be one factor that explains the greater beneficial effect of inhaled GC therapy compared to oral therapy.

Although numerous cellular and biochemical effects of GCs have been demonstrated, it is still unclear as to which are important in the mechanism of action. Thus, there are no good markers of the effects of GCs at their site of action. Clinicians treating asthmatic patients are left with functional markers, such as bronchial hyper-responsiveness and pulmonary function, and changes in airway cellularity as measures of the effects of glucocorticoid therapy. Peripheral (blood, sputum) markers of lung inflammation that bypass the need for invasive procedures such as bronchoalveolar lavage and bronchial biopsy would be useful in determining the response to GC treatment.[141-143]

Exhaled nitric oxide is a noninvasive measure of allergic inflammation that has received increasing attention. It is a gas produced in large quantities by airway epithelial cells that have been damaged by eosinophilic inflammation. Studies have demonstrated exhaled nitric oxide to be a useful tool in establishing the diagnosis of asthma[144,145] and it can provide information regarding asthma severity and control.[146,147] More importantly, it can serve as a pharmacodynamic parameter because exhaled nitric oxide levels fall in asthmatic patients treated with inhaled and oral GCs.[148,149] In addition, elevated nitric oxide levels are predictive of response to GC therapy.[150] This technology is FDA-approved for treatment of asthma.[151]

CHRONOPHARMACOLOGY

For disease processes that exhibit biological rhythms, a relatively new discipline known as *chronopharmacology* has emerged. In this discipline, the timing of therapeutic modalities is used to optimize their effect on disease control. Asthma is an example of such a disease because many patients demonstrate nocturnal worsening of pulmonary function. Etiologies for this nocturnal worsening and therapies designed to prevent the deterioration of pulmonary function during the evening hours have been investigated.

In patients with nocturnal asthma exacerbations, the following occur:

1. The number of peripheral blood eosinophils is higher than in asthmatics without nocturnal symptoms.[152]
2. Eosinophil counts are higher during the night than during the day.[153]
3. A lower concentration of methacholine is required to elicit a 20% drop in the forced expiratory volume in 1 second at 4 AM compared with 4 PM.[154]
4. The leukocytes demonstrate a reduced β-adrenergic receptor density and responsiveness at 4 AM versus 4 PM.[155]
5. The total number of leukocytes, neutrophils, and eosinophils in bronchoalveolar lavage fluid is elevated at 4 AM versus at 4 PM, corresponding to the observed reduction in the 1-second forced expiratory volume.[156]

Thus, therapies designed to prevent these changes may be useful in treating nocturnal asthma. Early studies have demonstrated that the timing of GC doses is important in the overall daytime control of asthma.[157,158] Alternative modalities include single daily doses of theophylline given in the evening to protect against the nocturnal decline in pulmonary function[159] and doses of GCs given at the unconventional time of 3 PM, which provides greater protection from nighttime worsening than when given at 8 PM or the more conventional 8 AM dosing.[157,160,161]

AGE-RELATED CHANGES

A number of variables, which may change with growth and development, can affect the absorption, distribution, and elimination of drugs. The airways are developed by week 16 of gestation, and growth in terms of the multiplication of alveoli occurs during the first few years after birth.[162] The changes in pulmonary arteries, primarily a reduction in the thickness of the vessel walls, occur rapidly during the first 3 days of life.[162] Thus with the exception of growth (in terms of size), no major changes in lung development would affect drug disposition.

Absorption

Absorption of drug from the gastrointestinal tract is influenced by a number of factors, including gastric acidity, gastrointestinal motility, mucosal membrane permeability, bacterial flora, enzyme activity, biliary function, and diet.[163] These factors change with aging and, in turn, affect the rate and extent of drug absorption.[164] As acid secretory capacity matures during the first few days of life, gastric acidity changes from a pH of 8 to 6 during the neonatal period, nears adult values for the first month of life, and then increases until adult values are attained at age 3 to 7 years.[163,165] Therefore, drugs that are weak acids should be more slowly absorbed in children than in adults because of the decreased gastric acidity. Conversely, better gastric absorption of weak bases should be observed in pediatric patients. Data consistent with these theories include increased bioavailability of penicillin

and ampicillin in children compared with adults and delayed absorption and reduced bioavailability of phenobarbital, phenytoin, and acetaminophen.[165] Phenobarbital absorption has also been correlated to age.[166]

Although much is known regarding gastric acidity in neonates and young children, limited information is available regarding other factors that may affect drug absorption. Gastric emptying time is prolonged in the neonate and infant and approaches adult values at 6 to 8 months of age.[165] Similarly, intestinal transit time can be prolonged because peristalsis is irregular,[167] a potential problem for sustained-release products such as theophylline and oral albuterol. These factors can influence drug absorption, as can the episodes of diarrhea common in this age group. Biliary function, which develops during the first month of life,[168] and the development of intestinal bacterial flora may also influence the absorption of drugs.

Distribution

A drug's volume of distribution relates to its plasma concentration, which is affected by body composition. Thus, age-related changes in body composition can affect the distribution of drugs. Neonates have a higher proportion of body mass in the form of water compared with older children and adults. The proportion of total body water decreases from 75% to 85% in the neonatal period to 55% in adulthood.[165] The result of such differences is manifested as higher loading dose requirements for drugs that distribute to total body water in infants and young children. Unlike total body water, body fat increases with age.[163] This results in smaller volumes of distribution for lipophilic drugs in young children.

Protein binding, as discussed in a previous section, also influences the distribution of drugs. Neonatal serum concentrations of albumin, the major binding protein, is approximately 80% of adult values and increases to normal within the first year of life.[163] Because only free drug is considered active, a lower serum albumin concentration and a lower proportion of bound drug can result in greater pharmacologic and possibly toxic effects with drug concentrations that appear to be therapeutic. The binding affinity of albumin for some drugs, including theophylline, appears to be decreased in the neonate as well.[164]

Elimination

In general, neonates are thought to demonstrate a reduced enzyme capacity for metabolizing drugs, which increases with age.[163,165] Insufficiencies of elimination pathways are often compensated for by metabolism via alternative pathways, as seen in neonatal methylation of theophylline to caffeine.[169] The expression of the cytochrome P-450 isoenzymes changes dramatically over time. The expression of CYP3A7 peaks soon after birth, followed by a rapid decline so that levels are undetectable by adulthood. CYP2E1 and CYP2D6 become detectable soon after birth, whereas CYP3A4 and CYP2C appear during the first week of life. CYP1A2 is the last CYP to appear at 1 to 3 months of life.[163] The differences in renal drug clearance between children and adults may not result from intrinsic enzyme capacities or quantity but can be attributed to changes in body composition (i.e., proportion of liver tissue).

Like hepatic enzyme activity, renal function (renal blood flow, glomerular filtration, and tubular function), when normalized for body surface area, is reduced in infants and children compared with adults. After birth, increased cardiac output and reductions in intrarenal vascular resistance result in increased kidney perfusion and increased renal function. However, this increase in renal function during the first week of life is not observed in premature newborns. Glomerular filtration, which is developed to a greater degree than tubular function at birth, gradually increases to adult values by 3 years of age. Premature infants have lower filtration rates than do full-term infants, and their filtration capacity develops more slowly. Differences in renal drug clearance between children and adults are thought to correspond to maturation of renal function.[165] These points highlight the need for individualization of doses based on desired drug concentrations and therapeutic and toxic effects for drugs cleared primarily by the kidney.

SUMMARY

Understanding the pharmacokinetic and pharmacodynamic properties of medications for use in childhood is required for rational and optimal drug therapy. Not only are the pharmacokinetic and pharmacodynamic properties important in the treatment of childhood pulmonary diseases, but equally important are the numerous factors involved in delivering a medication directly to the airway. Great strides have been made in our ability to deliver potent anti-inflammatory agents such as inhaled GCs to the airways of asthmatic children. We have come close to approaching the "ideal" inhaled GC—that being a medication that displays potent anti-inflammatory effects; displays high retention time in the lung and as a result produces long-lasting therapeutic effects; has little to no oral bioavailability; and displays little to no potential for adverse effects. All of the inhaled GCs in use today display these properties to varying degrees and because of this, they display significant efficacy while minimizing the potential for systemic effects.

Despite the strides in our understanding and treatment of pulmonary diseases, issues remain. First, drug delivery in infants and toddlers continues to present a challenge as none of the current devices provide efficient delivery. In addition, none of the available inhaled glucocorticoids is entirely devoid of adverse effects, especially at higher doses. We have also learned that there is significant variability of response to medications. As a result, a great deal of time and energy has been placed on the development and implementation of pharmacogenetics. Throughout the enzymatic and signaling pathways are several polymorphisms including beta-adrenergic receptors, enzymes involved in the synthesis and degradation of leukotrienes, and the CYP-metabolizing enzymes. These polymorphisms have the potential to influence the response to drugs on both the pharmacokinetic and pharmacodynamic levels. It is hoped that by better understanding the pharmacokinetics, pharmacodynamics and pharmacogenetics of a medication, clinicians may tailor medications to maximize benefit while minimizing unwanted and potentially harmful effects.

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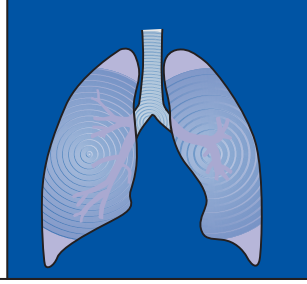

CHAPTER 17

Aerosol Therapy and Delivery Systems

Sunalene G. Devadason, Mark L. Everard, and Peter N. Le Souëf

TEACHING POINTS

- Advances in delivery systems have rendered traditional nebulizers obsolete for use in asthma.
- Pressurized metered dose inhalers attached to a spacer (pMDI-spacer) are the delivery method of choice for children with asthma.
- pMDI-spacers must be rendered static-free to perform adequately. For plastic spacers, coating with detergent is the most efficient and cheapest method of achieving this.
- To treat a plastic spacer for static, the spacer should be immersed in water containing detergent and left to drip dry without rubbing or rinsing. Rinsing will remove the detergent and render the exercise useless.
- Dry powder inhalers are not recommended for use in young children and, in all patients, require a mouthwash and gargle when used with inhaled steroids.
- Current drug delivery systems in children do not require that a lower dose be prescribed for younger children because the dose that children receive from a given device is reasonably proportional to the size of the child.
- Care must be taken to avoid side effects of inhaled drugs and to use the lowest possible dose.
- Newer nebulizer systems are likely to become the delivery system of choice in the future.

Inhalational drug therapy is the primary mode of treatment for asthma as well as other respiratory diseases such as cystic fibrosis. The efficiency of aerosol therapy, both for adults and children, has improved greatly in recent times. Factors such as the development of pro-drugs with greater topical activity and fewer adverse systemic effects[1]; new formulations to maximize the delivery of drug particles within inhalable size ranges; improved delivery systems to optimize airway targeting, minimize lung deposition, and decrease drug wastage have resulted in marked increases in clinical efficacy. However, the requirement for affordable and disposable inhalers, particularly for the more widespread treatment of asthma, has limited the advances that could be made in this field.

Greater advancements have been made in the optimization of aerosol devices and drug formulations for the treatment of cystic fibrosis and for the delivery of aerosolized drugs for systemic therapy. The use of aerosols as a noninvasive vehicle to permit rapid absorption of drug into the systemic circulation for the treatment of nonrespiratory diseases such as diabetes is becoming increasingly important.[2] Because the drugs used to treat these conditions are more costly and tend to have narrower margins between therapeutic efficacy and deleterious side effects, highly efficient aerosol delivery systems are required to deliver strictly quantified doses to targeted lung regions.

PRINCIPLES OF AEROSOL DELIVERY

An aerosol is a biphasic system containing a gaseous phase and a particulate phase. In other words, it is a gaseous suspension: a gas containing solid and/or liquid particles.[3] The definition of a particle is a body with a defined solid or liquid boundary bordering its gaseous environment.[3] The advantage of using aerosol therapy for the treatment of respiratory disease is that the drug is delivered directly to the site of action, allowing more rapid therapeutic effects using a lower nominal dose.

The most important consideration with aerosolized drugs is to maximize drug deposition in the required areas of the respiratory tract. Deposition of aerosolized particles in the respiratory tract is governed by three main factors: inertial impaction, gravitational sedimentation, and diffusion. In addition, the electrostatic charge on both the aerosol and the respiratory mucosa may also affect drug deposition.[2,4-6]

The degree of influence of each of these factors on aerosol deposition in the lungs is dependent on the particle size of the aerosolized particles (Fig. 17-1). The optimal particle size for deposition in the smaller airways is less than 3 μm,[4,6] although particles larger than 5 μm are still considered "respirable" particles.[4] Particles larger than 5 μm generally deposit in the oropharynx or upper airways.[4]

Particle size measurement is complicated by the fact that some of the aerosolized droplets may be irregularly shaped rather than strictly spherical. For convenience, particles of different shapes that behave in a similar aerodynamic manner are grouped together and visualized as spherical droplets with a common diameter. This is termed the aerodynamic diameter, which is defined as the diameter of a sphere of unit density with the same terminal sedimentation velocity in air as the particle or droplet in question[2] and is usually determined by the mass of the droplet.

Monodisperse aerosols consist of particles with the same aerodynamic diameter. However, aerosols generated by most forms of aerosol therapy are generally polydisperse in nature in that the aerosol is made up of particles of widely variable aerodynamic diameters. Polydisperse aerosols are usually

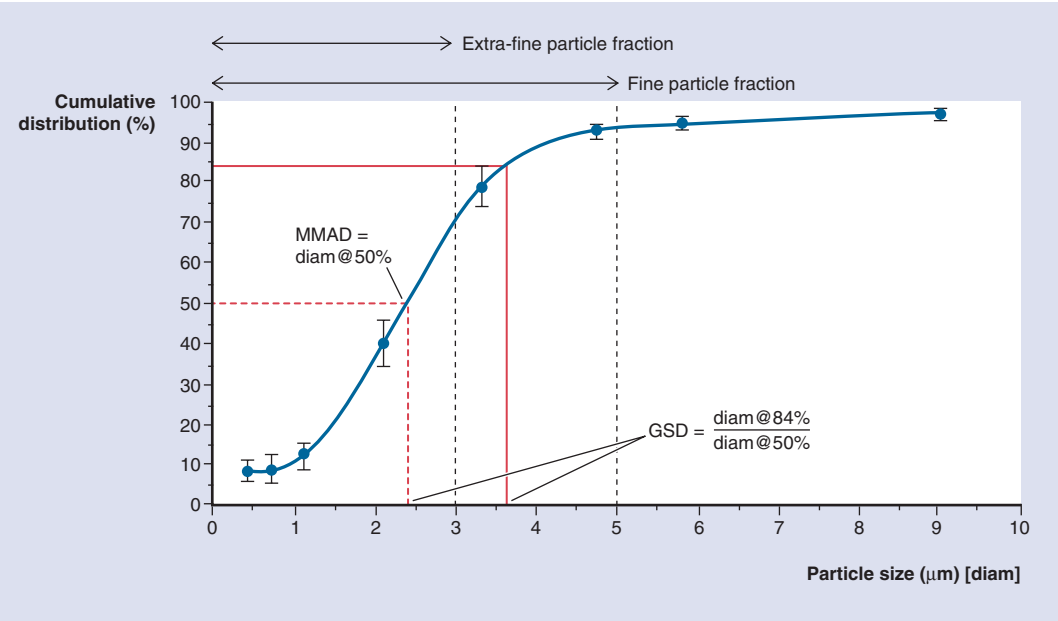

Figure 17-1 Aerosol particle size. GSD, geometric standard deviation; MMAD, mass median aerodynamic diameter.

characterized by their mass median aerodynamic diameter (MMAD) and geometric standard deviation (GSD).[4] That is, one half the mass of the aerosol will have an aerodynamic diameter below the MMAD, and one half of the mass will be in particles with diameters greater than the MMAD. Lung deposition for a highly polydisperse aerosol with an MMAD of 3 μm would be much lower than that for a monodisperse aerosol of the same diameter, and the reverse would occur if the MMAD was >5 μm.[7]

Minimizing the particle size of aerosolized drugs is essential because larger particles carry a much greater volume of drug than smaller particles owing to the cubic increase in volume with a unit increase in the diameter of the particles. Hence, aerosols that contain a large proportion of particles >15 μm in diameter will deliver most of the drug available for inhalation to the oropharynx—resulting in little therapeutic effect and increased systemic availability.

Physical Mechanisms of Deposition

INERTIAL IMPACTION

Inertial impaction has a greater effect on larger particles (>3 μm),[8] and in the oropharynx and upper airways where the velocity of the inhaled particles is highest. This is because particles carried by a gas or propellant possess momentum, which is determined by both the mass and the velocity of the particle.[5,6] When the particles approach a surface such as the back of the throat or a bifurcation of the airways, the direction of air flow will change. Inhaled particles may not follow the direction of air flow, and will instead accumulate on the surface. Particles with a higher momentum (i.e., larger particles or those with higher velocities) are more likely to accumulate in the oropharynx or the larger airways.

Particles >15 μm are unlikely to enter the trachea.[7] Even for particles <15 μm, further deposition of the larger particles will occur at airway bifurcations.[6] As the larger particles get filtered out and as the velocity of the particles decreases, impaction becomes less important as a mechanism of deposition in the smaller airways.[7]

SEDIMENTATION

Particles <3 μm will probably not deposit owing to inertial impaction. Sedimentation caused by gravity is the most important mechanism for deposition in the smaller airways. The effect of sedimentation is greatest on the larger particles (>0.5 μm)[6] that have escaped deposition owing to inertial impaction. Breath-holding after inhalation of the aerosolized particles helps deposition in the airways owing to sedimentation.[46]

DIFFUSION

Particles <0.5 μm will move by diffusion (impaction with gas molecules) toward the surface of the respiratory tract. Movement of particles by diffusion decreases with increasing particle diameter, and hence has a greater effect on small particles (<0.1 μm).[6] Deposition in the airways due to diffusion is helped by breath-holding after inhalation. Without breath holding, most small particles <0.1 μm are likely to be exhaled rather than deposited.

ELECTROSTATIC ATTRACTION

Deposition may occur because of attraction between charged particles in the inhaled aerosol and an induced charge on the mucosa of the respiratory tract.[5] The importance of this factor for aerosol therapy has not been investigated in detail but will presumably vary greatly depending on the drug formulation being administered.

In addition to the factors just discussed, irregularities in airway structure and inhalation flow patterns lead to nonuniform deposition of aerosolized drugs. "Hot spots" usually occur at airway bifurcations,[4,5] where large amounts of drug tend to deposit. The greater the degree of airway obstruction due to disease, the more central the deposition in the

airway—thereby reducing the therapeutic efficiency.[9] The depth of penetration of aerosolized particles in the airways also depends on physiologic factors such as tidal volume, respiratory rate, and breath-hold capability.[10]

Therapeutic Aerosol Devices

The relative merits of the devices used in children are summarized in Table 17-1. The pressurized metered dose inhaler with valved holding chamber or spacer (e.g., Aerochamber [ForestPharmacaticals, St. Louis, Mo], Volumatic [GlaxoSmithKline, London]) continues to be the delivery system of choice for use by children (Figs. 17-2 and 17-3), particularly in the younger age groups (infants and children younger than 6 to 7 years of age). Pressurized metered dose inhalers (pMDIs) are inexpensive, easy to use, and disposable; in particular pMDIs require no inspiratory effort on the patient's part in order for the metered dose to be dispensed.

When used without a spacer, pMDI actuation must be closely coordinated with the start of the patient's inhalation; a difficult feat for many older children, and impossible for young children to achieve. Valved holding chambers or spacers eliminate the need for coordination, but are less convenient and portable. However, spacers must be used with pMDIs when treating children younger than 6 to 7 years of age, and are highly recommended for all patients when using corticosteroids. Facemasks must be used for infants and toddlers (less than 3 years of age); however these encourage nasal inhalation which will filter out much of the aerosolized drug. Children more than 3 years of age can be taught to use a mouthpiece; this greatly increases the amount of drug delivered to the lungs.

Comparison of bronchodilator delivery with pMDI-spacer and nebulizer has shown increased efficiency of drug delivery via pMDI-spacer[11] and equivalent clinical outcomes in both adults and children,[12-14] even during severe exacerbations. The use of pMDI-spacers for delivery of bronchodilators in hospital emergency departments is becoming much more widespread.

Electrostatic charge greatly reduces drug delivery from plastic spacers,[15] but this problem can be reduced or eliminated by coating the inner surface of the spacer with detergent,[16] use of a metal spacer,[17] or by constructing spacers from patented plastic materials, which are more resistant to the build-up of electrostatic charge (Aerochamber Max, Trudell Medical, London, Ontario, Canada). Proper care must be exercised in using a detergent-coated plastic spacer. The spacer should be washed in water containing a diluted ionic detergent and then left to drip dry. The surfaces of the spacer should not be rubbed or touched and, most importantly, the spacer should NOT be rinsed because this will remove the detergent. A detergent-coated plastic spacer will have minimal static and detergent coating has been shown to

Figure 17-2 Spacers for use with pressurized metered dose inhalers.

Figure 17-3 Child inhaling from a pressurized metered dose inhaler and spacer.

Table 17-1
Relative Merits of Devices for Aerosol Delivery in Children

	Nebulizer	Pressurized Metered Dose Inhaler	Pressurized Metered Dose Inhaler-Spacer	Dry Powder Inhaler
Age Range	All	6 Years and over	All	6 Years and over
Expense	High	Low	Low	Low
Efficiency	Low	Moderate to good	Good to excellent	Good to excellent
Dependency on Technique	Low	High	Low	Low to moderate
Major Disadvantage	Inefficient, expensive, slow	Reliance on technique	Bulky, must be designed or treated to reduce static	High oropharyngeal deposition, gargle with steroids
Major Advantage	Delivery of drugs in cystic fibrosis	Portability, use for bronchodilators	Easy and efficient to use in children with asthma	Portability
Recommended for Use in Children with Asthma	No	Yes, but only for bronchodilators	Yes, device of choice	Yes, but limited age range

last for a month without static returning. Plastic spacers should not be stored in plastic bags or wrappings.

Breath-actuated pressurized inhalers, such as the Autohaler (3M, St. Paul, Minn), eliminate the need for patient coordination of actuation with inhalation, without the use of a holding chamber. Once the device has been primed, the patient's inhalation flow triggers actuation and release of the drug, which has been shown to improve drug delivery in adults with poor coordination.[18] Breath-actuated devices still require a 2 to 4 second inspiratory time, which may be difficult for some children (particularly those younger than 6 years of age) to achieve.[19]

Most older children and adolescents prefer dry powder inhalers (DPIs) because of their convenience and portability, and giving them a choice of inhalation device may be an important factor in improving adherence in this age group. However, the more common DPIs available for asthma therapy (e.g., Turbuhaler [AstraZeneca, London], Accuhaler/Diskus [GlaxoSmithKline]) require a forced inspiratory maneuver for the drug dose to be dispensed. Hence, the patient must be able to remember and consistently reproduce the optimal inhalation technique when using these devices. The higher the inspiratory flow, the greater the amount of respirable drug delivered, particularly when using the Turbuhaler. Because of the high resistance when inhaling through the Turbuhaler, greater inspiratory effort may be required from the patient to achieve an equivalent dose compared to the Accuhaler.[20] DPIs generally result in a higher oropharyngeal drug dose and patients should wash their mouths and gargle after inhaling corticosteroids. In addition, younger patients may not be able to consistently generate a sufficiently high inspiratory flow through DPIs—hence these devices are not recommended for children younger than the age of 6 to 7 years.

Much more efficient dry powder delivery systems have been developed (e.g., Pulmonary Inhaler, Nektar, San Carlos, Calif)—the patient's inspiratory effort is not required to dispense the metered dose because the drug is automatically dispensed into a holding chamber. These devices would not be cost effective when compared to current inhalers used for asthma therapy. A similar concept (namely, the use of a holding chamber) was tested for use with the Turbuhaler,[21] but did not achieve widespread use.

The use of jet nebulizers for asthma treatment has now ceased in many places in the world and is decreasing in most other places. Nebulizers still have a role in the treatment of cystic fibrosis. This has occurred as traditional nebulizers are less efficient in delivering drug to the lower airways, and are expensive, inconvenient and cumbersome as they generally require an external compressor and power supply. Ultrasonic nebulizers are not widely used, as they are not suitable for delivery of some drugs, particularly those in suspension formulations. Several new generation nebulizers or liquid aerosol delivery systems (e.g., Aeroneb [Nektar], eFlow [PARI Pharma, Munich], AERx [NovoNordisk, Hayward, Calif], I-neb [Respironics, Murrysville, Pa) have been developed that address most of these problems. These vibrating menbrane devices are battery powered and compact, and may even be breath actuated (i.e., releasing drug only during the optimal portion of the patient's inhalation). These devices are too costly to compete with pMDIs for the treatment of asthma, but may have a role in the treatment of cystic fibrosis for the delivery of DNase and antibiotics because the increased delivery efficiency of these expensive medications easily justifies the use of a more costly delivery system.

Drugs for Pediatric Use

ASTHMA THERAPY

When prescribed and administered correctly, inhaler therapy is able to control asthma symptoms in most patients by reversing airway obstruction and reducing airway inflammation.[22] The primary aerosolized medications currently used to treat asthma include short-acting beta$_2$ agonists, long-acting beta$_2$ agonists, and corticosteroids. These medications are generally delivered using either pressurized metered dose inhalers, or dry powder inhalers. Nebulizer use for asthma therapy has decreased significantly over the last decade and traditional nebulizers may now be obsolete for use in asthma.

Beta$_2$ Agonists

Short-acting beta$_2$ agonists such as salbutamol (albuterol) provide immediate relief of acute asthma symptoms by binding to the beta$_2$ receptors on the smooth muscles of the bronchioles, causing them to bronchodilate. Symptom relief lasts up to 3 to 4 hours.[23,24] Short-acting beta$_2$ agonists should be used only to relieve acute symptoms, and if required more than three times a week, anti-inflammatory therapy should be commenced. Long-acting beta$_2$ agonists such as salmeterol or eformoterol enhance bronchodilation for up to 12 hours after administration.[23] Eformoterol also has an immediate bronchodilatory effect, similar to salbutamol, whereas salmeterol has a more delayed onset of action and must be used with short-acting bronchodilators for acute relief of symptoms. Long-acting beta$_2$-agonists are often prescribed with corticosteroids in combination inhalers for treatment of severe, chronic, or refractory asthma.

Corticosteroids

Long-term therapy for chronic or severe asthma in children requires the use of prophylactic inhaled corticosteroids for suppression of airway inflammation. Corticosteroids are the most potent and effective form of anti-inflammatory treatment for severe asthma.[25] Long-term use of inhaled corticosteroids reduces airway inflammation and bronchial hyper-responsiveness, thereby decreasing asthma exacerbations and symptom severity.[26,28]

Fluticasone propionate (FP), currently one of the most widely used corticosteroids available, combines the advantage of high topical activity with low gastrointestinal bioavailability.[29] Adverse local effects[30] and systemic effects due to the systemic absorption of fluticasone via the airway mucosa have been reported[31-33] even within therapeutic dose ranges, particularly in children. Budesonide is still widely used, particularly via Turbuhaler, but it has lower gastrointestinal bioavailability than beclomethasone dipropionate (BDP) and is less topically active than FP.[29,34] However, budesonide is highly protein bound in plasma, reducing the effect of absorption through the airway mucosa into the systemic circulation.[34]

The development of newer synthetic steroids for inhalation may alleviate some of these concerns.[1] Ciclesonide is

one of the more promising candidates, having already been granted regulatory approval in many countries for use in adults and children older than 4 years of age for the treatment of asthma. Ciclesonide is inhaled as an inactive pro-drug and is activated intracellularly within the airways to a highly topically active form.[35] Because of a number of factors (low oral and gastrointestinal bioavailability of the inactive pro-drug and high protein binding of the active drug in plasma prior to hepatic inactivation), ciclesonide appears to have markedly reduced local and systemic effects,[36,37] even in children.[38]

Currently, inhaled corticosteroids are the most widely used drugs of concern in the pediatric age group. BDP has been reformulated as an extra-fine propellant-based aerosol (QVAR) that maximizes lung deposition in both adults[39] and children.[19] However, there is the potential for increased adverse side effects using this formulation because of high gastrointestinal bioavailability and increased absorption through the airway mucosa. The recommended prescribed dose of BDP is halved when switching to QVAR.[40]

Although administering corticosteroids via inhalation is associated with fewer adverse effects when compared to oral administration, local and systemic effects can still occur particularly when children are prescribed high daily doses over a prolonged period. Thus, to reduce unwanted side effects, the lowest effective dose required for effective symptom control should be used, and the delivery of drug to the lungs should be optimized. Local adverse effects in both adults and children can include dysphonia and oropharyngeal candidiasis due to deposition of drug particles in the mouth and throat. These effects can be minimized by rinsing the mouth and gargling after inhaler use. Other adverse side-effects include adrenal suppression and decreased bone density.[27,28,37]

Long-term use of inhaled corticosteroids in young children is of concern because of the potential impact on bone turnover and growth. These effects may include inhibition of new bone formation and bone reabsorption.[27] However, studies examining the effects of moderate corticosteroid use (<400 μg/day of FP) have found little effect on bone turnover[41] and final height.

CYSTIC FIBROSIS THERAPY

A number of different drugs for cystic fibrosis (CF) therapy (antibiotics, recombinant human DNase, mucolytics, hypertonic saline) are delivered via aerosol—generally using jet nebulization. Bronchodilators and corticosteroids are also sometimes prescribed for CF patients (via pressurized or dry powder inhaler). This section will focus primarily on inhaled antibiotics and DNase delivery.

Recombinant Human Deoxyribonuclease (rhDNase)

The presence of excessive levels of DNA has been found to contribute to the increased viscosity of the sputum of CF patients.[42] In addition, by binding to aminoglycoside antibiotics in sputum, DNA could reduce their efficacy.[43] The use of recombinant human deoxyribonuclease 1 (dornase alpha, rhDNase, Pulmozyme), delivered via jet nebulizer, has been shown to reduce the viscosity of CF sputum,[42] improve lung function, and reduce exacerbations in CF patients.[44] rhDNase can be aerosolized using a number of different jet nebulizer-compressor combinations; however, a small particle size, high-output system is recommended.[45]

Inhaled Antibiotics

Chronic bacterial infection of the lower airways is present in most CF patients from early life. Early prophylactic antibiotic treatment can reduce lung damage caused by these infections, and improve quality of life. The use of inhaled antibiotics such as tobramycin has been shown to improve clinical outcomes in patients chronically infected with *Pseudomonas aeruginosa*.[46,47] Other antibiotics, such as colomycin, are also widely used, although controlled trial evidence supporting the use of colomycin is not as convincing as for tobramycin.[48] A number of jet nebulizer-compressor systems may be used for aerosolization of antibiotics.

Ventilator Circuits

Traditionally, jet nebulizers were used to deliver medication to patients through ventilator circuits, but there are many problems with this form of therapy, since only a small proportion of the nebulized drug is actually delivered to the patient. The use of pMDIs with suitable adaptors allows more efficient delivery, particularly when used with small-volume chambers, which appear to be suitable for all patients from preterm baby to adult.[49-51] Medication delivery via endotracheal tubes is also possible using ultrasonic nebulizers.[51,52] Doses approaching 100% of the nominal dose can be delivered into the lower respiratory tract by actuating the medication through a catheter passed through the endotracheal tube.[53] However, not all drugs required for delivery to ventilator patients are available in pMDI formulations, requiring the continued use of nebulizers for this purpose.[54] More recently, vibrating membrane nebulizers have been investigated for use in ventilator circuits, and have been shown to markedly improve drug delivery.[55]

DOSE CONSIDERATIONS

Given that lung deposition studies for most inhalation devices in children from infancy up to about 10 years of age show that the amount reaching the lung is generally proportional to the size of the child, the same prescribed dose can be used in all children. Most drug dosage schedules recommend progressively lower doses with reducing age of the child, but these schedules appear to have been designed without reference to the available scientific data and with no proper evidence basis to this practice. Extreme care should be taken with prescribing high doses of inhaled drugs to all children, regardless of age, and every attempt should be made to ensure that side effects are avoided and that the lowest possible therapeutic dose is used.

CONCLUSIONS

In recent times, pMDI-spacers have become the most commonly used approach to aerosol therapy in children. They can be used for all ages and for both long-term, preventive therapy, and for short-term treatment of acute exacerbations. One of the main advantages of pMDI-spacer use is that normal tidal breathing can be used during aerosol administration, which makes them ideal for infants and younger children. However,

newer and more innovative devices are gradually becoming available and these may offer therapeutic advantages in terms of increased efficacy, convenience, and compliance—particularly for older children and adolescents. The ability of a child to utilize an inhaler device and to perform the required inhalation technique consistently must be evaluated when making the choice of an appropriate delivery system for children of different ages.

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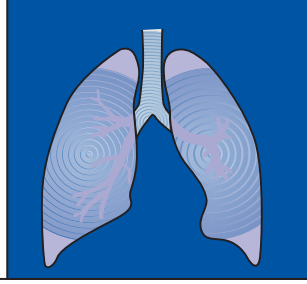

CHAPTER 18 Chest Physiotherapy

Maximilian S. Zach and Béatrice Oberwaldner

TEACHING POINTS

- Chest physiotherapy (CPT) for airway clearance is a spectrum of mechanical techniques for the noninvasive clearance of excessive secretions or aspirated material from the airways.
- Efficient intervention by CPT should be preceded by a detailed analysis of the patient's disease situation. Targeted CPT should be based on prevailing pathophysiology rather than on general diagnostic classifications.
- Therapist-administered techniques such as postural drainage, chest percussion, vibration, and compression, with assisted coughing or suction (conventional CPT) remain the only available CPT approach for infants and small children.
- Patients can be trained in self-administered CPT techniques from an age of 5 to 6 years and older.
- CPT has a traditional position in the treatment of cystic fibrosis and other chronic suppurative lung disorders.
- In addition to airway clearance, chest physiotherapists may offer assistance in a spectrum of other diagnostic and therapeutic procedures and programs such as breathing exercises, muscle training, rehabilitation and exercise programs, aerosol therapy, lung function testing, oxygen therapy, tracheostomy care, and long-term home mechanical ventilation.

The term *chest physiotherapy* (CPT) stands for a spectrum of physical and mechanical interventions aimed at interacting therapeutically with acute and chronic respiratory disorders. Experience shows that CPT in children differs in many aspects from that in adults.[1] Consequently, pediatric CPT is a specialized branch of the entire CPT spectrum that is tailored to the specific needs of newborns, infants, and children. In practice, a major part of pediatric CPT is dedicated to airway clearance, but many chest physiotherapists have also acquired competence in a variety of other caregiving strategies.

CPT FOR AIRWAY CLEARANCE

CPT for airway clearance is a spectrum of mechanical techniques for the noninvasive clearance of excessive secretions or aspirated material from the airways. Because it physically addresses the respiratory tract, CPT can be seen as a therapeutic application of respiratory physiology.

CPT is used to prevent or treat the mechanical, infectious, and biochemical sequelae of accumulated intrabronchial material.[2] Such obstructive material (in most cases, secretions) increases the resistance to airflow and the work of breathing and can cause hyperinflation and atelectasis, maldistribution of ventilation, and ventilation-perfusion mismatch. Accumulation of secretions and the resulting complications facilitate infection. Microorganisms and host-mediated inflammatory responses release proteolytic enzymes that damage the airway epithelium and wall, further impairing mucociliary and cough clearance.[3] Thus intrabronchial accumulation of secretions may initiate a vicious circle of infection, impaired clearance, and progressive airway damage. In such conditions, CPT may not only have antiobstructive effects but also prevent or delay tissue damage. A theoretical third therapeutic benefit from CPT should be improved access to the bronchial mucosal surface; after effective removal of secretions, a larger portion of inhaled medications should penetrate to the airway epithelium.

The most important features of each CPT technique are its effectiveness and safety. Techniques for long-term treatment should be easy to teach to patients and caregivers; they should not fatigue the patient but rather should be time efficient and comfortable.[4] Practical applicability and cost effectiveness demand that techniques be based on patient participation rather than on expensive equipment. One possible exception to this rule could be the very ill and exhausted patient; in this case, each technique that offers some benefit is acceptable, even if it involves expensive machinery, regular expert assistance, or both.

CPT Techniques

CONVENTIONAL CPT

The term *conventional CPT* is used for a spectrum of traditional techniques that were described in the early 1960s and, at least in part, stem from practices developed as early as 1934.[5] Basically, conventional CPT is a therapeutic regimen intended to be applied by a physiotherapist or trained caregiver. However, some techniques can be self-administered by the patient.

Techniques

The techniques can be differentiated into those for mobilizing secretions and those for transporting secretions. They are combined for tailoring individually targeted treatment sessions.

Postural Drainage

Postural drainage is based on the concept of gravity-assisted mobilization and transport of secretions. The patient is positioned to drain each segment of the lungs or a group of segments. These traditional positions, established by practical experience and guided by the anatomy of the bronchial tree, have been summarized and illustrated in relevant textbooks.[5,6] For older children and adults, positioning for postural drainage is assisted by using frames, tilt tables, or pillows; postural drainage for an infant is administered by positioning the child over the knees of the therapist. In the actively cooperating patient, postural drainage can be complemented by thoracic expansion exercises and by breathing control. In infants and toddlers, chest percussion, vibration, and compression can be applied during postural drainage.

Thoracic Expansion Exercises

Intended to aid in the mobilization of secretions, thoracic expansion exercises are deep inspirations with a 3-second hold at total lung capacity followed by a relaxed expiration. To expand particular areas of the patient's rib cage, the physiotherapist using proprioceptive stimuli teaches locally emphasized inspirations. Consequently, one can distinguish unilateral lower, bilateral lower, posterior lower, and apical thoracic expansion. Experienced therapists can effect thoracic expansion in preterm and newborn infants by positioning with manual inspiratory assistance. Laughing and crying are effective for thoracic expansion in infants and children.

Manual Hyperinflation

In mechanically ventilated lungs, an increase in volume is achieved by manual hyperinflation. The size of the bag, flow rate of gas, level and control of inspiratory pressure, and use of positive end-expiratory pressure are all important technical details that determine the efficacy and safety of this technique.[1]

Breathing Control

Breathing control is needed to help the patient recover between other, more energy-consuming CPT maneuvers and reduce breathlessness; it is tidal breathing with the patient using the lower chest while relaxing the upper chest and shoulders. The terms *diaphragmatic breathing* and *abdominal breathing* are often used for describing this technique.

Chest Percussion

Intended to mobilize secretions, clapping is manual percussion with cupped hands. In infants, the therapist's cupped hand is replaced by the fingertips or a small, cushioned face mask. Although chest percussion is essentially a physiotherapist-administered technique, patients can be taught to do self-clapping. In addition, mechanical percussors have been developed to allow for percussion administered by the patient or by a caregiver who is less experienced or is physically handicapped.

Chest Vibration

Chest vibration also aims to mobilize secretions. With the hands on the patient's thorax, the therapist produces vibrations of the chest wall during expiration. This technique can be combined with chest compression.

Chest Compression

As a support for the patient's own expiration, chest compression is intended to mobilize and transport secretions. In older patients, the chest is compressed by the therapist's arms that are wrapped around it or by manual pressure on the sternum, the lateral lower parts of the rib cage, or both. In infants, the chest is compressed by one or both hands; after the expiratory squeeze, the subsequent inspiration can be supported by thoracic expansion.

Assisted Coughing

Usually, a patient coughs spontaneously as soon as secretions have been mobilized. An attending physiotherapist can manually support the patient's chest during coughing. Frequently, the pressure waves produced by chest percussion, vibration, or both techniques, also activate the cough reflex. Experienced therapists can induce coughing by applying gentle digital pressure to the trachea in the suprasternal notch. Coughing should continue until airways have been cleared from all mobilized sputum. Care must be taken to avoid mobilization without complete expectoration because this leads to erroneous shifting of secretions from one part of the lower respiratory tract to the other.

Suction

In patients with artificial airways, the transport of secretions is mechanically hampered by the endotracheal tube or the tracheostomy cannula. In addition, the underlying disease, concomitant medication, or both can reduce the activity of the cough reflex. In these cases, suction must substitute for coughing. The catheter is introduced into the artificial airway and advanced no more than 1 cm beyond without suction. Then suction is applied while the catheter is slowly rotated and withdrawn. Correct performance of the suction procedure is essential for minimizing negative side effects. Details to be considered are preoxygenation, instillation of saline before the suction procedure, diameter of the suction catheter in relation to the size of the trachea, length and gradation of the catheter, position and number of the side holes, magnitude of the negative pressure applied, duration of the suction procedure, and manual or mechanical hyperinflation after suctioning.[1,7] Suction procedure policies regarding most of these technical details differ among centers.[8] In some patients whose lungs have not been intubated and who cough ineffectively or not at all, the larynx and upper trachea can be cleared by deep pharyngeal suctioning.

Physiologic Background

The efficacy of postural drainage for clearing the lower respiratory tract and improving lung functions has been documented in several studies.[9-15] However, it has remained unclear whether this improved drainage results from gravity or depends on a posture-effected redistribution of ventilation.[16,17] Such posture-induced redistribution of ventilation is age dependent and differs between children and adults.[18] With few exceptions,[19] the therapeutic value of postural drainage has been established by studies of adults; thus it remains unclear whether and to what extent these findings are also valid for children. It was shown that in some infants postural drainage with a head-down tilt may cause gastroesophageal reflux.[20] Whether these findings are

of clinical relevance or not has remained subject to discussion.[1,21]

The rationale for using thoracic expansion exercises is based on the concept that high lung volumes enhance air entry behind partially obstructing mucous plugs. With a deep inspiration, airways are distended enough for inspired air to pass on toward the periphery; furthermore, airflow through collateral channels is enhanced.[17] Breathing control is a strategy for economizing the energy cost of breathing (i.e., for achieving the necessary gas exchange with minimal effort).[5]

The scientific and physiologic bases of chest percussion have remained undefined. Some researchers have shown a deterioration of lung function and arterial oxygen tension with clapping,[22,23] but others, by incorporating clapping into more complex CPT regimens, did not observe such negative effects.[24,25] Pressure waves produced by clapping, vibrations, and compression may induce bronchospasm in patients with hyperreactive airways.[12,26] Although the relevant literature has thus far focused on whether chest percussion has negative side effects, it has remained unclear whether and how percussion achieves a therapeutic effect. Conclusive studies to document the efficacy of clapping per se are lacking. Whether clapping produces transthoracic pressure waves that shake secretions from the airway walls or mobilizes secretions by stimulating the cough reflex remains to be shown. Experienced pediatric chest physiotherapists claim that chest percussion has its maximal efficacy in infants and loses its therapeutic value progressively with increasing age. This observation complies with a concept of transthoracic pressure waves that decrease in efficacy with increasing size and stiffness of the chest. There is no evidence that CPT performed with mechanical percussors is more effective than manual clapping.[27-29] Consequently, patients and parents may choose between these two percussion techniques based on their personal perception of comfort, benefit, convenience, and practicability.[29]

Isolated mechanical chest vibration as a technique for mobilizing excess bronchial secretions was investigated in a radioaerosol study, but results remained inconclusive.[30] Another investigation of patients with atelectasis documented a vibration-effected increase in the partial pressure of arterial oxygen.[31] It appears that many of the existing questions related to chest percussion may also apply to chest vibration.

Chest compression also lacks a specific scientific background; as a technique for supporting the patient's expiration, however, it finds some physiologic basis in the mechanisms of a forced expiratory maneuver.

The efficacy of coughing for transporting secretions is also based on the mechanisms of forced expiration; these mechanisms are discussed in more detail in the next section. In some patients, coughing may be as effective as more complex CPT techniques for clearing secretions from airways.[32-34] Such findings, however, might not apply to patients with instability of the airway wall (i.e., bronchiectatic airway wall damage).[35] In such a situation, the high positive transthoracic pressures, which are developed during a cough, can result in complete airway collapse, thereby effectively interrupting the expiratory airstream through the bronchus.[36] Because this occurs frequently, the forced expiration technique (FET) and other related CPT methods might be more effective than coughing; this speculation is based on the finding that the transpulmonary pressures developed with coughing exceed those occurring in a forced expiratory maneuver.[37]

Suction interrupts mechanical ventilation and thereby affects gas exchange, can facilitate bacterial contamination of the lower respiratory tract, and can cause atelectasis and other complications.[38] Deep suctioning damages the airway by effecting suction biopsy of the mucosa.[39] If it occurs repeatedly, such suction trauma can result in airway obstruction by granulation tissue and scarring, a complication most frequently found at the entry into the segmental bronchi of the right lower lobe. Consequently, suction depth is a critical detail of the procedure. In addition, suctioning should be performed only when necessary; any suction routine with fixed time intervals should be avoided. Manual or mechanical hyperinflation after suctioning is recommended to prevent suction-induced atelectasis; bagging increases the compliance of the respiratory system.[40]

Practical Aspects

For clinical application, these techniques can be combined into different individually tailored CPT sessions. Therapist-administered techniques such as postural drainage, chest percussion, vibration, and compression, with assisted coughing or suction, are routinely applied in infants and small children and remain the only available CPT approach in this age group. Older patients can cooperate with breathing control and thoracic expansion exercises, or they can be trained in one of the self-administered techniques discussed later. Parents of children with chronic conditions are trained by an experienced therapist to competently administer conventional CPT at home.

Properly performed conventional CPT is neither painful nor unpleasant for children; thus after a short adaptation period, it is usually well tolerated. To familiarize the small patient with this therapeutic routine, it seems important to reach adherence to regular therapy at an early age.[41] A treatment session can be time consuming, especially with generalized lung disease.

FET AND ACTIVE CYCLE OF BREATHING TECHNIQUES

The FET was first described in England in the late 1970s.[42,43] As a self-administered technique for clearing the airways, it was first and most extensively studied in patients with cystic fibrosis (CF), but it can also be applied to other chronic disorders with abundant intrabronchial secretions.

Technique

In the FET, the forced expiratory maneuver used for mobilizing and transporting secretions has the form of a "huff." For producing a huff, the patient, using chest wall and abdominal muscles, exhales forcefully, but not violently, through the open mouth. Care must be taken to keep the glottis open. For loosening secretions in the periphery, a huff should cover the range from middle to low lung volume; subsequently, lung volume of huffing can be adjusted to the momentary location of the transported secretions. As soon as secretions reach the upper airways, they can be raised by a huff from high lung volume. The expiratory flow rate used varies individually with the airflow obstruction and compressibility of airways;

huffs must be long enough to effectively move secretions. The FET is performed while the patient is in gravity-assisted positions or sitting.

The active cycle of breathing techniques adheres to the following sequential protocol[44]: breathing control, thoracic expansion exercises, breathing control, thoracic expansion exercises, breathing control, FET (one or two huffs), and breathing control. This sequence can be repeated until all secretions are removed; individual modifications can adapt the protocol to each disease situation.

Physiologic Background

Like coughing, the FET uses expiratory airflow for mobilizing and transporting secretions, thus applying the physiology of a forced expiration.[45,46] The technique attempts to mobilize secretions from the periphery by having the patient huff in a low lung volume. The efficacy of the technique depends on the upstream movement of the equal pressure points in the airways. With an ongoing forced expiration, the dynamic compression of airways creates a wave of choke points that run upstream toward the periphery. A mucous plug, once reached and caught by such a choke point, is propelled downstream by the airflow (Fig. 18-1). In addition, the airflow velocity increases locally with this dynamic compression of the airway; accumulated intrabronchial secretions are mobilized by markedly increased shearing forces and intensified gas-liquid interactions. Radioaerosol studies indicate that coughing and the FET lose effectiveness progressively from the central airways to the periphery of the lung.[34]

The FET is a well-investigated technique. It produces more sputum than conventional CPT in a shorter period of time.[42] Two studies comparing the efficacy of the FET and positive expiratory pressure (PEP) mask therapy have arrived at somewhat contradictory results.[14,47] Airway clearance by the FET can result in a statistically significant improvement of lung function.[15] A fall in oxygen saturation, occasionally observed with conventional CPT, can be prevented with the use of the entire active cycle of breathing techniques.[48]

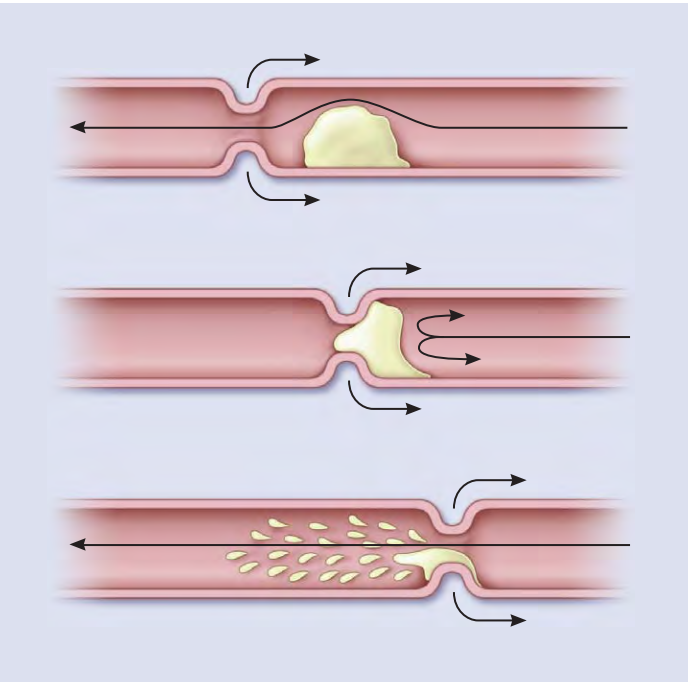

Figure 18-1 Mobilization of mucus by a forced expiration. *Top*, The choke point moves upstream and approaches the mucous plug. *Middle*, The mucous plug is caught in the choke point. *Bottom*, The expiratory airstream ejects the mucus through the choke point.

Practical Aspects

The FET is an effective, self-administered CPT technique that remains independent of any mechanical adjunct. Children as young as 3 to 4 years of age can be taught to huff; blowing games can assist training in this age group.

AUTOGENIC DRAINAGE

Autogenic drainage (AD) is a self-administered CPT technique developed in Belgium and first described in the early 1980s.[49] The accumulated clinical experience with this technique stems mainly from its application in the treatment of CF.

Technique

AD is a special breathing technique that commences at low lung volumes (i.e., in the expiratory reserve volume) and then, with mobilization of secretions, is first elevated to the level of tidal breathing. With the accumulation of secretions in more central airways, the AD breathing level is further elevated into the inspiratory reserve volume, and finally, secretions are raised by a huff. The single inspiration and expiration of AD breathing exceeds the tidal volume dimension. Each inspiration is followed by a short pause; each expiration, performed with an open mouth and glottis, is mildly forced but simultaneously tries to avoid compression-induced interruption of airflow. Massively forced expiratory maneuvers and coughing are avoided. AD is usually performed with the patient in a sitting position.

Physiologic Background

AD can be seen as a modification of the FET, so comparable physiologic principles apply. The technique aims to individually determine an "ideal" expiratory flow rate that is high enough for mobilizing and transporting secretions but still low enough for avoiding positive transthoracic pressures of such magnitude that destabilized bronchi are occluded. Clearly, such a compromise is determined by the most collapsible airway segments in the system. By commencing at low volumes and by approaching high lung volumes in a stepwise manner, the technique tries to follow the movement of mobilized secretions.

There is a discrepancy between the widespread clinical application of this technique in Europe and the paucity of controlled investigations of its value. One prospective study in CF patients indicates that the technique is clearly more effective than spontaneous coughing.[50] Another investigation found AD to be as effective as the active cycle of breathing techniques at clearing mucus in patients with CF.[51] Other relevant articles are descriptive.[52] So far, the relative value of AD compared to most other self-administered techniques remains to be defined.

Practical Aspects

Because the patient must develop significant proprioceptive abilities for feeling the movement of secretions and the occlu-

sion of bronchi, it takes considerable time to properly learn this technique. Furthermore, a daily AD routine also tends to require more time than CPT by some other techniques. On the other hand, AD is less energy consuming and is less prone to induce bronchospasm than more aggressive forms of CPT.[50]

PEP MASK THERAPY

PEP mask therapy uses the same concept as pursed-lips breathing; as a CPT technique, it was developed in Denmark in the late 1970s[47] and has found widespread acceptance. Basically, it is a self-administered CPT technique for the treatment of CF, but it may also be of some value in other conditions that produce abundant endobronchial secretions.

Technique

The PEP mask is a cushioned anesthesiology mask connected to a one-way breathing valve. An endotracheal tube adaptor for neonates is plugged into the outlet of the valve and serves as an expiratory resistor. A set of such resistors with different internal diameters allows for individual variation of the stenosis. Other types of resistors are also offered by some manufacturers.

Therapy is performed with the patient seated with the elbows resting on a table and the mask pressed tightly but comfortably over the mouth and nose. Using diaphragmatic breathing, the patient inspires a volume larger than the tidal volume and then exhales actively, but not forcefully, to functional residual capacity. The resistor is chosen individually for achieving a PEP from 10 to 20 cm H_2O and an inspiratory-to-expiratory ratio of 1:3 to 1:4. A manometer connected to the outlet part of the valve allows monitoring of expiratory pressures and serves as a visual feedback to the patient. From 10 to 20 such breathing cycles are performed with the mask in place; then the mask is removed, and secretions are raised by a huff. Ideally, this sequence of PEP breaths, followed by huffing, is repeated until the airways are cleared from all mobilized secretions. In an attempt to facilitate aerosol distribution to the peripheral airways, PEP breathing can be combined with aerosol inhalation.[53] In such a case, a mouthpiece can substitute for the mask.

Physiologic Background

It is believed that exhaling against resistance can create enough backpressure to maintain the patency of unstable airways. This theory is supported by work that demonstrated a marked attenuation of dynamic airway compression by PEP.[54] Thus, PEP mask therapy can be used to treat patients with obstructive lung disease complicated by instability of the airway wall (i.e., bronchiectasis). PEP mask therapy is thought to increase collateral airflow to areas where the airways are obstructed by secretions, thereby facilitating subsequent expiratory mobilization of mucus.

PEP mask therapy is a well-studied technique. In some comparative investigations, it was found to be superior to other CPT techniques in terms of sputum production and other clinical measures.[47,55,56] A radioaerosol study showed PEP mask therapy in combination with FET to be more effective in terms of mucus clearance than FET alone.[57] Other authors either failed to find significant differences when comparing PEP mask therapy with other forms of CPT or found PEP mask therapy to be somewhat less effective.[14,58-62] PEP mask therapy has been reported to cause various changes of lung functions, such as an increased partial pressure of oxygen and tidal volume and a decreased residual volume and work of breathing.[47,55,63,64] From the sum of these published data, one can conclude that PEP mask therapy is effective for clearing airways of excess secretions in chronic lung disorders, especially CF. However, its relative value, when compared to other CPT techniques, needs to be more clearly defined.

Practical Aspects

PEP mask therapy is an attractive technique for patients with chronic lung disease who depend on a self-administered method that is not time consuming. PEP mask therapy sessions typically take only half of the time required for a conventional CPT session but raise equivalent quantities of sputum.[65] In addition, the patient does not depend on cumbersome equipment for effective self-treatment. PEP mask therapy can be taught to children beginning at approximately 4 years of age.

HIGH-PRESSURE PEP MASK THERAPY

High-pressure PEP mask therapy, developed in Austria in the early 1980s, incorporates forced expiratory maneuvers into the PEP mask technique.[66] It can be used by patients with CF and other chronic respiratory conditions that produce excessive bronchial secretions.

Technique

The instrument used for this technique is the same as that described in the previous section, but it is equipped with another manometer for monitoring higher pressures. Therapy is performed with the patient seated with the elbows resting on a table and the shoulders moved close to the neck to cover and support the lung apexes. PEP breathing for 8 to 10 cycles is done as described in the previous section; then the patient inhales to total lung capacity and subsequently performs a forced expiratory maneuver against the stenosis. Effected mobilization of secretions usually results in coughing at low lung volume. After expectorating sputum, the patient repeats the same sequence of breathing maneuvers until no more sputum is produced. Care must be taken not to terminate these forceful expirations before residual volume is reached; the sustained expiratory pressures achieved usually range between 40 and 100 cm H_2O.

The dimension of the expiratory resistor is determined individually by a spirometer-assisted method.[66] For this purpose, the outlet of the PEP mask is connected to a spirometer, and the patient performs forced expiratory vital capacity maneuvers through a series of resistors with different internal diameters (Fig. 18-2).

Physiologic Background

The effects of high-pressure PEP mask therapy are speculatively explained by increased collateral airflow to underventilated lung regions; air expired from there mobilizes obstructing secretions. In addition, a forced expiration against a marked resistive load tends to squeeze pendelluft from hyperinflated into obstructed and atelectatic lung units. Mobilization of mucous plugs might be supported by backpressure-effected dilation of airways. The same backpressure

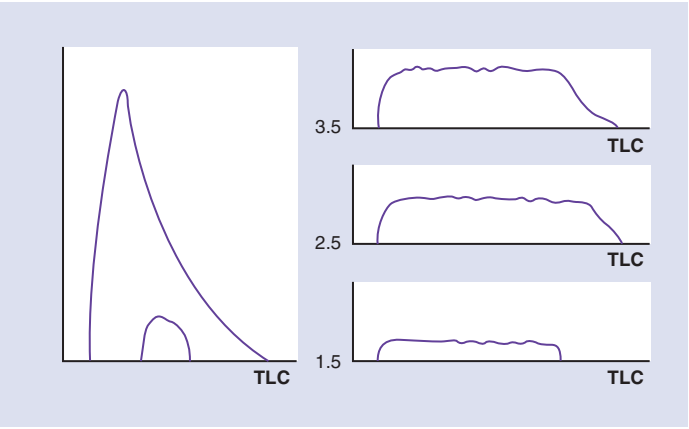

Figure 18-2 Finding the optimal expiratory resistor for high-pressure PEP mask therapy. Patient with CF, age 15 years. *Left,* Maximum expiratory flow-volume curve of the patient. *Right, top,* With a 3.5-mm internal diameter resistor, there is a stenosis-effected plateau formation, but the terminal portion of the tracing is still curvilinear (inhomogeneous emptying of different lung units). *Right, middle,* With a 2.5-mm internal diameter resistor, there is a plateau at a lower flow rate, and the terminal portion of tracing has straightened. *Right, bottom,* With a 1.5-mm internal diameter resistor, the patient terminates expiration before the residual volume is reached. The 2.5-mm resistor is chosen for further treatment. TLC, total lung capacity.

will prevent collapse and occlusion of those airways with instable walls owing to bronchiectatic destruction. As in the FET, upstream movement of the equal pressure points with the ongoing forced expiration and a progressive incorporation of the peripheral airways into the compressed downstream segment appear to be prerequisites for efficacy. Consequently, incomplete maneuvers, either caused by the choice of an inappropriate resistor or by an incorrectly performed technique, result in impaired clearance.[66]

High-pressure PEP mask therapy is a relatively well investigated technique, but studies published so far have been limited to CF patients. In a long-term investigation, the technique decreased airway obstruction and hyperinflation.[66] In hospitalized patients, high-pressure PEP mask therapy resulted in a stepwise improvement of lung function, and these changes correlated to the weight of produced sputum.[67] When compared to AD, the technique produced more sputum in a shorter period of time.[50]

Practical Aspects

To avoid prolonged use of suboptimal resistors, patients using this technique need regular reevaluation by specialized therapists who are supported by a well-equipped center. Backpressure-induced airway distention imposes some stress on airway walls; consequently, high-pressure PEP mask therapy occasionally induces bronchospasm in patients with airway hyperreactivity.[50,68] Such patients should use another CPT technique or adopt a routine of bronchodilator premedication. As evident from substantial clinical experience, the technique carries no increased risk of pneumothorax.[68] Because it takes considerable expiratory muscle strength and endurance to repeatedly exhale forcefully against a marked resistive load, high-pressure PEP mask therapy is an energy-consuming technique that does not meet the needs of an exhausted patient.

From the viewpoint of the patient, the technique is attractive because it involves highly effective but brief treatment sessions. The technique can be used properly and safely by most patients older than 5 years.

ORAL HIGH-FREQUENCY OSCILLATION THERAPY

In oral high frequency oscillation and intrapulmonary percussive ventilation, an eccentric cam piston or the diaphragm of a loudspeaker produce pressure waves that are superimposed on normal tidal breathing. Oscillation of airway walls is thought to mobilize secretions. In contrast to high-frequency oscillations of the chest wall, however, oral high-frequency oscillation therapy does not enhance tracheal mucus clearance in relevant animal studies.[69] In one study of healthy subjects, oral high-frequency oscillation increased mucociliary clearance.[70] In patients with CF, this technique was as effective as conventional CPT in enhancing sputum expectoration.[71,72] Another study has shown this technique to be no more effective than other CPT methods.[73] It follows that the relative efficacy of this technique remains to be defined. No guidelines have yet been established on how to fine-tune the technique to the patient or the disease state.

HIGH-FREQUENCY CHEST COMPRESSION THERAPY

High-frequency chest compression therapy has been developed, introduced, and investigated in the United States.[74] It is applied by a device that consists of a vinyl-coated polyester inflatable vest, which covers the entire torso of the patient, and a variable air-pulse delivery system. This apparatus applies high-frequency compressions to the patient's chest to mobilize secretions. The "best" compression frequencies for an individual are thought to be those associated with the highest expiratory flow rates and the largest expired volumes. These frequencies are determined by measuring the airflow and volume at the mouth during tidal breathing while the patient receives high-frequency chest compression therapy at frequencies between 5 and 22 Hz.

One long-term study found this technique to be superior to conventional CPT in terms of the lung function of CF patients.[74] Other investigators found both techniques equally effective in improving lung functions and sputum expectoration in hospitalized patients with CF.[72,75] In patients whose lungs were mechanically ventilated, this technique was as effective and safe as conventional CPT.[76] The relative value of high frequency chest compression, when compared to other self-administered CPT techniques, remains to be evaluated. One practical drawback is that this technique depends on expensive and cumbersome equipment.

OSCILLATING PEP

Oscillating PEP or "flutter therapy" tries to combine PEP breathing and oral high-frequency oscillation. Self-administered flutter treatment is performed by breathing through a pipelike instrument; in the pipe's outlet, a steel ball oscillates in the expiratory airstream and thus serves as a variable resistive load. Results of a comparative study indicated that the active cycle of breathing techniques raises more sputum than flutter therapy in patients with CF.[77,78] Another study in CF patients found the flutter technique to be more effective than conventional CPT in raising sputum.[79] There might be an optimal oscillation frequency for each

individual, and patients might benefit from fine-tuning the technique to their disease situations; so far, however, there are no objective guidelines for determining an individual optimal frequency.

PHYSICAL EXERCISE

Strenuous physical exercise and sports can facilitate expectoration of sputum in patients with CF.[80] Several mechanisms may contribute to this effect: Exercise-induced hyperventilation accelerates mucociliary clearance[81,82] and increases gas-liquid pumping in airways filled with secretions; subtle, submersion-induced chest compression occurs with swimming, and other sports occasionally cause chest shaking and vibration.

In some children with CF, regular physical exercise may effectively substitute for CPT.[83] In adults with CF, however, CPT produces more sputum than does exercise.[84] From these seemingly discrepant study results, one can conclude that sports may probably substitute for CPT in some patients with mild to moderate lung disease. However, these patients still need to be trained in a CPT technique to clear their airways when they are unable to exercise. For more severely diseased patients, CPT and physical exercise should be considered complementary rather than competing treatment strategies.

Indications and Contraindications

GENERAL ASPECTS

Indications

In general, CPT for airway clearance should be considered in all disease situations that have expected or already established complications from accumulated intrabronchial secretions or aspirated material. CPT is then prescribed to substitute for the patient's failing mucociliary and cough clearances. Efficient intervention by CPT should be preceded by a clear analysis of the prevailing mechanisms of the patient's disease. Because several pathophysiologic variations can occur within the frame of one diagnostic entity, it seems prudent to base the use of pediatric CPT on an analysis of disease mechanisms rather than on general diagnostic classifications.

CPT is targeted to the intrathoracic airways and thus can interact only with bronchial pathology. It is effective mainly for the clearance of the central airways and loses its efficacy progressively toward the periphery. With the possible exception of some breathing exercises and positioning, CPT has no place in the treatment of alveolar, interstitial, vascular, and pleural disease.

CPT is also indicated on diagnostic grounds when secretions from the lower respiratory tract are a more relevant substrate for bacteriologic investigation than a throat swab. Effective clearance of airways by CPT is a prerequisite for the application of therapeutic aerosols that address the bronchial mucosa.

Contraindications

The decision against applying CPT, like the decision for applying CPT, should be based on a detailed understanding of the disease. When contemplating contraindications, the clinician should remember that CPT involves a variety of mechanical interventions with different and specific risks and benefits. For example, some disease situations might preclude the use of chest percussion, vibration, and compression but not thoracic expansion exercises.

Some components of CPT are contraindicated when they threaten to cause significant hemorrhage (in bleeding disorders, some cases of vascular or cardiac surgery, massive intrabronchial bleeding) or cardiac dysrhythmias (in various forms and stages of cardiac disease or surgery). Occasionally, conditions of the chest wall (trauma, infections, neoplasms, rickets, and other disorders with increased risk of rib fracture) reduce or even forbid effective mechanical access to the patient's thorax.

The critically ill child with raised intracranial pressure presents a special CPT problem in that CPT might be needed to prevent deterioration in respiratory functions but might also cause further acute rises in intracranial pressure. In this case, special CPT management with more frequent, but shorter, treatment periods is advisable.[85] The head-down position is contraindicated, and any handling and endotracheal suction should be reduced to a minimum.[1]

Some forms of CPT might cause bronchospasm in patients with airway hyperreactivity.[12,26] Such cases can be managed by bronchodilator premedication or by tailoring of an individual CPT regimen to avoid more aggressive mechanical irritations of the intrathoracic airways.

SPECIFIC DISORDERS

Acute Conditions

With few exceptions, CPT should always be considered for the treatment of atelectasis or local hyperinflation despite whether the condition occurred as a complication of bronchiolitis, bronchial asthma, aspiration pneumonitis, bronchial stenosis, or intubation and mechanical ventilation.[24,86,87]

Children with uncomplicated acute bronchiolitis or acute severe asthma do not benefit from CPT.[88,89] Similarly, there is no reason to prescribe CPT for children with croup or epiglottitis.[1] CPT is, at best, useless in acute pneumonia with lobar or segmental consolidation,[90,91] a finding that is not surprising when the predominantly alveolar localization of the inflammatory process is considered. Foreign-body aspiration is routinely treated by bronchoscopy; however, CPT performed over several days after the removal of the foreign body often supports an uncomplicated recovery.[1]

Because an endotracheal tube interrupts the mucociliary escalator and hampers cough clearance, CPT should be considered for any child whose lungs are ventilated mechanically for more than a few hours. In mechanically ventilated lungs, intrabronchial accumulation of secretions is further enhanced by mucus inspissation, which is caused by fluid restriction and the use of diuretics, by the suppression of cough resulting from sedatives and neuromuscular blockage, and by poor humidification of inspired gas. Thus, CPT is important in neonatology, pediatric intensive care, and pediatric surgery. For cases of lobar atelectasis or unilateral lung collapse in newborns, infants, and children whose lungs are mechanically ventilated, most centers have developed some routine of nonendoscopic bronchial lavage; such procedures usually consist of saline instillation, bagging, expiratory vibration, and chest compression followed by endotracheal suctioning.[92]

In neonatology, CPT might be prescribed for premature infants with hyaline membrane disease whose lungs are ventilated and for neonates with meconium aspiration syndrome, aspiration of food, and any other disorder requiring mechanical ventilation. Because CPT has potentially serious side effects in this patient group,[93,94] it should always be applied on an as-needed and not on a routine basis. Properly performed CPT removes secretions, improves oxygenation, and may prevent postextubation atelectasis in newborns with respiratory disease.[87,95,96] A prerequisite for applying CPT effectively and safely in premature infants and newborns is a profound knowledge of the special respiratory anatomy and physiology in this age group; specifically, the therapist should modify the approach to match an extremely compliant thorax, a special mechanical situation of the diaphragm, the closing airways, an age-specific interrelation of body position and distribution of ventilation, and an actively elevated functional residual capacity. Respiratory care of the newborn is described in more detail in relevant textbooks and manuals.[1,97]

In the pediatric intensive care unit, CPT is often needed after the repair of congenital cardiac defects, after pulmonary surgery, and for patients with congenital diaphragmatic hernia, gastroschisis, exomphalos, and tracheoesophageal fistula.[1] In addition, patients with intubated and ventilated lungs and with severe neurologic disorders or various critical medical conditions benefit from CPT. The preoperative and postoperative CPT management of children undergoing cardiac and transplantation surgery requires specialized knowledge and experience.[1] Treatment frequency should be determined and adjusted on the basis of careful and repeated reassessment of the individual. Any chest physiotherapist working in a pediatric intensive care unit must be profoundly familiar with the special environment, its staff, machinery, and techniques. CPT strategies for intensive care are described and discussed in special texts.[1,98]

Chronic Diseases

CPT has a traditional position in the treatment of CF.[3] A meta-analysis of relevant studies confirmed that CPT effects significantly greater sputum clearance in CF patients than no treatment.[99] Other forms of chronic suppurative lung disease, such as localized bronchiectasis, primary ciliary dyskinesia, and some cases of agammaglobulinemia, also benefit from daily CPT. In addition, neurologically handicapped children, who chronically aspirate secretions and food, often need regular CPT. Occasionally, CPT should be prescribed for a child with bronchopulmonary dysplasia or any other chronic respiratory problem characterized by excess intrabronchial secretions. In contrast, the asthma syndrome constitutes no routine indication for CPT.

Increasingly, chest physiotherapists provide care for children with neuromuscular disease. In addition to long-term home ventilation and airway clearance, some of these patients may benefit from individualized respiratory muscle training.[100] Because of muscle weakness, the effectiveness of cough is often severely impaired; chest physiotherapists can augment cough in these patients by using special cough-simulating machinery for insufflation and subsequent exsufflation.[101]

OTHER FACETS OF CPT

In addition to airway clearance, the CPT team of a pediatric respiratory center may be involved in other caregiving programs as well as diagnostic and therapeutic procedures. Such involvement differs substantially among hospitals and centers and regions and countries, the most relevant modifying factor being the availability of other specialized health care professionals such as respiratory therapists, specialized technicians, nurses, and medical doctors. Thus the subsequent list, which is based on local experience, intends to stimulate a possible wider perspective on the job description of pediatric chest physiotherapists. In the United States, the respiratory therapist is responsible for many of the same areas as the chest physiotherapist in Europe.

Breathing Exercises

Breathing exercises encompass a wide spectrum of therapeutically applied breathing patterns and body positions. One end of this spectrum is characterized by the breathing maneuvers for airway clearance, maneuvers needed for properly inhaling an aerosol, and maneuvers for adapting a patient's breathing pattern to various physical activities. On the spectrum's other end are ill-defined and occasionally obscure breathing maneuvers that have managed to survive in some institutions and physiotherapy schools in spite of lacking any physiologic basis or scientific proof of efficacy.

Muscle Training and Exercise Programs

Training programs, especially when targeted on chest and shoulder girdle, can increase respiratory muscle endurance.[102] In addition, body-building exercises may increase upper body muscle mass. By disguising disease-related chest deformities, this effect might improve a patient's body image. Chronic obstructive lung disease affects posture and thoracoabdominal musculature; targeted exercise programs may counteract this development and help the patient maintain good posture and mobility. Under the guidance of an experienced chest physiotherapist, any patient may find an easier and safer access to such programs. These interventions should start early when postural deficits are just emerging.[103]

Exercise programs, either organized in the form of repeated sports lessons or as a training camp, can improve the respiratory status of pediatric patients with chronic lung disease.[80,83] Relatively simple training programs were shown to improve cardiopulmonary fitness in children with CF.[104] In addition, the chest physiotherapists conducting these programs gain valuable insight into patients' respiratory status, exercise tolerance, compliance with medication, and psychosocial problems and habits.

Aerosol Therapy

A pediatric respiratory center must provide a wide spectrum of techniques for aerosol delivery, ranging from nebulizers to dry powder or metered dose inhalers to spacers. The efficacy and safety of aerosol therapy depend on the meticulous standards for the maintenance of equipment, hygiene, dosing, and training patients and parents to perform inhalation techniques. Within a medical center, many health care profession-

als administer aerosol therapy, but quality control and adoption of new techniques are the responsibilities of the center's chest physiotherapists. Other responsibilities include updating other health care professionals on new techniques and equipment and organizing individual or group training sessions for patients and parents.

Lung Function Testing

Pediatric chest physiotherapists should be trained in recording and interpreting several simple and straightforward lung function tests such as spirometry, flow-volume curves, peak expiratory flow, transcutaneously measured blood gas tension, and pulse oximetry. This enables them to closely monitor the patient's therapy, thereby introducing an additional factor of control and safety. Because of their special expertise in training children to perform complex breathing maneuvers, they frequently succeed in obtaining valid lung function recordings in very young children.

Assistance with Other Diagnostic and Therapeutic Procedures

With the widespread introduction of flexible fiberoptic bronchoscopy, the pediatric airway has become more easily accessible for the pediatric pulmonologist. Incorporation of the chest physiotherapist into the endoscopy team provides the opportunity to further improve personal knowledge about this organ system. With time, the chest physiotherapist develops into a valuable assistant for the endoscopist. Occasionally, bronchoscopic lavage is performed for the removal of impacted intrabronchial secretions.[105] In such cases, simultaneously performed CPT might increase the sputum yield of the procedure. In addition to endoscopy, the chest physiotherapist can offer assistance with exercise testing and in the sleep laboratory.

Long-Term Oxygen Therapy

Long-term oxygen therapy can be applied via a concentrator or, for supporting the patient's mobility, via a portable system (small tank or liquid oxygen container). Minitracheostomies may facilitate oxygen delivery to the patient. The caregiving system required for prescribing long-term oxygen therapy may be set up, maintained, and updated by the center's CPT team.

Tracheostomy Care

A small group of children with complex congenital or acquired lesions of the upper respiratory tract or progressive neuromuscular disease require tracheostomy for securing the patency of the upper airway or for applying long-term mechanical ventilation. Pediatric tracheostomy care is a comprehensive treatment encompassing many details such as selection of the ideal cannula, the changing and proper fixation of cannulas, suction, humidification, the use of filters and valves, and the training of parents and other caregivers. Chest physiotherapists can be responsible for such a program; in fact, some current concepts for pediatric tracheostomy care have been developed by chest physiotherapists.[106]

Home Mechanical Ventilation

Home mechanical ventilation has been widely accepted as a caregiving strategy for children with chronic respiratory insufficiency related to etiologies such as bronchopulmonary dysplasia, spinal muscular atrophy, phrenic nerve paralysis, diaphragmatic hernia, thoracic and abdominal wall deformities, high-level myelodysplasia and spinal cord injury, childhood myopathies, and central hypoventilation syndrome.[107] Home mechanical ventilation can be applied via a tracheostomy or noninvasively through the nose or the mouth. Guidelines for home mechanical ventilation have been developed.[108] As with tracheostomy care, the success and safety of a home mechanical ventilation program depend on the availability of a comprehensive and highly specialized treatment plan and on the meticulous training of parents. Again, such programs can be organized and carried out by a center's CPT service.

Psychologic Support

Many pediatric chest physiotherapists find themselves as patient- and parent-elected troubleshooters for psychosocial problems. By frequently talking to patients and by touching them, they gain the confidence of patients and parents and become profoundly familiar with their personal problems, which is especially important when working with children who suffer from chronic respiratory disease. With this type of knowledge, the chest physiotherapist often provides a vital, albeit unofficial, link among patients, parents, and staff.

SCIENTIFIC BASIS OF CPT

Relevant Problems and Misconceptions

EFFICACY

More than three decades ago, a conference on the scientific basis of CPT was opened by the statement that CPT lacks an established scientific basis and evidence of lasting clinical benefit.[109] Since then, various aspects of CPT have been subject to prospective and controlled clinical studies. However, many techniques and methodological details have thus far remained empirical. That the proponents of specific techniques tend to champion their methods at symposia and meetings has not helped clarify the situation; thus controversy reigns in the field. It follows that the scientific basis of CPT is still fragile and incomplete.

Evaluating the efficacy of CPT is a difficult task because numerous confounding variables cannot be eliminated from such studies. Each CPT technique consists of several methodological components; different therapists and centers often tend to emphasize different parts of the technique and neglect others. When comparing the performance of CPT among centers, one finds major technical differences, a situation that illustrates an urgent need for standardization. Consequently, comparative studies of different techniques frequently find that a technique is most effective where it was developed or is most intensively practiced. Because of the pathophysiologic heterogeneity of diagnostic entities and the methodological heterogeneity of CPT techniques, the "best" CPT technique appears to be a misconception, and the

ongoing search for such a technique is ineffectual. It may be more appropriate to evaluate which CPT regimens are more effective for individuals rather than evaluating whether any one technique is the most effective for all patients and disease situations.[110] However, research aimed at improving the efficacy of CPT by better matching the specific pathophysiologic and methodological details does not exist yet.

PHYSIOLOGIC BASIS

Another handicap for establishing a more substantial scientific basis of CPT is the incomplete understanding of each technique's physiologic basis. Most techniques have been developed by trial and error at the bedside; traditionally, therapists have focused on *whether*, not *how*, a specific technique works. Any future concept of tailoring specific CPT techniques to individual patients and disease situations requires a clearer understanding of the mechanisms responsible for each technique's efficacy.

CPT Studies

SHORT-TERM STUDIES

Short-term studies evaluate the effects of one or a few treatment sessions. Their potential clinical relevance is based on the speculation that a specific, documented short-term effect of CPT might alter the disease course. So far, clinicians have been unable to determine which diagnostic technique can most accurately assess the CPT-effected removal of secretions.

Sputum Weight

One of the simplest and most straightforward strategies is to quantify expectorated sputum by its weight. Contamination by saliva might introduce some error, but such an error progressively loses significance with increasing sputum volumes. Clearly, one cannot investigate a technique for emptying a ketchup bottle when the bottle contains hardly any ketchup in the first place.[111] For adolescents and adults, a daily sputum volume in excess of 30 mL must be obtained for documenting the efficacy of CPT.[111,112]

Lung Function Measurements

Assessment of lung function and blood gases is another traditional approach to the evaluation of short-term CPT effects. Numerous studies have documented beneficial lung function changes after the application of different CPT techniques, but many attempts to correlate the dimension of lung function changes to the weight of raised sputum have remained unsuccessful.[9,12,33] One study of CF patients, however, finally established such a cause-and-effect relationship.[67] This traditional difficulty in documenting a lung function-sputum weight correlation is most likely explained by airway-related noise. CPT-effected shifting of secretions from one lung unit to the other without complete expectoration, therapy-induced bronchospasm in patients with airway hyperreactivity, and occasionally applied concomitant medications are all confounding variables that tend to disguise the potentially beneficial effects of sputum expectoration on lung function. Blood gas measurements might be particularly sensitive to this type of airway-related noise.

Radioaerosol Studies

Radioaerosol studies are considered a promising strategy for assessing the effects of CPT.[113] Treatment-effected movements of the inhaled tracer are observed directly with a gamma camera. One handicap of this diagnostic approach, which particularly applies to children, is the radiation. Another caveat relates to the maldistribution of ventilation that invariably develops with any intrabronchial accumulation of secretions: Inhaled tracer particles tend to deposit least in the most obstructed lung units, which on the other hand, should benefit most from CPT.

Other Diagnostic Techniques

Occasionally, the effects of CPT can be directly observed when CPT is applied in the course of an endoscopic investigation. With few exceptions, conventional chest radiographs are too insensitive for direct visualization of accumulated intrabronchial secretions. However, they remain the routine diagnostic approach for assessing the effects of CPT on segmental or lobar atelectasis.

LONG-TERM STUDIES

The long-term effects of repeatedly applied CPT on chronic respiratory disease can be evaluated only by long-term studies. Such studies are extremely difficult to perform because the long-term course of chronic respiratory disease is usually variable and characterized by exacerbations, remissions, and the effects of other concomitant treatment strategies. Another limitation is introduced by patients, who often do not comply with CPT recommendations.[114] For obvious ethical reasons, it is frequently impossible to set up an equally diseased control group without CPT. In spite of all these limitations, a few studies, performed mainly with CF patients, have tried to establish a scientific basis for the long-term prescription of CPT in chronic pediatric lung disease.[66,74,115,116] Systematic reviews of this literature, however, are invariably hampered by the present paucity of well-designed, sufficiently powered, long-term studies.[117]

CONCLUSIONS

The relevant literature provides some first fragments for a scientific basis of pediatric CPT but also illustrates the urgent need for additional controlled investigations. Thus clinical and scientific audits should be an integral part of CPT practice.[118]

ORGANIZATIONAL ASPECTS

Professional Situation

At present, CPT-related organizational concepts, required level of specialization, interaction with other health care professionals, legal and administrative basis for practice, and employment conditions all differ widely among countries, medical schools, and hospitals. For example, some overlap exists, but there are also some important differences between the professional concepts of *CPT* and *respiratory therapy*, the former being of predominantly European and the latter of North American origin. One end of the professional spectrum is characterized by a profoundly structured and highly trained CPT team in the organizational framework of a pediatric respiratory center; on the other end, a specialized CPT service

is completely absent. In the latter case, some CPT techniques are applied by other health care professionals or, occasionally, by physiotherapists from other pediatric subspecialties. Whether such CPT, which might lack quality and therapeutic intensity, should be prescribed at all or whether it threatens to produce more complications than benefits remains a matter of discussion. In some countries, employment of chest physiotherapists is characterized by hospital-based services; in other countries, many physiotherapists, including those who specialize in CPT, work in private practice—a situation that may impede the intensive interaction between other caregivers and the physiotherapist. The prerequisites for establishing an effective pediatric CPT service are the specialized theoretical and practical training courses that are offered by physiotherapy schools and training hospitals and that include a major pediatric component.

Improving the Efficacy of CPT

When pediatric CPT is based within the framework of a pediatric respiratory center, intensive interaction between the chest physiotherapists and all other health care professionals is mandatory for improving the efficacy of treatment. A "respiratory progress chart" for each patient can assist the health care team in monitoring the disease and patient responses to CPT.[119] Such written documentation also intensifies the flux of information between medical physicians and physiotherapists. In addition, all members of the CPT team should take part in patient- and problem-related staff conferences for maximal integration into all relevant caregiving programs. Various delivery systems aimed at correcting CPT misallocations are developed and evaluated.[120]

Other health care professionals, including medical physicians, often have no clear knowledge of CPT and its potential indications, contraindications, and risks. Thus, the build-up of an effective CPT service includes ongoing education of professionals and administrators. Another important factor for improving the efficacy of a center's CPT team is an intensive exchange of thoughts and visits with other pediatric CPT groups.

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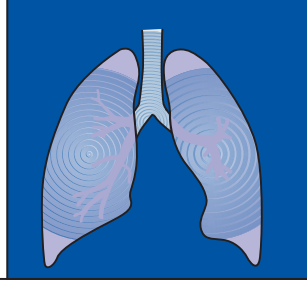


CHAPTER 19

Respiratory Failure and Acute Respiratory Distress Syndrome

Juan A. Gutierrez, Trevor Duke, Robert Henning, and Mike South

TEACHING POINTS

- Hypoxemia is present in the two main types of respiratory failure: nonventilatory, or type 1, and ventilatory, or type 2. Hypercarbia is present in the second, most common type. Clinically significant hypercarbia is always associated with hypoxemia, unless supplemental oxygen is provided.
- The causes of hypoxemia are multiple, but the most common type is caused by increased venous admixture, especially in the form of ventilation/perfusion inequality.
- Pulmonary edema can be of hydrostatic origin, sometimes called cardiogenic, or it can be caused by increased capillary permeability. In practical terms, especially in the critically ill patient, elements of both types of pulmonary edema may be present.
- ARDS is a type of respiratory failure caused by acute lung inflammation with pulmonary edema resulting from increased permeability. Advances in critical care, including the use of protective lung strategies, are improving the outcome of this serious condition.

RESPIRATORY FAILURE

This chapter covers the pathophysiologic mechanisms involved in respiratory failure, with particular emphasis in the clinically relevant aspects. In this context, we will discuss how these factors lead to specific pulmonary conditions, such as acute respiratory distress syndrome and acute lung injury. Respiratory failure is the cause for a significant proportion of deaths during infancy and childhood, even more in underdeveloped countries. As we will review in this chapter, there are specific anatomic and functional characteristics that place the pediatric patient at risk, in particular, when compared with adults.

Definition

Respiratory failure is defined as the impaired ability of the respiratory system to maintain adequate oxygen and carbon dioxide homeostasis.[1] In respiratory failure, the respiratory system may be unable to mobilize enough oxygen and carbon dioxide required by the body's metabolism.

Commonly used criteria are a partial pressure of arterial carbon dioxide ($PaCO_2$) of 50 mm Hg or higher, or a partial pressure of arterial oxygen (PaO_2) of less than 60 mm Hg in a subject breathing air at sea level. However, these are arbitrary criteria of limited utility in the clinical context, in particular in pediatric patients. For example, patients with congenital heart defects with right-to-left shunt (cyanotic heart defects), live with baseline PaO_2 well below the 60 mm Hg limit. We have to take into account the prior status of the patient, the inspired oxygen concentration (FIO_2), the barometric pressure, and the age of the patient.[2]

As indicated in Boxes 19-1 through 19-3, respiratory failure may be caused by disorders at any point in the respiratory system, which includes the central and peripheral nervous system, the respiratory muscles; the thoracic cage and pleura; the large and small airways; the pulmonary epithelium and interstitium, and the pulmonary circulation. Although an abnormality at a single point can produce respiratory failure, such as the acute obstruction of the trachea by a foreign body, more commonly we see combined abnormalities at different levels of the respiratory system. When the subject has a chronic condition affecting one of the levels, such as tracheobronchomalacia, a disorder affecting a second level, for example central nervous system depression by sedatives, is often responsible for precipitating or aggravating respiratory failure.

Respiratory failure can be acute or chronic. **Acute respiratory failure** is an immediately life-threatening condition that develops over minutes to hours. **Chronic respiratory failure** is a potentially life-threatening condition that develops over months to years (e.g., the gradually deteriorating gas exchange in a child with kyphoscoliosis and diaphragmatic weakness resulting from Duchenne-type muscular dystrophy).

Classification of Respiratory Failure

Respiratory failure has been traditionally divided into two types. Although this classification is useful from a conceptual point of view, they are usually both present in different degrees in most patients.

- Type 1, or hypoxemic or nonventilatory: There is hypoxemia, but the $PaCO_2$ is low or normal. This situation is rare as a pure entity.
- Type 2, or ventilatory or global respiratory failure: hypoxemia and hypercapnia are present.

Hypoxemia is present in both types of respiratory failure. From a clinical point of view, it may be more useful to consider the causes of the hypoxemia rather than the type 1 or 2 classification.

BOX 19-1 Central Nervous System Causes of Respiratory Failure

Medications
- Narcotics
- Sedatives
- General anesthetic agents
- Diuretics that cause metabolic alkalosis (e.g., furosemide)
- Sodium bicarbonate
- Prostaglandin E_1
- Poisoning

Metabolic conditions
- Hypoxia
- Extreme hypercapnia
- Severe alkalosis
- Hyperglycemia
- Hypoglycemia
- Hyponatremia
- Hypocalcemia
- Hyperammonemia, including Reye's syndrome and urea cycle disorders, and some organic acidemias, including maple syrup urine disease
- Medium-chain acyl-coenzyme A dehydrogenase deficiency
- Leigh disease
- Cerebral edema of any cause

Infections
- Meningitis
- Encephalitis
- Brain abscess
- Bulbar poliomyelitis
- Postinfectious demyelinating disorders of the brain stem

Brain stem malformations
- Syringobulbia

Arnold-Chiari malformation
- Encephalocele
- Joubert syndrome
- Dandy-Walker syndrome

Bony abnormalities affecting the brain stem
- Achondroplasia
- Osteogenesis imperfecta

Bulbar hemorrhage

Brain stem trauma and raised intracranial pressure of any cause

Seizures

Central alveolar hypoventilation

BOX 19-2 Neuromuscular Disorders Causing Respiratory Failure

Medications
- Muscle relaxants
- Anticholinesterases
- Aminoglycosides
- Dantrolene
- Glucocorticoids
- Heavy metal poisoning

Metabolic Conditions
- Severe hypophosphatemia
- Hypokalemia or hyperkalemia
- Hypermagnesemia
- Uremia
- Carnitine deficiency
- Acid maltase deficiency
- Acute intermittent porphyria

Infections
- Poliomyelitis
- Tetanus
- Botulism
- Diphtheria

Trauma
- Spinal cord trauma
- Phrenic nerve trauma
- Diaphragm trauma

Other
- Myasthenia gravis
- Muscular dystrophy
- Hoffman-Werdnig syndrome
- Kugelberg-Welander syndrome
- Guillain-Barré syndrome
- Prolonged starvation
- Multiple sclerosis
- Polyneuropathy of critical illness
- Dermatomyositis or polymyositis
- Envenomations (tick, tetrodotoxin, snake)

CAUSES OF HYPOXEMIA

There are basically two causes of hypoxemia: hypoventilation and increased venous admixture. Hypoventilation will be discussed first. Increased venous admixture is more complex and includes the following mechanisms: right-to-left shunt; ventilation/perfusion ($\dot{V}/\dot{Q}$) inequality; and diffusion block.

These mechanisms can combine and their contribution to the hypoxemia varies from one disease to another, from one patient to another with the same disease, and even from one time to another in the same patient. The physiology of these entities is discussed in detail in Chapter 14; however, although some redundancy will be unavoidable, this chapter will frame these concepts into a clinical context.

Hypoventilation

Hypoventilation (reduced alveolar ventilation) causes hypoxemia by increasing the partial pressure of carbon dioxide in alveolar gas (P_{ACO_2}) (type 2 respiratory failure). As P_{ACO_2} increases, it displaces oxygen from the alveolar gas so that the partial pressure of oxygen in alveolar gas (P_{AO_2}) (and therefore Pa_{O_2}) decreases, as is shown from the alveolar gas equation, which follows:

BOX 19-3 Pulmonary Causes of Respiratory Failure

Disorders of Bellows Function

Chest wall
- Kyphoscoliosis
- Asphyxiating thoracic dystrophy
- Collodion skin
- Circumferential chest burns
- Chest wall edema

Pleura
- Hemothorax
- Pleural effusion
- Pneumothorax: open or closed
- Bronchopleural fistula

Lung
- Pulmonary hypoplasia

Airway Disorders

Upper airway obstruction
- Nose
- Pharynx
- Larynx
- Trachea
- Bronchi

Small airway obstruction
- Asthma
- Viral bronchiolitis
- Bronchiolitis obliterans
- Inhalation injury to small airways

Lung Parenchymal Disorders

Pneumonia
Pulmonary edema
Pulmonary fibrosis
Pulmonary alveolar proteinosis

Pulmonary Vascular Disorders

Primary pulmonary hypertension
Pulmonary arteriovenous malformations
Pulmonary embolism

Eq 19.1 $$P_{AO_2} = P_{IO_2} - P_{ACO_2}/R + [P_{aCO_2} \times F_{IO_2} \times (1 - 1\ R)/R]$$

where P_{IO_2} is the partial pressure of oxygen in inspired gas, and R is the respiratory quotient (approximately 0.8 in children on a normal diet). This equation is often simplified to:

Eq 19.2 $$P_{aO_2} = F_{IO_2} \times (P_B - PH_2O) - P_{aCO_2}/R$$

Where: FIO2 = fractional concentration of oxygen in room air ≈ 0.21; P_B = barometric pressure at sea level ≈ 760 mm Hg; P_{aCO_2} = partial pressure of arterial carbon dioxide ≈ 40 mm Hg; R = respiratory quotient ≈ 0.8

A patient who is hypercapnic is always hypoxemic unless he or she is receiving supplemental oxygen. Pure hypoventilation may result from neuromuscular, central nervous system, or chest wall disease. However, if these conditions persist, especially if they lead to reduced tidal volume (V_T) and reduced sighing, small airway closure and atelectasis are likely to ensue, with consequent $\dot{V}/\dot{Q}$ inequality, shunt, or both. Thus hypoventilation alone is a relatively uncommon cause of hypoxemia, except in acute conditions.[3,4] In hypoventilation the individual fails to increase the ventilation in the face of rising CO_2. The inadequate response to hypercapnia may result from abnormalities at the following three levels:

- At the sensor level: chemoreceptors fail to generate and communicate the order to increase the ventilation to the central and peripheral nervous system. Insensitivity of the chemoreceptors of the respiratory center to changes in the P_{aCO_2} may be the primary problem, such as in central alveolar hypoventilation syndrome.
- At the effector level: disorders of the airways, lung parenchyma, chest wall, and/or respiratory muscles prevent these structures from responding to increased neural output from the respiratory center. This is the most commonly affected level.
- Hypoxemia and extreme hypercapnia may themselves depress central respiratory drive. The immaturity of the respiratory system can also be part of the problem, such as apnea in newborns. Although the newborn's ventilatory response to carbon dioxide is similar to the older child's and adult's, the carbon dioxide response in the newborn is depressed by hypoxemia.[5-7] The newborn with recurrent apnea is also less able than older infants to sustain inspiratory effort in the face of increased inspiratory loads.[8,9]

MECHANICAL FACTORS

The respiratory drive and the resulting neuromuscular response may be adequate when the dynamic compliance of the respiratory system is high but may become inadequate when compliance decreases. This is especially important in a young infant, whose compliant rib cage and horizontal rib position reduce the mechanical efficiency of the respiratory muscles in expanding the thoracic volume. Respiratory muscle fatigue and distortion of the chest wall may also impair the ability of the respiratory system to increase the minute ventilation and restore P_{aCO_2} in the presence of $\dot{V}/\dot{Q}$ inequality, shunt, or diffusion defects.[10]

Airway obstruction: As hyperinflation increases in obstructive conditions such as asthma and bronchiolitis, the precontraction length of the diaphragmatic muscle fibers decreases, so the force of contraction decreases, resulting in a reduced V_T and raised P_{aCO_2}.[11,12] At any level of alveolar ventilation, depending on the mechanical characteristics of the respiratory system, there are combinations of respiratory rate and V_T at which respiratory work is minimized but at which gas exchange is not optimal.[13] When alveolar ventilation and work of breathing are low, the combination of rate and V_T selected may optimize gas exchange, but at higher levels of V_T and work of breathing, mechanical loading is adjusted to reduce respiratory work at the expense of gas exchange.[13] For example, when the respiratory system elastance decreases in pneumonia, the work of breathing is minimized when the respiratory pattern is a shallow tachypnea. In this pattern, however, the dead space to tidal volume ratio (V_{DS}/V_T) is

high. When elastance is severely increased, the increase in the dead space to tidal volume ratio resulting from extreme tachypnea may result in reduced alveolar ventilation and, therefore, raised $PaCO_2$ and reduced PaO_2.

Respiratory muscle failure: The integrity of the pumping action of the respiratory muscles is as essential to life as the actions of the cardiac muscle.

RESPIRATORY MUSCLE FUNCTION

The muscles of the respiratory pump have a large reserve, and they can sustain high levels of ventilatory work over prolonged periods. The primary muscle of inspiration is the diaphragm, which is innervated from cervical spinal roots 3 to 5. At rest, only 10% to 15% of diaphragmatic muscle motor units are active.[14] Diaphragmatic contraction leads to inspiration by two main mechanisms: a simple, piston-like caudal displacement of the dome of the diaphragm, and elevation of the lower ribs into which the diaphragm inserts as the muscle sheet contracts across the relatively incompressible abdominal contents. The upper ribs are raised by mechanical coupling, and because of the oblique attachments of the ribs, the transverse diameter of the chest increases as the ribs rise. In infants, the compliant chest wall limits the latter effect.[15] During quiet respiration, usually only the diaphragm is active, but as the need for alveolar ventilation increases (e.g., in exercise) or the work required to maintain ventilation increases (e.g., in obstructive airway disease), first the accessory inspiratory muscles and then the so-called expiratory muscles are recruited into use. The accessory inspiratory muscles include the sternocleidomastoid, scalene, internal intercostal, and external intercostal muscles. They are usually inactive during quiet respiration but become recruited as increased effort is required by exercise or pulmonary disease. They make the ribs more horizontal and raise the rib cage. In infants, these muscles have a limited ability to support inspiration because the ribs are almost horizontal at rest.[16-18] The rib cage develops a more adult configuration by about 2 years of age, but before this age, the intercostal muscles play an important role in preventing deformation of the compliant chest wall during inspiration.[19-22] The abdominal muscles (external and internal oblique, rectus abdominis, and transversus abdominis) and the interosseous internal intercostal muscles cause expiration and are used in forced expiratory activities such as coughing. However, they also increase the efficiency of inspiration by two mechanisms: pulling the rib cage down and inward beyond the point at which the elastic recoil of the chest wall exceeds the collapsing force of the lungs, so that this recoil will assist the next inspiration, and by pushing the diaphragm upward to a point where the muscle fibers reach their optimal resting length for maximal contraction.

The stimulus for muscle contraction begins in the central nervous system and is transmitted as an axonal action potential to the neuromuscular junction. The release of acetylcholine from the small neuronal end plate at its synapse with the muscle cell membrane greatly amplifies the signal and, by opening cationic channels, causes muscle cell depolarization. The change in membrane polarity reaches the tubular sarcoplasmic reticulum, and calcium ions are released. Free calcium ions combine with troponin, a protein that prevents actin and myosin filaments from reacting. Calcium causes troponin to change its physical configuration, and the actin and myosin filaments can then slide over one other, shortening the muscle and generating force. Relaxation occurs when calcium is pumped back into the sarcoplasmic reticulum. Both the sliding reaction of actin and myosin filaments and the return of calcium to the sarcoplasmic reticulum are active steps requiring hydrolysis of adenosine triphosphate (ATP). In addition to producing ventilation of the alveoli, the respiratory muscles have a number of other functions, including stabilization of the compliant chest wall in infants; expulsive efforts such as coughing, sneezing, vomiting, and defecation; and stabilization of the chest and abdomen in motor activities involving the trunk.

The respiratory muscles may become weak and fail under a number of conditions. Respiratory muscle weakness may be the primary and sole cause of alveolar hypoventilation, for example, in severe infantile botulism. More commonly, the problem is respiratory muscle fatigue from increased work of breathing. For example, in a child with severe acute asthma, the progression to respiratory failure occurs when the diaphragm becomes fatigued and cannot maintain the increased work of breathing caused by increased airway resistance. The causes of respiratory muscle fatigue include diseases of the central and peripheral nervous system, the neuromuscular junction, and skeletal muscle (see Boxes 19-1 and 19-2), which affect diaphragmatic muscle function and, in some cases, cause alveolar hypoventilation. Compression caused by lung hyperexpansion may impair blood flow to the diaphragm (e.g., in severe asthma). Low cardiac output, such as that occurring in several severe pulmonary conditions (see later section on cardiorespiratory interactions) may also limit the required increase in diaphragmatic blood flow.[23]

The force of diaphragmatic contraction is proportional to the mass of the muscle. Low diaphragmatic muscle mass may occur in states of malnutrition,[24] and provision of sufficient nutrition to achieve positive nitrogen balance can be difficult in ill infants, particularly preterm babies.[25] Reduced body muscle mass is a feature of some chronic respiratory disorders. The mass of the diaphragm and the maximal force of contraction are reduced in some adults with chronic obstructive airway disease. Respiratory muscle function in chronic pediatric respiratory disorders, such as cystic fibrosis, has not been studied in as much detail as in adult COPD.

Hypoxemia and hypercapnia lead to reduced muscle contractility and increase the tendency to fatigue.[26,27] If these abnormalities exist as a result of pulmonary disease, a vicious cycle of deterioration ensues.

Metabolic derangements, including hypophosphatemia,[28] hypocalcemia,[29] and hypomagnesemia,[30] can all lead to reduced diaphragmatic contractility. The levels of sodium and potassium are essential for the normal function of all muscles, including the respiratory muscles. Viral infection may reduce skeletal muscle force generation, and one study showed significant reductions in respiratory muscle strength during acute viral upper respiratory tract infections in normal adults.[31] The impact of viral infection on respiratory muscle function in patients with chronic pulmonary disease or in children has not been studied. Respiratory muscle weakness has been described for human immunodeficiency virus infections.[32] Bacterial infections, including pneumococcal sepsis,[33] and gram-negative infection with endotoxic shock[34] signifi-

cantly reduce diaphragmatic contractile force in experimental models.[35]

Ventilator-induced diaphragmatic dysfunction is an ill-defined entity associated with the use of mechanical ventilation. The mechanisms involved include muscle atrophy, oxidative stress, and structural injury. The implications for the ventilator weaning of critically ill patients have been reviewed by Vassilakopoulos and colleagues.[36]

The biochemical events leading to muscle fatigue are complex. Fatigue may occur in a number of ways, including depletion of acetylcholine at the neuromuscular junction, depletion of ATP or of substrates used to generate ATP within muscle (glycogen, glucose, free fatty acids), reduced rate of calcium release from the sarcoplasmic reticulum, and reduced supply of substrate to the muscles because blood flow does not match demands. When subjected to greatly increased workloads, the diaphragm may require a blood flow rate that is 10 to 20 times greater than resting rates to meet its metabolic demands.[37,38] Some evidence indicates that once the diaphragm begins to fatigue, there is a reduction in central nervous system respiratory drive to this muscle. This limits fatigue but may contribute to respiratory failure if other respiratory muscles cannot help maintain the ventilatory requirements.

A mixture of weakness and fatigue may occur. For example, a patient with Duchenne muscular dystrophy may be able to sustain the work of normal breathing but may not be able to do so when the work of breathing is increased by pulmonary disease, such as pneumonia. Alveolar hypoventilation occurs with less severe pulmonary consolidation than it would in a previously normal patient.

DEVELOPMENTAL ISSUES

As noted earlier, differences in chest wall configuration and compliance between young infants and older children can place normal infants at a disadvantage when trying to meet the increased ventilatory requirements imposed by pulmonary disease or increased metabolic demands. Differences in the microstructure and properties of the respiratory neuromuscular system of infants may also be important. In older children and adults, each muscle fiber in the diaphragm is innervated by only one motoneuron, and each motoneuron innervates 200 to 300 muscle fibers. Each fiber of the neonatal diaphragm receives innervation from several motoneurons, and this persists for the first few weeks of life.[39] The significance of this polyneural innervation is unknown, but it may have a role in reducing the susceptibility to diaphragmatic fatigue. Skeletal muscle fibers, including those of the diaphragm, may be classified into two basic groups, type I or II, according to histochemical and electrophysiologic characteristics. Type I fibers do not stain in the myofibrillar adenosine triphosphatase reaction, have a high capacity for oxidative phosphorylation, develop their maximal force generation slowly ("slow-twitch"), and are resistant to fatigue.[40] Type II fibers rapidly develop their maximal force generation ("fast-twitch"), but this group may be subdivided according to other properties. Type IIa fibers have intermediate oxidative phosphorylation and are fatigue resistant. Type IIb fibers have poor oxidative phosphorylation and fatigue easily. Type IIc fibers are found only in fetal and neonatal diaphragmatic muscle; they are highly oxidative and resistant to fatigue.

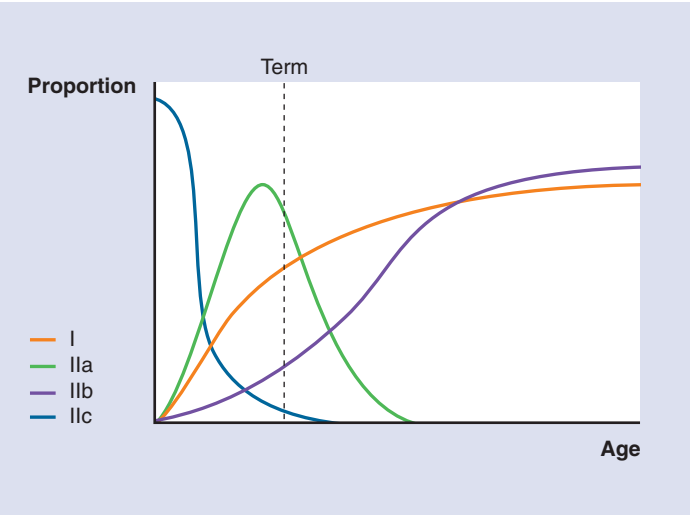


Figure 19-1 Graphic representation of changes with age in the proportion of the skeletal muscle fibers in the baboon diaphragm. Data are unavailable for the human diaphragm but are thought to be similar.

Type IIh fibers are also found only in fetal and neonatal muscle and probably represent a transition phase from type IIa to IIb fibers[41,42] (Fig. 19-1). There are certainly differences in the fiber composition between adults and newborns, but the extent and importance of these differences, particularly with regard to the fatigability of the diaphragm, has been the subject of some controversy. Initial investigations suggested that young infants have lower proportions of type I fibers and that overall, the neonatal diaphragm has a reduced ability for oxidative phosphorylation and hence an increased tendency to fatigue. More recently, it has been demonstrated[41-43] that some of these observations may have resulted from postmortem changes. In fresh specimens of neonatal diaphragm, there are fewer type I fibers, but these are replaced by the highly oxidative and fatigue-resistant type IIc fibers.

In newborn rats, the quantity of acetylcholine released by the diaphragmatic neuronal end plates in response to an action potential is less than that released in adult rats.[44] At high frequencies of stimulation, the neonatal diaphragmatic neuromuscular junction may be prone to transmission failure.

In vitro and in vivo studies of diaphragmatic action in humans and animals also have conflicting results. There is some evidence that the infantile diaphragm can generate forces as great as those in adults,[45] but other evidence suggests that the maximal force generated increases with postnatal age.[41] In vitro, fetal diaphragm muscle strips suffer fatigue less than strips from adults.

Many researchers now believe that diaphragmatic fatigue is a more common feature of thoracopulmonary disease in infants than in adults, but that this is probably a result more of the mechanical disadvantages caused by chest wall configuration and compliance than of an increased tendency to fatigue in the diaphragm muscle itself.

Increased Venous Admixture

Disorders of oxygenation increase the difference in the partial pressure of oxygen between alveolar gas and arterial blood

($P_{AO_2} - P_{aO_2}$). This difference may be considered equivalent to an admixture of venous blood to the oxygenated blood emerging from the pulmonary capillaries. Venous admixture includes the effects of anatomic shunt, diffusion defects, and ventilation of lung units with low perfusion (low $\dot{V}/\dot{Q}$).[46]

ANATOMIC EXTRAPULMONARY SHUNT

Anatomic right-to-left shunt (Fig. 19-2) occurs when venous blood enters the aorta through anatomic structures that bypass the pulmonary circulation. This includes desaturated blood from the bronchial and thebesian veins as well as abnormal extrapulmonary shunts (intracardiac shunts and shunts via the ductus arteriosus) and intrapulmonary shunts.

The bronchial and thebesian veins drain into the pulmonary circulation distal to the gas-exchanging vessels in the alveoli (physiologic shunt), reducing the P_{aO_2} below the partial pressure of end-capillary oxygen ($P_{c'O_2}$). The bronchial veins (which contain deoxygenated blood) drain into the pulmonary veins (which contain oxygenated blood), and the thebesian veins drain into the cavity of the left ventricle. In normal adults, this obligatory shunt represents less than 1% of the cardiac output and reduces the P_{aO_2} by approximately 5 mm Hg.[47]

In children with congenital heart disease, venous blood may enter the arterial circulation at the level of the atria via a patent foramen ovale or an atrial septal defect; this may also occur across a ventricular septal defect or a patent ductus arteriosus when the pulmonary artery pressure is high or if there is common mixing of venous and arterial blood (e.g., in a univentricular heart or a truncus arteriosus).

In the absence of structural cardiac abnormalities, venous blood may enter the arterial circulation via the foramen ovale or ductus arteriosus, provided that these structures are not permanently closed, when the pulmonary vascular resistance is high (e.g., in meconium aspiration syndrome[48] or hyaline membrane disease [HMD] in the newborn). The foramen ovale is closed functionally by 2 hours of age in the normal human but retains the ability to open in 30% of children and adults when right atrial pressure exceeds left atrial pressure.[49] Extrapulmonary right-to-left shunts of 27% to 73% (mean, 52%) have been measured by cardiac catheterization in meconium aspiration syndrome,[50] and a $P_{AO_2} - P_{aO_2}$ difference of more than 610 mm Hg has been reported resulting from these shunts.[51]

In most cases of HMD, shunting via the ductus arteriosus plays a minor role in the production of arterial hypoxemia, representing only 4% of cardiac output and less than 10% of total venous admixture,[52] although in some cases of persistent pulmonary hypertension of the newborn associated with HMD, shunting via the ductus arteriosus is responsible for significant right-to-left shunting in the presence of severe hypoxemia, hypercapnia, or acidosis. The improvement in P_{aO_2} with increasing F_{IO_2} in these circumstances is attributable to a reduction in pulmonary vascular resistance, which

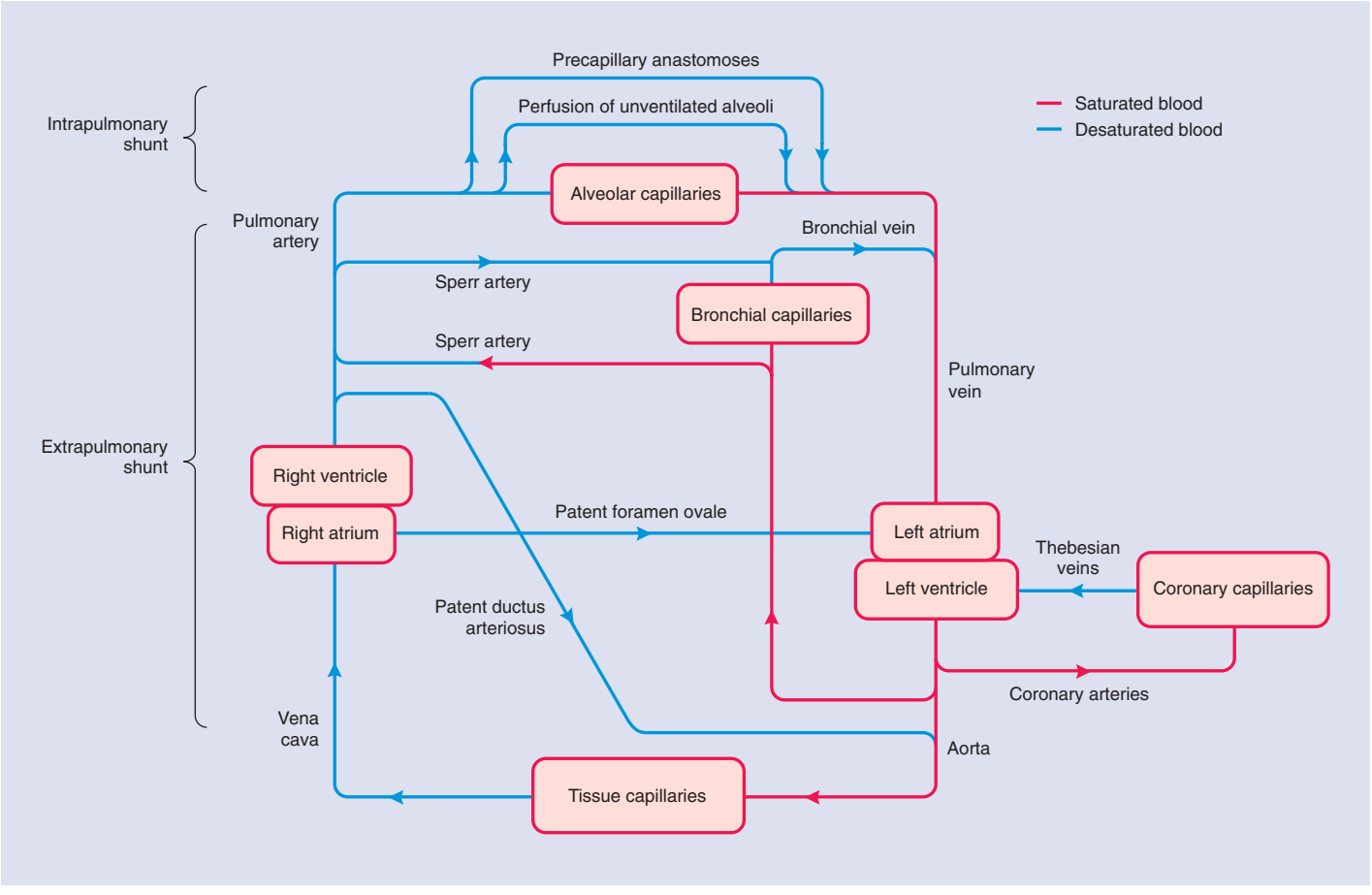


Figure 19-2 Diagram of the circulation showing the intrapulmonary and extrapulmonary right-to-left shunts.

is caused by the increased F_{IO_2} with consequent reduction in the shunt.[53]

ANATOMIC INTRAPULMONARY SHUNT

An intrapulmonary shunt may take the form of discrete extra-alveolar arteriovenous connections or may involve blood that traverses completely unventilated alveoli. Except in the case of pulmonary arteriovenous malformations, the most common malformations of the pulmonary circulation, the existence of true anatomic shunt vessels passing from the pulmonary artery to the pulmonary vein remains controversial. Some 36% to 47% occur as part of Osler-Weber-Rendu disease, whereas others appear as isolated congenital abnormalities. Shunts as large as 79% of the cardiac output have been reported in children with pulmonary arteriovenous malformations, and the Pa_{O_2} is less than normal in 80% of cases.[54] Von Hayek,[55] in 1960, reported the existence of "Sperr" arteries that form a network linking the bronchial arteries to the pulmonary artery and the pulmonary artery to the bronchial veins (and thence to the pulmonary veins, bypassing the alveoli). These muscular bypass channels may regulate the flow of desaturated blood into the systemic circulation (see Fig. 19-2).

Although some investigators have described muscular arterial connections between the bronchial and pulmonary arteries that appear in infancy and disappear by adulthood[56] and the presence of vessels that transmit 60- to 200-μ glass microspheres has been shown in postmortem specimens,[57-59] a careful histologic study by Hislop and Reid[60] did not find any precapillary arteriovenous connections in the lungs of 18 normal children. However, a study using intravenously infused krypton-81m in infants and children with recurrent apnea appeared to show blood traversing the lung without perfusing gas exchanging surfaces during apneic episodes.[61] This finding may imply that functional pulmonary arteriovenous connections exist, although the histologic evidence is inconclusive. It has been suggested that functional arteriovenous shunts, opening acutely, may explain the rapid onset of arterial desaturation occurring early in apneic spells.[62]

Intrapulmonary shunting in infants is due mainly to the perfusion of airspaces not involved in gas exchange.[63] In the normal term neonate, the $P_{AO_2} - Pa_{O_2}$ is greater than it is in adults, mainly because of intrapulmonary shunting, although in normal term babies, unventilated alveoli are not found after the first few hours of life.[64] In preterm infants breathing 100% oxygen in whom there is no clinical or radiologic evidence of lung disease, the $P_{AO_2} - Pa_{O_2}$ is 400 mm Hg at 26 weeks of conception and 250 mm Hg at 32 weeks of conception.[65] Perfusion of immature terminal airspaces where there are few alveoli may contribute to this venous admixture.[65,66]

The collapse of small airways in infants as a result of incomplete smooth muscle and cartilage development in the bronchial wall[67] and low airway conductance is thought to predispose to the closure of some small airways in expiration.[68,69] The pressures needed to open a closed airway are greater than those that caused it to close: The reduction in airway pressure distal to a point of closure and the stability of a fluid meniscus formed at the site of an airway closure tend to keep the airway closed.[70] Airway closure prevents the ventilation of alveoli supplied by that airway: The blood perfusing those alveoli is an intrapulmonary right-to-left shunt.

Routes of collateral ventilation among groups of alveoli (which might assist in the re-expansion of collapsed alveoli) are poorly developed in infancy. Kohn's pores appear gradually with increasing postnatal age, and Lambert's channels between terminal bronchioles and adjacent alveoli appear after the age of 7 years.[71]

Gas trapping resulting from small airway closure appears to be common in small infants (especially in preterm infants,[72] in whom it is associated with a large $P_{AO_2} - Pa_{O_2}$ that decreases with increasing age as the thoracic trapped gas volume decreases).[72] Intrapulmonary shunt resulting from perfusion of the unventilated trapped gas compartment contributes to the $P_{AO_2} - Pa_{O_2}$ in these infants. In healthy full-term infants, the $P_{AO_2} - Pa_{O_2}$ approaches zero by 2 weeks of age as thoracic gas volume (and gas trapping) decreases, whereas in preterm infants, the $P_{AO_2} - Pa_{O_2}$ remains elevated despite a decreasing thoracic gas volume at several months of age, presumably because atelectasis contributes both to the declining thoracic gas volume and to the $P_{AO_2} - Pa_{O_2}$.[72]

In neonates with meconium aspiration syndrome, right-to-left shunting is the main cause of arterial hypoxemia.[48] Total shunts of 27% to 73% of cardiac output have been measured in these infants.[50] Although some of the venous admixture occurs at the level of the ductus arteriosus and foramen ovale in the presence of pulmonary hypertension, much venous admixture is attributable to intrapulmonary shunt, with perfusion of collapsed lung segments or of lung units containing trapped gas whose composition approaches that of mixed venous blood.[48]

Intrapulmonary shunt accounts for much of the $P_{AO_2} - Pa_{O_2}$ in atelectasis, pneumonia, and ARDS in children and adults, mainly because of continued perfusion of unventilated alveoli. In pneumococcal pneumonia, this continued perfusion is due to impairment of hypoxic pulmonary vasoconstriction, possibly by bacterial products or by immune mediators.[73,74] The cause of venous admixture in cystic fibrosis varies from patient to patient. In some patients, intrapulmonary shunt accounts for most of the $P_{AO_2} - Pa_{O_2}$ difference, and the degree of shunt may increase with exercise.[75]

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

$\dot{V}/\dot{Q}$ inequality, sometimes called $\dot{V}/\dot{Q}$ mismatch, is the most important cause of arterial hypoxemia in practice. The concentration of oxygen in the alveoli of a lung unit and in the pulmonary venous blood draining that unit depends on the partial pressure of oxygen in the inspired gas and desaturated pulmonary artery blood perfusing that unit as well as on the ratio of $\dot{V}/\dot{Q}$. The same applies to carbon dioxide.[47]

The P_{AO_2} is determined by the pressure of inspired oxygen, the P_{ACO_2}, and the respiratory quotient; whereas Pa_{CO_2} is determined largely by alveolar ventilation and the body's rate of producing carbon dioxide (see earlier section). When the blood flow to a lung unit decreases (and therefore the $\dot{V}/\dot{Q}$ ratio increases), the P_{AO_2} and the Pc'_{O_2} of that unit approach the partial pressure of oxygen (P_{O_2}) of inspired gas (150 mm Hg when breathing room air). When the ventilation of a lung unit decreases (and the $\dot{V}/\dot{Q}$ ratio decreases), the P_{AO_2} and Pc'_{O_2} of that unit approach the P_{O_2} of mixed venous

blood. When all the units in a lung have a $\dot{V}/\dot{Q}$ ratio of 1, the P_{aO_2} is approximately 100 mm Hg, and the $P_{AO_2} - P_{aO_2}$ is 10 to 20 mm Hg in adults breathing room air at sea level[76] in the absence of shunt or diffusion defect.

When some units have a $\dot{V}/\dot{Q}$ ratio less than 1, the blood emerging from those units has a P_{O_2} approaching 40 mm Hg and a partial pressure of carbon dioxide (P_{CO_2}) approaching 45 mm Hg. Because of the shape of the oxygen-hemoglobin dissociation curve, increasing the $P_{c'O_2}$ of high $\dot{V}/\dot{Q}$ units cannot significantly increase the content of oxygen in end-capillary blood (C_{cO_2}) and, therefore, cannot compensate for the low C_{cO_2} of blood emerging from low $\dot{V}/\dot{Q}$ units, particularly because low $\dot{V}/\dot{Q}$ units contribute more blood flow than high $\dot{V}/\dot{Q}$ units.

In a spontaneously breathing subject, increased alveolar ventilation stimulated by chemoreceptors prevents the P_{aCO_2} from rising. (Indeed the P_{aCO_2} may be lower than normal because of a ventilatory response to arterial hypoxemia.) Because the carbon dioxide response curve is approximately linear in the working range—in fact it is hyperbolic (Fig. 19-3)—increasing alveolar ventilation to the high $\dot{V}/\dot{Q}$ units can remove enough carbon dioxide to compensate for the high P_{aCO_2} in the low $\dot{V}/\dot{Q}$ units (see section on the effect of $\dot{V}/\dot{Q}$ inequality on carbon dioxide). However, if alveolar ventilation does not increase in response to a raised P_{aCO_2} (e.g., because of a central nervous system or neuromuscular disorder or because of mechanical ventilation in a child), increased $\dot{V}/\dot{Q}$ inequality also increases P_{aCO_2}.

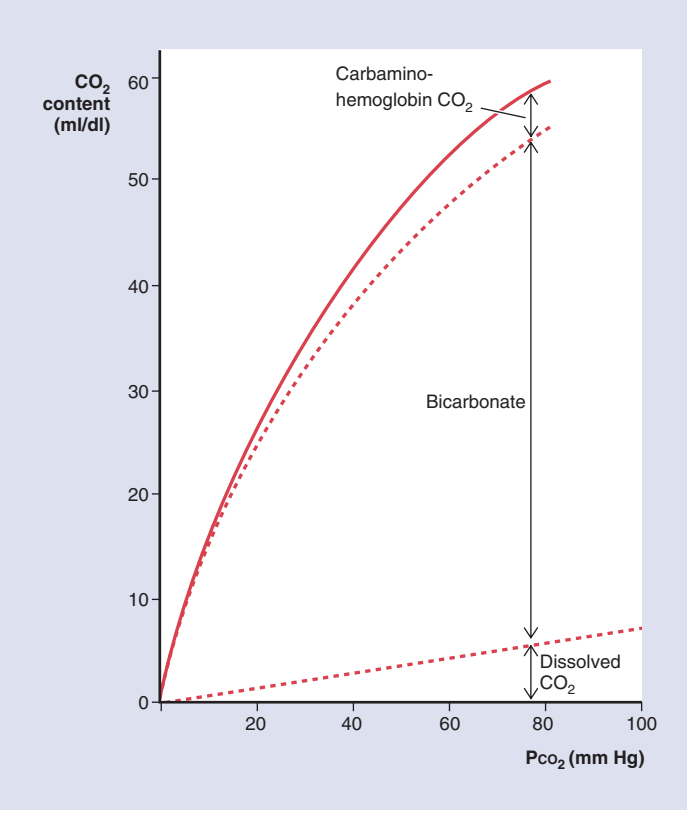


Figure 19-3 Carbon dioxide dissociation curve for whole blood *(continuous line)*. Oxyhemoglobin *(upper dotted line)* carries less carbon dioxide as carbamino compounds than reduced hemoglobin (Haldane effect). The dissociation curve is virtually a straight line over the normal physiologic range of P_{CO_2}. (Adapted from Swenson ER, Hlastala MP: Carbon dioxide transport and acid-base balance: Tissue and cellular. In Chernick V, Mellins RB [eds]: Basic Mechanisms of Pediatric Respiratory Disease: Cellular and Integrative. Philadelphia, BC Decker, 1991, p 148.)

Effect of $\dot{V}/\dot{Q}$ Inequality on Carbon Dioxide Transfer

Although carbon dioxide transfer is less affected by $\dot{V}/\dot{Q}$ inequality than oxygen transfer, $\dot{V}/\dot{Q}$ inequality is the most common cause of hypercapnia in lung disease.[2] The main reasons follow:

1. Both oxygen and carbon dioxide are gases of intermediate solubility; their transfer is less efficient in the presence of $\dot{V}/\dot{Q}$ inequality than the transfer of very soluble or very insoluble gases (Fig. 19-4).
2. Although in the presence of $\dot{V}/\dot{Q}$ inequality, increasing the ventilation of high $\dot{V}/\dot{Q}$ units can lower the P_{ACO_2} and thereby the P_{aCO_2} in these units, the carbon dioxide dissociation curve is hyperbolic rather than linear in the normal operating range so that high $\dot{V}/\dot{Q}$ units may be unable to wash out enough carbon dioxide to compensate for the failure of low $\dot{V}/\dot{Q}$ units to eliminate carbon dioxide.[2]

Furthermore, the altered P_{aO_2} and pH and the increased work of breathing associated with lung disease contribute to respiratory muscle fatigue and limit the maximal alveolar ventilation of which the patient is capable.

A lung with $\dot{V}/\dot{Q}$ inequality cannot transfer as much oxygen and carbon dioxide as a lung with a $\dot{V}/\dot{Q}$ ratio of 1, all else being equal. If the same amounts of oxygen and carbon dioxide are being transferred, the P_{aO_2} will be lower and P_{aCO_2} will be higher than in a lung with homogeneous $\dot{V}/\dot{Q}$ ratios—all else being equal.[47]

In a computer model of a lung in which some compartments were ventilated in series (e.g., via *pendelluft* or Kohn's pores or in which some alveoli arise from more proximal

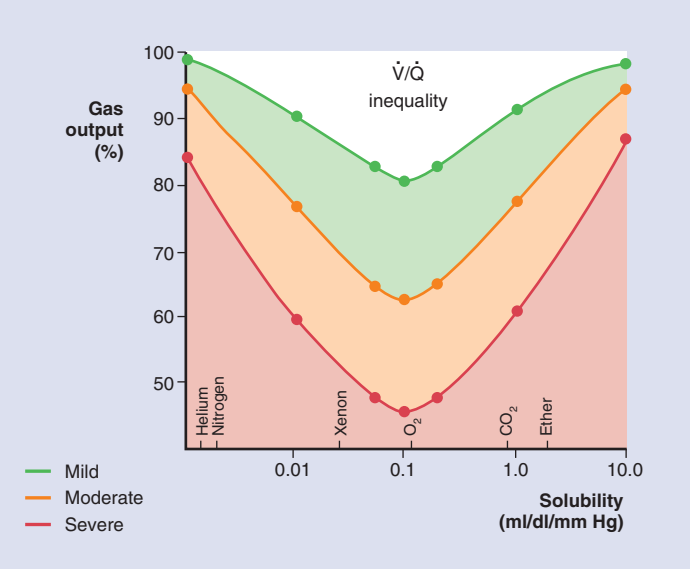


Figure 19-4 Effect of $\dot{V}/\dot{Q}$ inequality on the transfer of gases of different solubilities in the lung. $\dot{V}/\dot{Q}$ inequality has a greater effect on the transfer of gases of intermediate solubility, such as oxygen, than on the transfer of more soluble gases, such as carbon dioxide, or less soluble gases. (From West JB: Causes of carbon dioxide retention in lung disease. N Engl J Med 284:1232-1236, 1971.)

bronchioles), West[77] found that carbon dioxide transfer is reduced more than oxygen transfer. This was because a "parasitic" alveolus that receives all of its inspired gas from a second alveolus is effectively rebreathing gas with a P_{O_2} of approximately 110 mm Hg and a P_{CO_2} similar to that of mixed venous blood. Although oxygen transfer from this parasitic alveolus is almost normal, carbon dioxide transfer is low. Carbon dioxide removal may be less efficient in a lung in which series ventilation of alveoli is prominent (e.g., centrilobular emphysema) than in a lung with other forms of $\dot{V}/\dot{Q}$ mismatch.

If all of the observed $P_{AO_2} - P_{aO_2}$ is due to $\dot{V}/\dot{Q}$ inequality and none is due to shunt, breathing 100% oxygen should correct the hypoxemia. This is because if the low $\dot{V}/\dot{Q}$ units are ventilated even a little, their nitrogen content is washed out over several minutes so that their alveoli contain only oxygen, carbon dioxide, and water vapor, as follows:

Eq 19.3 $$P_{AO_2} = P_B - P_{H_2O} - P_{ACO_2}$$

where P_B is barometric pressure and P_{H_2O} is the saturated vapor pressure of water at 37° C (47 mm Hg). This method may be used to determine how much of the observed $P_{AO_2} - P_{aO_2}$ is due to $\dot{V}/\dot{Q}$ inequality and how much is due to shunt.[78] Inaccuracy may be introduced into this method, converting some low $\dot{V}/\dot{Q}$ units with partly obstructed airways to true shunt because of absorption atelectasis. This has been predicted in theory and observed in adults using the multiple inert gas technique of $\dot{V}/\dot{Q}$ quantitation[79] and in newborn lambs,[80] but it is not seen in adults with bacterial pneumonia.[74]

In a patient with a given degree of $\dot{V}/\dot{Q}$ inequality, the P_{aO_2} is reduced further by a low partial pressure of venous oxygen (P_{vO_2}). P_{vO_2} particularly influences lung units with a low $\dot{V}/\dot{Q}$ ratio or shunt. Measures aimed at raising the P_{vO_2} (e.g., by raising cardiac output or reducing whole-body oxygen consumption [D_{O_2}]) may raise P_{aO_2} in conditions in which shunt and low $\dot{V}/\dot{Q}$ ratio are prominent (e.g., pneumonia, ARDS).[74,81] Cardiac output may be increased (at the expense of increased myocardial oxygen demand) by the use of plasma volume expansion, vasodilator medications (which improve left ventricular performance by reducing afterload), or inotropic medications such as dopamine.

None of these methods is ideal, however. Plasma volume expansion may increase the water content of the lung, thereby increasing respiratory system elastance and impairing gas diffusion. Vasodilator medications dilate systemic and pulmonary vessels indiscriminately and may increase perfusion and oxygen delivery (D_{O_2}) to nonessential tissues such as muscle at the expense of essential tissues such as the brain and heart. Some vasodilator medications such as glyceryl trinitrate and sodium nitroprusside may impair hypoxic pulmonary vasoconstriction (HPV), increasing $P_{AO_2} - P_{aO_2}$ in the presence of lung disease.[82] Catecholamines such as dopamine, which are used for their inotropic effect, also increase the body's rate of producing oxygen and carbon dioxide, mainly by their effect on fat catabolism.[83] Dopamine and dobutamine both reduce P_{aO_2} by about 10 mm Hg in patients with severe lung disease by increasing the perfusion of unventilated lung units (shunt) and of low $\dot{V}/\dot{Q}$ lung units.[84]

The use of any of these measures intended to improve oxygenation by raising mixed venous P_{O_2} depends on whether the potential gains are greater than the potential disadvantages. Trial and error—titrating dose against effect with close observation of blood gases, mixed venous P_{O_2}, and indicators of organ function (conscious state, urine output, and plasma lactate concentration)—is the method generally used.

Causes of $\dot{V}/\dot{Q}$ Inequality

The phasic nature of alveolar ventilation and pulmonary blood flow and the difference in frequency of these two flows mean that instantaneous ventilation and perfusion of the lung are frequently unequal,[85] although the $\dot{V}/\dot{Q}$ ratio averaged over a period of minutes may be equal to 1. In fact, at low inspiratory flow rates, the ratio of ventilation per alveolus at the lung apex compared to ventilation at the base is about 0.6, but this ratio approaches 1 (i.e., ventilation becomes more evenly distributed) as inspiratory flow rate increases.[86] As underperfused areas may become more ventilated with an equally distributed ventilation, the effect of this is an even greater maldistribution of the $\dot{V}/\dot{Q}$ ratio throughout the lungs at high inspiratory flow rates.

The effect of short-term fluctuations in the $\dot{V}/\dot{Q}$ ratio on gas exchange is buffered by the functional residual capacity (FRC).[76] For example, after a stepwise reduction in the $\dot{V}/\dot{Q}$ ratio of a lung unit, the P_{O_2} and P_{CO_2} in the alveolar gas and end-capillary blood in that lung unit exponentially approach values closer to those in mixed venous blood. The larger the alveolar gas volume in relation to the alveolar ventilation and blood flow, the slower the exponential change. When a series of stepwise changes in the $\dot{V}/\dot{Q}$ ratio in alternating directions occur, the larger the alveolar gas volume (or FRC), the smaller the amplitude of the fluctuations in P_{O_2} and P_{CO_2} in alveolar gas and end-capillary blood.

Regional $\dot{V}/\dot{Q}$ Inequality.

In the adult lung, blood flow decreases rapidly from the base to the apex, whereas alveolar ventilation decreases less rapidly (Fig. 19-5). Thus the $\dot{V}/\dot{Q}$ ratio is much higher at the lung apex than at the base, and much of the pulmonary blood flow passes through lung units whose $\dot{V}/\dot{Q}$ ratio is less than 1 and whose end-capillary P_{O_2} is correspondingly low.[46] This means that in the normal upright adult, gas exchange is less efficient than it would be if the $\dot{V}/\dot{Q}$ ratio were 1 in all lung units. Similarly, in the adult lying supine, both ventilation and blood flow increase from ventral to dorsal, whereas in the adult subject lying on one side, both ventilation and blood flow are greater in the dependent lung.

Children differ in the following respects:

1. Because a child's pulmonary artery pressure is similar to an adult's but the child's lung is smaller, more of the child's lung is perfused continuously throughout the cardiac cycle because the pressure in the pulmonary capillaries remains higher than the intra-alveolar pressure surrounding the capillaries, even close to the apex of the lung. Because of the child's smaller lung dimensions, the head of hydrostatic pressure that is distending vessels in the lung base is less than that in the adult, so the difference in the vascular radius between the lung base and apex—and therefore the difference in pulmonary vascular

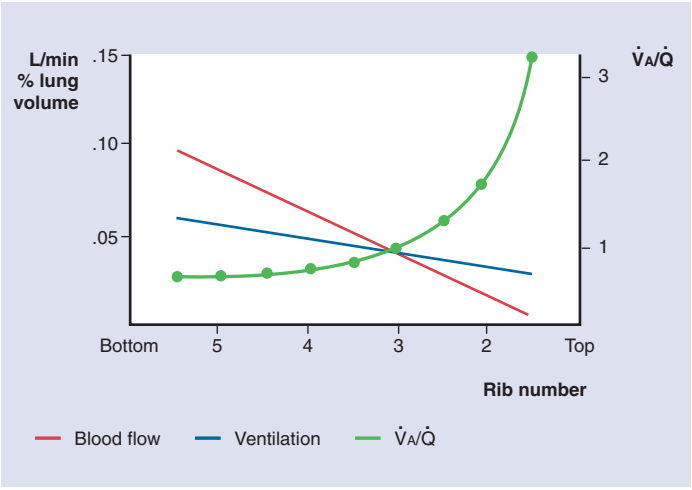


Figure 19-5 Distribution of ventilation, blood flow, and $\dot{V}/\dot{Q}$ ratio from the base to the apex of the upright lung. $\dot{V}/\dot{Q}$, alveolar ventilation/perfusion ratio. (From West JB: Ventilation, Blood Flow and Gas Exchange, 3rd ed. Oxford, Blackwell, 1977, p 30.)

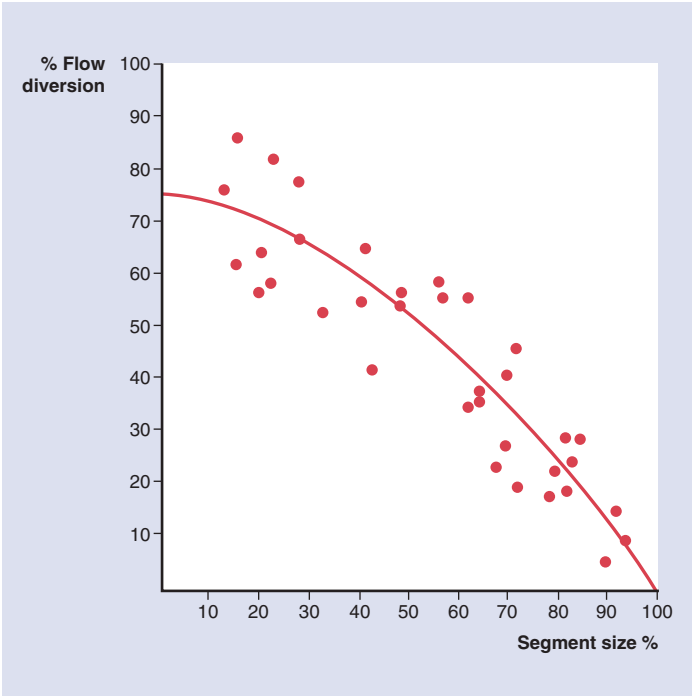


Figure 19-6 Effectiveness of hypoxic pulmonary vasoconstriction as the size of the hypoxic segment of lung increases. (From Marshall BE, Marshall C, Benumof J, Saidman LJ: Hypoxic pulmonary vasoconstriction in dogs: Effects of lung segment size and oxygen tension. J Appl Physiol 51(6):1543-1551, 1981.)

resistance between the lung base and apex—are less and pulmonary blood flow is more evenly distributed over the lung.[64] This effect is often seen in children with high pulmonary artery pressures resulting from left-to-right cardiac shunt or from pulmonary venous hypertension. In these children, blood flow to the lung apex is increased, and flow to the lung bases is reduced.[87]

2. In children younger than 18 years of age, ventilation is distributed preferentially to the upper areas of lung and away from dependent areas.[88]

In young children, the closing volume is higher than the FRC.[89] Airways in dependent areas of the lung are the first to close during expiration and the last to reopen during inspiration—so in infants, inspired gas preferentially ventilates nondependent areas of lung. In humans of all ages, as preinspiratory lung volume decreases below the closing volume, ventilation inhomogeneity increases. Regional variability in static mechanical properties within the lung (especially in elastic recoil) may explain some of the reduced ventilation of the lung bases in children.[90]

The net effect of these two differences is that there is less $\dot{V}/\dot{Q}$ inequality in the lungs of the normal child and adolescent than in the adult. Also, in an adult with unilateral lung disease, the $P_{AO_2} - P_{aO_2}$ is greater with the diseased lung in a dependent position, but in a child up to the age of 18 years, the $P_{AO_2} - P_{aO_2}$ is greater with the diseased lung in uppermost position.[91,92]

In an adult with unilateral drug disease, gas exchange (especially oxygenation) is consistently better when the patient lies with the normal lung dependent than when the patient lies supine or with the diseased lung dependent. This strategy results in a greater improvement in oxygenation than in carbon dioxide elimination.[93] In contrast, children with unilateral lung disease are managed with the diseased lung dependent, in which position the P_{aO_2} is usually higher than when the diseased lung is uppermost. Conventional treatment of unilateral pulmonary interstitial emphysema includes managing the child in the decubitus position with the abnormal lung down.[94]

In some newborns, gas trapping in the first few days of life is associated with a raised $P_{AO_2} - P_{aO_2}$.[49,72] This gas trapping may occur in narrow compliant airways in which occlusive bubbles readily form, and the relative lack of collateral ventilation channels in the newborn lung may contribute to the resulting regional hypoventilation[95] and to $\dot{V}/\dot{Q}$ inequality.

ROLE OF HYPOXIC PULMONARY VASOCONSTRICTION (HPV) IN $\dot{V}/\dot{Q}$ INEQUALITY

Constriction of pulmonary vessels in response to alveolar hypoxia decreases the arterial hypoxemia that occurs with regional alveolar hypoventilation and thereby reduces the $P_{AO_2} - P_{aO_2}$ in situations of $\dot{V}/\dot{Q}$ inequality and shunt. The smaller the hypoxic segment of lung, the more powerful the HPV and the greater the diversion of blood flow from the hypoxic segment.[96] Thus HPV plays a greater role in the reduction of venous admixture when the hypoxic segments are small and scattered than when a lobe is hypoxic (Fig. 19-6).

According to micropuncture studies, the vessels that constrict in response to hypoxia are the small pulmonary arteries and veins,[97] with the precapillary pulmonary arteries being the most important site of HPV.[98] The principal stimulus to HPV is low alveolar oxygen (P_{AO_2}).[64] A major reduction in the mixed venous P_{O_2} can reduce the effectiveness of HPV by reducing the P_{aO_2} in well-ventilated areas of lung more than in less well-ventilated regions and diverting blood flow to hypoxic areas of the lung, thereby reducing the P_{aO_2}.[99] Measures that increase the P_{VO_2} by increasing cardiac output or by reducing the $\dot{V}_{O_2}$ (e.g., by cooling or the use of muscle relaxants) may therefore be expected to increase the P_{aO_2} in patients with shunt or $\dot{V}/\dot{Q}$ inequality.[99]

Although the adequate stimulus to HPV (low P_{AO_2}) is known, the nature of the sensor and the mode of stimulus transmission to the vascular smooth muscle cells have not been identified for certain. It appears that some form of chemical messenger is involved: A pulmonary artery to which some lung tissue is adherent contracts in response to hypoxia, and a pulmonary artery from which all lung has been stripped will not contract.[100] Possible chemical messengers include leukotrienes C_4 and D_4 (inhibitors of which suppress HPV),[101] the calcium slow channel (facilitation of calcium entry into cells augments HPV),[102] and oxygen radicals.[98,103]

Inhibition of endothelial nitric oxide (NO) production by hypoxia is likely to be a major contributor to HPV. NO is an important endothelium-derived relaxing factor that is produced in the pulmonary vascular endothelium and diffuses into the subjacent smooth muscle cells. There it activates guanylate cyclase, which increases the intracellular level of cyclic guanosine monophosphate and results in relaxation of vascular smooth muscle.[104,105] The relaxation of pulmonary vascular smooth muscle induced by NO is impaired by chronic hypoxia but may be restored by the administration of L-arginine, a NO precursor.[106] NO production is reduced by hypoxia in both the adult and the fetal pulmonary arteries.[107,108] However, because the primary stimulus to HPV is in the alveolar gas phase, it is not clear how the stimulus is transmitted to the vascular endothelium to inhibit NO production.

In adults with ARDS, inhaled NO (iNO) acts as a selective pulmonary vasodilator, reducing pulmonary artery pressure without reducing systemic blood pressure. Because it is delivered by inhalation, iNO dilates the pulmonary arteries supplying the well-ventilated lung units more than the pulmonary arteries in less well-ventilated units, thereby improving $\dot{V}/\dot{Q}$ matching and increasing P_{aO_2}.[109]

Lung units with low $\dot{V}/\dot{Q}$ ratios have high P_{ACO_2} values as well as low P_{AO_2} values. An increased P_{CO_2} acts as a pulmonary vasoconstrictor in these lung units, augmenting the effect of the low P_{AO_2}, although the raised P_{CO_2} and its accompanying low pH are each a weaker vasoconstrictor stimulus than hypoxia. The P_{CO_2} in the pulmonary artery, not the alveoli, is the main carbon dioxide vasoconstrictor stimulus.[110]

HPV in the newborn is more vigorous than in the adult and is triggered at a higher P_{AO_2} threshold;[111] despite this, the $P_{AO_2} - P_{aO_2}$ in the newborn remains higher than in the adult for some days after birth.[65]

$\dot{V}/\dot{Q}$ Inequality in Lung Disease

NEONATES

In HMD, early studies using urinary-alveolar nitrogen gradients were unable to demonstrate significant $\dot{V}/\dot{Q}$ mismatch,[112] so all of the observed $P_{AO_2} - P_{aO_2}$ was attributed to right-to-left shunt—both intrapulmonary shunt and that at the level of the foramen ovale and ductus arteriosus. More recent data show the existence of appreciable $\dot{V}/\dot{Q}$ inequality as well as a shunt component in HMD; up to 40% of the cardiac output passes through high $\dot{V}/\dot{Q}$ lung units, and about 3% passes through low $\dot{V}/\dot{Q}$ units.[113,114] It has been suggested that the commonly observed reduction in P_{AO_2}, which follows a decrease in F_{IO_2} in infants with HMD, means that $\dot{V}/\dot{Q}$ inequality is a major cause of hypoxemia in this condition.[115] However, because extrapulmonary shunting occurs in both HMD and meconium aspiration syndrome and because the amount of shunting is greater at high pulmonary artery pressures, the reduction of F_{IO_2} may increase venous admixture by lowering the P_{AO_2} and thereby increasing HPV, total pulmonary vascular resistance, and the amount of the extrapulmonary shunt. Continuous positive airway pressure increases the total perfusion of lung units with high $\dot{V}/\dot{Q}$ in HMD by recruiting the alveoli of low $\dot{V}/\dot{Q}$ units into the high $\dot{V}/\dot{Q}$ compartment,[113] although it does not appear to recruit completely unventilated alveoli, whose perfusion continues to represent intrapulmonary shunt.[114]

A low $\dot{V}/\dot{Q}$ contributes significantly to venous admixture in meconium aspiration syndrome,[63] although extrapulmonary shunting at the level of the ductus arteriosus and foramen ovale as well as intrapulmonary shunt cause most of the venous admixture in this condition. In atelectasis and pneumonia in the newborn, there is evidence from animal experiments that inflammatory mediators suppress the local HPV response and thereby exacerbate the arterial desaturation caused by $\dot{V}/\dot{Q}$ inequality to a greater extent than in adults.[95]

CHILDREN

Asthma

$\dot{V}/\dot{Q}$ inequality is the major source of hypoxemia in asthma, with very little contribution from shunt.[116-118] As the severity of the asthma attack increases, the proportion of the cardiac output that traverses low $\dot{V}/\dot{Q}$ units increases from 10% to 28%.[117,118] In some asymptomatic asthmatic adults, up to 50% of lung units lie behind closed airways. These units have a small $\dot{V}/\dot{Q}$ ratio (i.e., nonshunt) because of collateral ventilation.[116] Although this issue has not been addressed in children, it is possible that shunt may be more prominent in infants, whose collateral ventilation pathways are less well developed.[95]

Adults with moderately severe asthma have a bimodal distribution of $\dot{V}/\dot{Q}$ ratio in the lungs even when their condition is asymptomatic (Fig. 19-7): one peak at $\dot{V}/\dot{Q} = 1$ and another of low $\dot{V}/\dot{Q}$ ratio (approximately 0.1).[116] During an acute asthma attack, it appears that there is no relation between the 1-second forced expiratory volume (absolute or percent predicted) and measures of $\dot{V}/\dot{Q}$ inequality,[118] possibly because spirometric findings are determined by the resistances of large airways, whereas gas exchange may be more influenced by edema, mucus production, and muscular contraction in small airways.[119] There is also little relation between the clinical severity of asthma and the degree of $\dot{V}/\dot{Q}$ mismatch, so a patient with the most severe clinical evidence of asthma may have the same $\dot{V}/\dot{Q}$ inequality as a patient with the least clinically severe attack.[119]

Inhaled albuterol abolishes $\dot{V}/\dot{Q}$ inequality in asthmatic children after histamine challenge.[120] Increased perfusion caused by vasodilation with albuterol could worsen $\dot{V}/\dot{Q}$ matching; however $\dot{V}/\dot{Q}$ inequality is unaffected by nebulized albuterol[118] but is exacerbated by intravenous albuterol, intravenous terbutaline,[121] and nebulized isoproterenol[116,118] in adult asthmatics. The difference in effect on $\dot{V}/\dot{Q}$ distribution between the inhaled and the intravenous route is thought to result from the fact that pulmonary vaso-

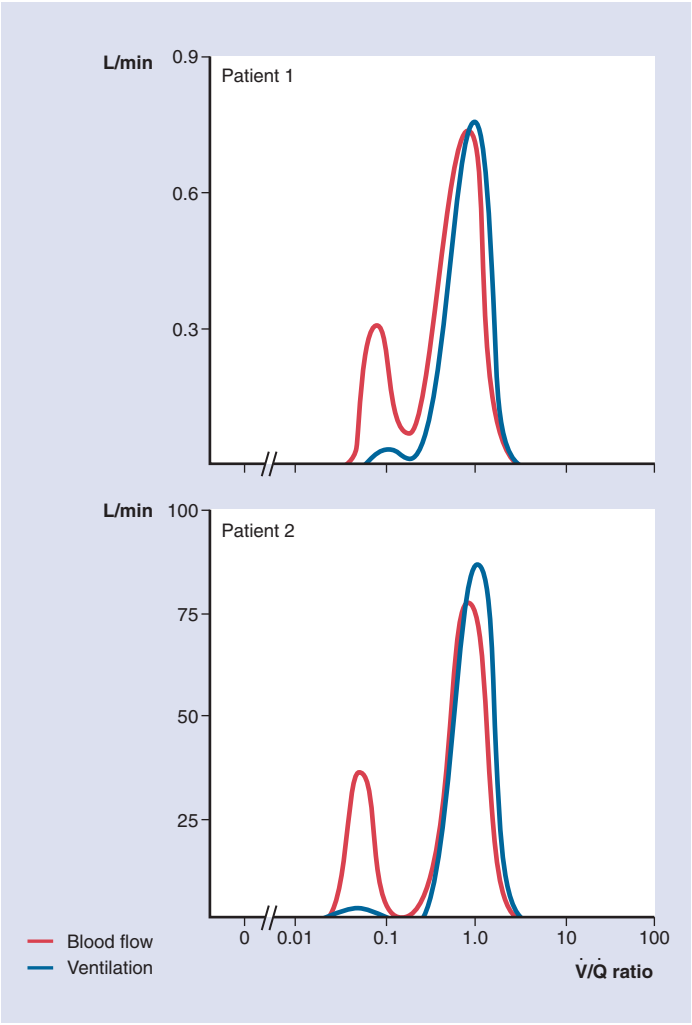


Figure 19-7 Distribution of ventilation and blood flow between lung units of different $\dot{V}/\dot{Q}$ ratios in two patients with asthma. Note that there is some perfusion of lung units with low $\dot{V}/\dot{Q}$ ratios ($\dot{V}/\dot{Q} = 0.1$) but that there was no perfusion of lung units with $\dot{V}/\dot{Q} = 0$ (shunt). (From Wagner PD: *Am Rev Respir Dis* 118:511-524, 1978.)

dilator medications given intravenously dilate the vessels supplying all lung units, including underventilated units, impairing HPV, whereas inhaled pulmonary vasodilator medications act preferentially on well-ventilated lung units to which they have greater access. Thus inhaled NO reduces the $\dot{V}/\dot{Q}$ inequality and $P_{A}O_2 - PaO_2$ in ARDS,[109] and inhaled halothane causes less $\dot{V}/\dot{Q}$ inequality than intravenous sodium nitroprusside for the same total reduction in pulmonary vascular resistance[122] in dogs with pulmonary atelectasis. Infusion of glyceryl trinitrate or prostaglandin E_1 increases the $\dot{V}/\dot{Q}$ inequality and $P_{A}O_2 - PaO_2$ in patients with ARDS.[82] Inhalation of 100% oxygen in asthma increases the $P_{A}O_2 - PaO_2$, either by causing absorption atelectasis in low $\dot{V}/\dot{Q}$ units or by reducing HPV.[117]

Cystic Fibrosis

Although intrapulmonary shunt is the main source of $P_{A}O_2 - PaO_2$ in some patients with cystic fibrosis, $\dot{V}/\dot{Q}$ inequality makes a major contribution to hypoxemia in others. The effect of exercise also varies from patient to patient. In some, exercise reduces $\dot{V}/\dot{Q}$ inequality, whereas in others, $\dot{V}/\dot{Q}$ inequality is increased or converted to shunt. Despite an apparent increase in venous admixture with exercise in cystic fibrosis, the PaO_2 is not necessarily reduced.[79] Vasodilator medications reduce the PaO_2 by impairing HPV in cystic fibrosis.[123]

Pneumonia

The role of $\dot{V}/\dot{Q}$ inequality in producing venous admixture varies from patient to patient. In about one half of patients with pneumonia, $\dot{V}/\dot{Q}$ inequality makes the major contribution, and shunt is less important.[74] HPV is relatively ineffective at reducing the perfusion of underventilated alveoli in pneumonia—perhaps because of inflammatory mediators.[73,74]

ARDS

Although the majority of patients with ARDS show evidence of some $\dot{V}/\dot{Q}$ inequality,[124] most of the venous admixture found in this condition is due to shunt, and only a small proportion comes from $\dot{V}/\dot{Q}$ mismatch[75] (Fig. 19-8). The shunt fraction appears to be directly related to the amount of pulmonary edema present.

The use of positive end-expiratory pressure (PEEP) ventilation does not reduce the amount of extravascular lung water in ARDS,[119,125] but improves PaO_2 by reducing the blood flow to unventilated alveoli, and probably by decreasing atelectatic areas, in particular after the application of a recruitment maneuver.[125] However, it also increases alveolar dead space by increasing the ventilation of unperfused alveoli.[75] During the resolution of ARDS, shunts gradually decrease via conversion to normal $\dot{V}/\dot{Q}$ units without passing through a phase of low $\dot{V}/\dot{Q}$ ratio.[119] As the cardiac output increases in ARDS, the shunt fraction also increases, possibly because the raised PvO_2 resulting from increased cardiac output suppresses HPV in unventilated areas of the lungs. In fact, the effects of raised PvO_2 on shunt fraction and on end-capillary PO_2 tend to cancel each other out, so PaO_2 does not change as cardiac output increases.[119]

DIFFUSION BLOCK

In practice it is difficult to separate the contribution of diffusion block to hypoxemia from that of $\dot{V}/\dot{Q}$ inequality because the two almost always occur together. The rates of diffusion of oxygen and carbon dioxide between blood and alveolar gas follows Fick's law:

$$\dot{Q} = k(P_1 - P_2) \times A/T \qquad \text{Eq 19.4}$$

where $\dot{Q}$ is the rate of diffusion of the gas in milliliters per minute, k is a constant, $P_1 - P_2$ is the partial pressure difference of the gas between the alveolus and blood, A is the total area of the alveolar membrane, and T is the thickness of the alveolar membrane. Thus any reduction in the partial pressure gradient for a gas (e.g., resulting from high $P_{A}CO_2$ or low $PvCO_2$ in the case of carbon dioxide), thickened alveolar capillary membrane (e.g., resulting from pulmonary edema), or reduced surface area (e.g., resulting from atelectasis) reduces the rate at which that gas is transferred. Carbon dioxide diffuses through the alveolar membrane 20 times faster than oxygen.

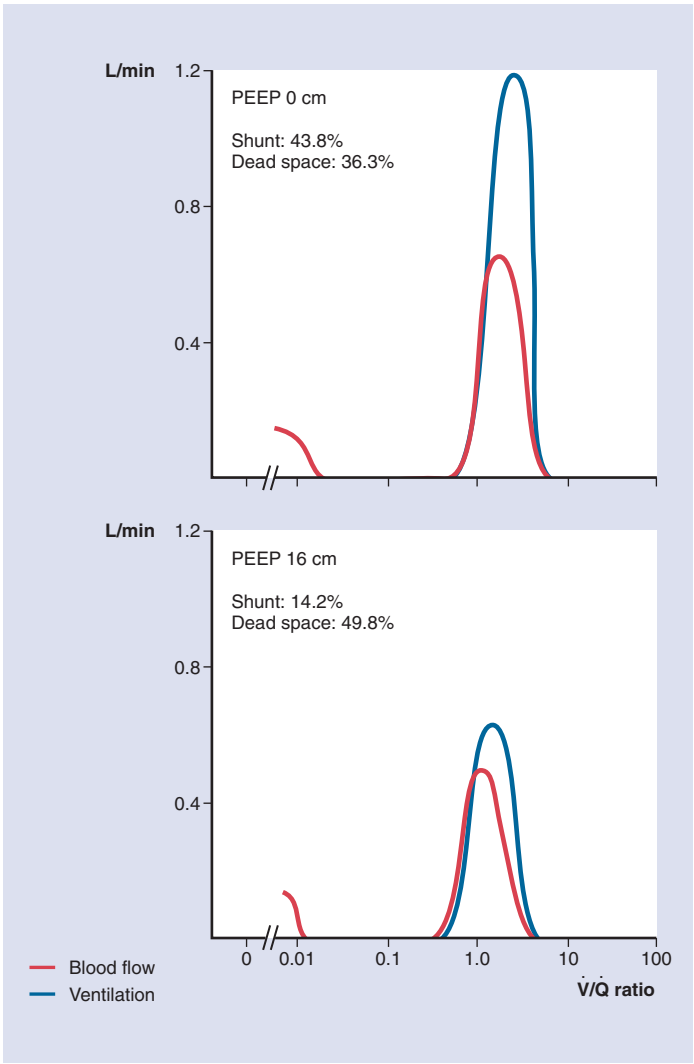


Figure 19-8 Distribution of ventilation and blood flow between lung units of different V̇/Q̇ ratios in acute respiratory distress syndrome (ARDS), showing the large contribution of shunt (**A**). Positive end-expiratory pressure (PEEP) improves oxygenation in ARDS by reducing the perfusion of shunt blood flow at the expense of an increase in dead space ventilation (**B**). (From Dantzker DR, Brook CJ, Dehart P, et al: Ventilation-perfusion distributions in the adult respiratory distress syndrome. Am Rev Respir Dis 120(5):1039-1052, 1979.)

The passage of oxygen from the alveolus into the blood and thence into red cells to attach to hemoglobin takes a finite minimum time. Each red cell remains in the pulmonary capillary an average of 0.75 second.[47] Normally the hemoglobin is loaded with oxygen by the time it is a third of the way through the pulmonary capillary. However, the time taken for hemoglobin loading is greater when the alveolar membrane is thickened or its area reduced, when the partial pressure gradient is reduced by a low P_{AO_2} (e.g., at high altitude), and when the circulation transit time is reduced (e.g., in a hyperdynamic circulation).

The diffusion characteristics of the normal lung as measured by the diffusing capacity for carbon monoxide ($\dot{D}_{LCO}$) remain almost constant throughout life.[49] In HMD (in which the alveolar membrane is thickened and the total alveolar area reduced by atelectasis), some studies have shown a reduction in the $\dot{D}_{LCO}$ lasting more than 72 hours after birth despite an increase of the FRC to normal in that time.[126] However, other studies have demonstrated no difference in the $\dot{D}_{LCO}$ between babies with HMD and normal newborns.[76]

A significant reduction in the $\dot{D}_{LCO}$ standardized for total lung capacity has been demonstrated in a variety of childhood illnesses in which the lungs are affected. These include interstitial pulmonary fibrosis,[127] Henoch-Schönlein purpura,[128] the active phase of childhood connective tissue disorders (including juvenile rheumatoid arthritis, systemic lupus erythematosus, and dermatomyositis),[129] interstitial pneumonitis after bone marrow transplantation,[130] amiodarone-induced pneumonitis,[131] and the acute phase of histoplasmosis.[132]

Because $\dot{D}_{LCO}$ and V̇/Q̇ inequality have not been studied simultaneously in these conditions, the contribution to hypoxemia of a reduced diffusion capacity independent of V̇/Q̇ inequality is not certain. In adolescents and young adults with cystic fibrosis, the presence of a reduced diffusion capacity is associated with marked airflow obstruction and severe arterial desaturation on exercise,[133] although V̇/Q̇ inequality makes a much greater contribution than impaired diffusion to hypoxemia in cystic fibrosis.[75]

LUNG WATER AND PULMONARY EDEMA

Pulmonary edema is the accumulation of abnormal amounts of fluid in the extravascular spaces of the lung and is common in many conditions. The primary site of pathology may be pulmonary (e.g., aspiration pneumonitis) or elsewhere (e.g., cardiomyopathy). Although many diverse conditions can lead to pulmonary edema, they all do this via at least one of a small number of mechanisms. The presence of excess fluid in the airspaces decreases lung compliance, increases airway resistance, and impedes gas exchange; hence respiratory failure is a common endpoint.

Water Turnover in the Normal Lung

The normal lung is approximately 80% water by weight. Approximately 25% of this water is within the pulmonary circulation, and the remaining (extravascular) water is within the interstitial spaces and pulmonary lymphatics.[134] Less than 0.5 μm of tissue separates water that is under hydrostatic pressure in the capillary circulation from the alveolar airspaces; therefore maintenance of the barrier that prevents water from flooding the airspaces is critical to the preservation of alveolar gas exchange.

Water distribution at the level of the alveolar-capillary gas exchange unit can be considered as being in four compartments: vascular, interstitial, alveolar, and lymphatic. There is a continual flux of water from the vascular compartment, via the interstitial compartment, to the lymphatic compartment. This compartmental model allows consideration of normal and pathologic mechanisms but is an oversimplification of the real situation. In the normal lung, alveolar arterioles and venules contribute significantly to the water flux from the circulation to the pulmonary lymphatic system, and some of the water that passes from the vascular compartment to the interstitium is reabsorbed into the circulation at other locations.

The vascular compartment is separated from the interstitial space by the capillary endothelium, which is thought to

be relatively permeable to water and small molecules but not to circulating proteins. The alveolar compartment is separated from the interstitial space by its epithelium, which is much less permeable to fluids and solutes. The alveolar-capillary interstitial space is continuous with that of the perivascular and peribronchial regions and thus with the lymphatic system that drains these spaces.

Pulmonary arterial pressure produces a positive hydrostatic pressure within the vascular compartment, whereas the forces of elastic recoil probably produce a subatmospheric pressure within the lung interstitium. This hydrostatic pressure difference tends to move fluid out of the capillary circulation into the interstitial space. However, because the endothelial membrane is impermeable to macromolecules, an osmotic gradient tends to keep water within the vascular compartment. The hydrostatic force varies considerably from the highest to the lowest point in the lungs, but on average, it exceeds the osmotic force. Hence there is a small, continuous flux of fluid from the vascular compartment to the interstitial space. Because the alveolar epithelial membrane is relatively impermeable, this fluid tracks to the perivascular and peribronchial interstitium, where it flows into the pulmonary lymphatic system.

The capillary endothelial and alveolar epithelial membranes are composed of single layers of cells. At the point where the two layers touch, the basement membranes are fused, and there is no true interstitial space. Where the two layers are not in direct contact, there is an interstitial space consisting of a matrix of proteins and proteoglycans.[135,136] The passage of water and solutes between the compartments is determined by the membrane structures, and the flow through the interstitium is affected by the properties of the matrix. Substances may cross membranes either between the cells or through them. The endothelial and epithelial membranes vary in both their transcellular and pericellular permeability.

The endothelial membrane is formed from a homogeneous cell type with relatively permeable cell-to-cell junctions (gap junctions, tight junctions, and zonula adherens), and most flux occurs between the cells. Transcellular fluid and solute flux can occur,[137] but the degree to which it contributes to the permeability of the endothelial membrane is controversial.

The alveolar epithelial membrane is made up from two different cell types (types I and II), and they vary in their mechanisms of transcellular fluid transport. The epithelial membrane is characterized by tight apposition at the cell-to-cell junctions. The membrane has well-developed mechanisms for the active transcellular transport of ions and hence water. In fetal life, the active transport of chloride into the alveolar space leads to the secretion of fluid into the alveoli. This is the source of the "lung fluid" that passes up the airway and into the amniotic cavity.[138] In postnatal life, the active transport of sodium out of the airspace results in reabsorption of water that may have leaked into the alveolus.[139] This mechanism becomes more active during healing after alveolar injury. Type II alveolar cells may be more active in the reabsorption of sodium and water than the type I cells, and this fits with the observation that type II cells are not prominent until toward the end of fetal maturation but are very prominent in the healing lung.

Pulmonary edema occurs when the rate of fluid flux out of the vascular compartment exceeds the rate at which it can be cleared from the lung. A number of safety mechanisms help prevent the accumulation of excessive amounts of extravascular water. First, if an increased amount of fluid but not protein passes from the vascular to the interstitial compartment, then the osmotic gradient between the compartments increases and encourages fluid to remain within the circulation. This mechanism cannot occur if there is a pathologic increase in endothelial protein permeability. Second, the perivascular interstitium has limited capacitance, and fluid accumulation quickly increases the interstitial hydrostatic pressure and thus reduces the flux of water. Third, the pulmonary lymphatic system has a tremendous reserve capacity and can clear interstitial fluid formation at a rate at least 10 times the basal level.[134,140] Fourth, accumulation of interstitial fluid leads to hyperpnea (possibly by the stimulation of juxtacapillary J receptors), and increased breathing movements augment pulmonary lymphatic flow.

Formation of Pulmonary Edema

Pulmonary edema occurs when the rate of fluid flux from the vascular to the interstitial compartment exceeds the rate at which it can be cleared by reabsorption or by the lymphatic system. It is thought that a phase of interstitial edema appears first and that, later, fluid leaks through the epithelial membrane to form alveolar edema.

The route by which interstitial fluid leaks into the alveolus is still uncertain. It may be that fluid breaches the cell-to-cell junctions of the alveolar epithelial membrane,[141] or it may be that fluid tracks to the peribronchiolar interstitium and then through the more permeable epithelium of the terminal bronchioles and back into the alveoli.[140-143] In lung injury from noxious substances that have been inhaled (e.g., toxic gas) or aspirated (e.g., gastric acid), direct leak through the damaged alveolar epithelium is most likely.

Etiology of Pulmonary Edema

The various causes of pulmonary edema (Box 19-4) may be classified by primary abnormality into two types: increased hydrostatic pressure (Box 19-5) or increased permeability. The increased hydrostatic pressure pulmonary edema is sometimes called cardiogenic pulmonary edema, as one of the main causes in adults is a left ventricular function failure, with the consequent elevation in the end-diastolic left ventricular pressure and left atrial pressure. In general, left atrial pressures of more than 25 mm Hg are associated with overt pulmonary edema. The two forms of pulmonary edema are sometimes difficult to distinguish clinically. Tools useful for the differentiation are some radiographic criteria (such as the width of the vascular pedicle, the vascular distribution, etc.),[144] echocardiographic evaluation,[145] pulmonary artery catheterization,[146] and, more recently, brain natriuretic peptide.[147] Although convenient,[148] this classification ignores the fact that in many conditions, both types of edema coexist. For example, the edema associated with increased pulmonary microvascular hydrostatic pressure in left-sided heart failure is often exacerbated by an increase in capillary endothelial permeability brought about by stretching of the porous cell-

BOX 19-4 Causes of Pulmonary Edema Classified by Mechanism

Increased Hydrostatic Pressure Gradient

Increased capillary pressure (see Box 19-5)
Decreased interstitial pressure
- Upper or lower airway obstruction
- Lung re-expansion

Increased Permeability

Pneumonia (bacterial or viral)
Acute respiratory distress syndrome (ARDS)
Generalized sepsis
Aspiration
Near-drowning
Inhalation of smoke or toxic gases
Thermal inhalation injury
Oxygen toxicity
Hypersensitivity reactions

Decreased Oncotic Pressure Gradient

Decreased intravascular oncotic pressure
- Hypoalbuminemia
- Water overload

Increased interstitial oncotic pressure secondary to increased permeability

Decreased Lymphatic Drainage

Congenital pulmonary lymphangiectasis
Decreased drainage after lung transplantation

Uncertain or Mixed Pathogenesis

Neurogenic pulmonary edema
Narcotic abuse

BOX 19-5 Causes of Increased Capillary Pressure Classified by Primary Site

Increased Systemic Arterial Pressure

Aortic coarctation
Renal hypertension

Increased Left Atrial Pressure

Mitral valve disease
Cor triatriatum

Increased Pulmonary Venous Pressure

Obstructed anomalous pulmonary venous drainage
Pulmonary veno-occlusive disease
Mediastinal tumor or fibrosis

Increased Left Ventricular End-Diastolic Pressure

Aortic valve disease
Left ventricular outflow obstruction
Cardiomyopathy (including anthracycline toxicity)
Myocarditis
Myocardial ischemia
Pericarditis or effusion
Dysrhythmias

to-cell junctions. In inflammatory lung diseases such as ARDS and pneumonia, in which the permeability of the capillary endothelium to proteins increases, the osmotic gradient that resists fluid flux into the interstitium is reduced. The resulting increase in extravascular lung water is greatly exacerbated by increases in capillary hydrostatic pressure (e.g., resulting from left ventricular dysfunction or the administration of plasma expanders). If colloid plasma expanders are infused as the capillary permeability is increased, the colloid molecules (human serum albumin, gelatin, dextran, and starch) enter the interstitial space; when the endothelium again becomes impermeable to protein and colloids, the osmotic gradient between the plasma and lung interstitium remains low, and the duration of pulmonary edema is prolonged.[149] Additionally, it has been well demonstrated that high levels of brain natriuretic peptide are not as useful in critically ill patients, in whom they could be elevated even in the absence of congestive heart failure.[150] There is no consensus on the usefulness of brain natriuretic peptide in pediatric patients,[151] although there are reports that indicate that there is also considerable overlap in pediatric critically ill patients with and without left ventricular dysfunction.[152] More details on the mechanisms of pulmonary edema formation, clinical features, and management are given in the chapters dealing specifically with the relevant conditions, but some miscellaneous conditions are covered here.

Increased Permeability of the Alveolar-Capillary Membrane

Increased permeability of the alveolar-capillary membrane may occur as a direct result of the primary disease mechanism (e.g., inhaled toxins, bacterial toxins) or the effects of circulating mediators (e.g., cytokines, eicosanoids, complement). Neutrophil adhesion to the pulmonary capillary endothelium, which is mediated by selectin or integrin complexes or by platelet-activating factor on the endothelial cell membrane, leads to the release of proteases or oxygen-derived free radicals. Depletion of endothelial cell ATP production caused by oxidant damage impairs the membrane sodium-potassium pump, leading to osmotically induced cell swelling. Disassembly of the cytoskeleton as a result of paucity of ATP contributes to the endothelial cells' becoming globular in shape, opening up intercellular tight junctions, and increasing microvascular permeability.[153]

Decreased Oncotic Pressure Gradient

Hypoproteinemia, either as a primary condition (e.g., in liver disease or malnutrition) or as a result of water overload, does not usually lead to pulmonary edema. However, it may exacerbate the edema associated with other conditions. For example, excessive infusion of crystalloid solutions greatly increases extravascular lung water in a patient with raised capillary hydrostatic pressure caused by left ventricular failure.

Decreased Interstitial Pressure

A small number of children with acute obstruction, particularly of the upper airway (e.g., laryngotracheobronchitis, epiglottitis, laryngospasm), develop pulmonary edema.[154] This can occur after even very brief periods of obstruction[155,156] and is often manifested only after the obstruction has been relieved by endotracheal intubation. A simplistic view of the etiology suggests that decreased interstitial hydrostatic pressure tends to draw water across the capillary endothelium into the interstitial space. The reason that fluid enters the alveolar airspace is less clear, as is the reason that often the edema appears only after removal of the obstruction. Other factors that may be important include an increase in capillary endothelial permeability caused by hypoxia and a shift of blood from the systemic to the pulmonary circulation as a result of circulating catecholamines.

Neurogenic Pulmonary Edema

Brain injury from a variety of causes (e.g., trauma, hypoxia, ischemia, meningitis) is sometimes complicated by the development of pulmonary edema. The mechanisms have not been well studied in humans, but a number of experimental animal models of brain injury have given some insight into the causes.

The pathogenesis of neurogenic pulmonary edema is thought to result mainly from increased capillary hydrostatic pressure, probably from a component of myocardial dysfunction,[157] but the relatively high protein content of the edema fluid suggests that the increased permeability of the alveolar-capillary membrane may also be important. The main feature of neurogenic pulmonary edema is the activation of both the neural and humoral components of the sympathetic nervous system.[158,159] Generalized vasoconstriction leads to a shift of circulating volume to the pulmonary circulation. Systemic vasoconstriction increases left ventricular afterload, and relative left ventricular failure tends to increase pulmonary capillary pressure. The increased permeability, previously documented, may result from stretching of the porous cell to cell junctions or from endothelial damage caused by some circulating mediators (not yet proved). The hemodynamic disturbances described can be transient, yet the features of pulmonary edema can persist for much longer. This suggests that the circulatory changes may be the initial event and that damage to the capillary endothelium with protein leakage causes the condition to persist.

Disturbances in Lung Function Caused by Pulmonary Edema

The development of pulmonary edema profoundly affects the mechanical and gas-exchanging properties of the lungs. Lung compliance is reduced by several mechanisms. The presence of large amounts of interstitial edema reduces the distensibility of the lungs and promotes the collapse of the alveoli and small airways. Flooding of the alveoli with fluid physically disrupts the surfactant layer at the air-fluid interface, and the presence of protein and cellular debris impairs the activity of surfactant.[160,161] These effects lead to greatly increased surface tension in the fluid lining of small airspaces and tend to collapse these spaces (atelectasis). Airway resistance is increased by the physical presence of fluid in the small airways and by the compression of the small airways by fluid that has accumulated in the peribronchial interstitium. The combined effects of reduced lung compliance and increased airway resistance greatly increase the work of respiration, which may lead to respiratory muscle fatigue and respiratory failure.

The gas-exchanging properties of the lung are impaired by the presence of pulmonary edema. Interstitial edema probably causes only a small reduction in gas exchange because the fused basement membranes of the alveolar-capillary membrane prevent accumulation of fluid at this point. Alveolar edema significantly impairs oxygenation. Lung units may be unventilated because they are flooded with fluid or because the airways supplying them are obstructed. Blood flow to unventilated lung units may be reduced by hypoxic vasoconstriction, but significant $\dot{V}/\dot{Q}$ mismatch usually remains with consequent hypoxemia.

Hyperventilation with hypocapnia is a common feature in the early course of pulmonary edema. Arterial hypoxemia and anxiety probably provoke increased ventilation. Stimulation by edema of the J receptors in the airways also leads to rapid, shallow respirations.

Pulmonary arterial hypertension is a frequent feature of pulmonary edema. It may lead to right-sided heart failure if sufficiently severe. Pulmonary hypertension is probably a result of hypoxic vasoconstriction in poorly ventilated lung units and direct vascular compression from edema in the perivascular interstitium.

Summary

Pulmonary edema is a feature of many conditions of diverse etiology. The effects on lung mechanics and gas exchange make it one of the common causes of respiratory failure.

CARDIORESPIRATORY INTERACTIONS

Interactions among the functions of the circulatory and respiratory systems are very complex.[162] The functions of the respiratory system have a modest effect on cardiac function under normal conditions, and this effect may vary qualitatively or quantitatively if there is respiratory or cardiac disease.

Physiologic Cardiorespiratory Interactions

Diagrams of the circulatory and respiratory system often show the right and left sides of the heart as two separate pumps connected in series via the circulation of the lungs. This is obviously a gross oversimplification. The facts that the two sides of the heart share a common muscular septum, share common circular muscle fibers, and are enclosed together in the pericardial cavity (Fig. 19-9) mean that they do not act independently. Similarly, the fact that the two sides of the heart and the pulmonary circulation are contained, along with the rest of the lung tissues, within the closed thoracic cavity means that changes in lung volume and intrathoracic pressure influence circulatory function.

The output from either cardiac ventricle is determined by its venous filling (preload), the force of muscular contraction (contractility), and the pressure gradient against which it has

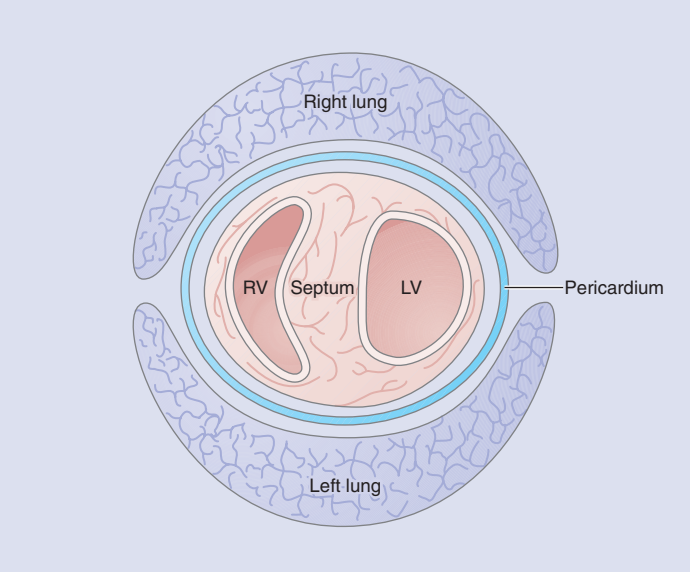


Figure 19-9 Diagrammatic cross section of the cardiac ventricles and lungs, which interact during respiration and the cardiac cycle. The right ventricle (RV) and left ventricle (LV) share a common septum, and the right is wrapped around the left. The muscle fibers of the free walls of the two ventricles are in continuity. The pericardial sac surrounds the two ventricles and in turn is surrounded by the lungs, pleura, and chest wall. See text for details of this interaction. (From Robotham JL: Hemodynamic events: A physiological approach. In Montenegro HD [ed]: Chronic Obstructive Pulmonary Disease, New York, Churchill Livingstone, 1984, pp 183-217.)

to eject (afterload). The afterload is determined by the transmural pressure gradient, which is the difference in pressure between the ventricular cavity and the surrounding intrathoracic pressure. The output of either ventricle may also be influenced by the pressure or volume of the other ventricle. The anatomic reasons for this ventricular interdependence have already been outlined.

Changes in intrathoracic pressure have differing effects on the preload and afterload of the two ventricles. The capacitance vessels (veins), which supply the right ventricle, lie outside the thoracic cavity, whereas the arterial circulation that the ventricle supplies is within this cavity. The reverse is true for the left ventricle.

EFFECTS OF SPONTANEOUS RESPIRATION IN A HEALTHY SUBJECT

Table 19-1 outlines how inspiration and a fall in intrathoracic pressure affect circulatory function in a healthy subject. Several of the effects cancel each other out, but the overall results are a transient increase in right ventricular output and a decrease in output from the left ventricle. The cyclic respiratory effects are easily seen in the pressure waveform trace from a peripheral systemic arterial catheter in a spontaneously breathing subject. Systolic arterial pressure varies up to 10 mm Hg between inspiration and expiration.

Because the ventricles are connected in series, such differences in output cannot be sustained. In a prolonged inspiration, the output from the left ventricle falls initially (because of the mechanisms previously outlined), and then within three or four cardiac cycles, it rises again as the increased output from the right ventricle reaches the left. The effects of expiration and a rise in intrathoracic pressure are essentially the reverse of those seen in inspiration.

Table 19-1
Effects of a Normal Inspiration

Effect	Mechanism (Because of a Fall in Intrathoracic Pressure)
Increase in right ventricular preload	Increase in the pressure gradient from the systemic veins to the right atrium
Increase in right ventricular afterload	Increase in the transmural pressure gradient of the right ventricle
Decrease in right ventricular afterload	Distention of the pulmonary vascular bed and reduction in its resistance to flow
Decrease in left ventricular preload	Distention of the pulmonary vasculature and a fall in the pressure gradient from the pulmonary veins to the left atrium
Increase in left ventricular preload	Fall in left atrial pressure and increase in the pressure gradient from the pulmonary venous return to the left atrium
Decrease in left ventricular filling	Increased right ventricular filling with ventricular interdependence from septal shift
Increase in left ventricular afterload	Increased transmural pressure gradient of the left ventricle

Apart from breath-holding (apnea), neither respiratory phase is prolonged. The cyclic changes in ventricular output with respiration merge from one breath into the next, and the observed changes in cardiac output depend to some degree on the relative cardiac and respiratory rates.

Cardiovascular Effects of Pathologic Pulmonary Conditions

Many respiratory conditions are complicated by pulmonary arterial hypertension. The way that pulmonary hypertension reduces left ventricular filling and increases right ventricular afterload can profoundly affect cardiac function, and this subject is discussed in detail in Chapter 53.

Respiratory conditions that lead to reduced lung compliance (e.g., pneumonia, HMD, pulmonary fibrosis) or increased airway resistance (e.g., asthma, bronchiolitis, emphysema) lead, for any given level of respiratory effort, to greater swings in intrathoracic pressure than would occur in a child with normal lungs. These swings are manifested as indrawing of the soft tissues and even the ribs in the relatively compliant chest wall of a child with these conditions. These large swings persist while normal or increased respiratory effort is maintained but diminish as respiratory muscle fatigue ensues.

The effects of obstructed expiration on the cardiovascular system are similar to those of the Valsalva maneuver. Venous return and flow in the pulmonary system are severely reduced by the high intrathoracic pressure early in expiration, but there is a small initial increase in cardiac output and blood pressure as a result of expulsion of blood from the lungs and compression of the left ventricle and thoracic aorta. The reduced venous return then reduces the cardiac output and blood pressure, provoking a baroreceptor response to tachycardia and vasoconstriction that causes a rebound hypertension when the forced expiration is released and venous return increases.

Obstructed inspiration causes cardiovascular effects similar to those of a Müller maneuver (forced inspiration against a closed glottis). Low intrathoracic pressure increases systemic venous return and expands the pulmonary blood volume, but venous return to the left ventricle, the systemic cardiac output, and the blood pressure decrease early in inspiration but approach normal later in inspiration.

Conditions causing hyperinflation of the lungs and high airway resistance (e.g., asthma) can lead to substantial changes in cardiac performance. Increased negative pressure during inspiration and positive pressure during active expiration lead to big swings in intrathoracic pressure and exaggeration of the normal cyclic changes in right and left ventricular preload and afterload.[163] The variation in left ventricular stroke volume leads to a palpable swing in systolic systemic arterial pressure with respiration.[164] This *pulsus paradoxus* is an exaggeration of the normal pattern, and it can be used as a tool to evaluate the severity of the hyperinflation.[165] Pulsus paradoxus can also be observed in other conditions, such as pericardial tamponade.[166] In severe airway obstruction, pulmonary vascular resistance is increased by elevated lung volume, hypoxic vasoconstriction, and acidosis.

Respiratory Effects of Cardiovascular Disorders

Increased left atrial pressure resulting from reduced left ventricular contractility or compliance, pulmonary venous obstruction, mitral valve disease, pericardial disease, or hypervolemia causes pulmonary edema and affects lung mechanics and gas exchange (see earlier section). As the cardiac output decreases, increased tissue oxygen extraction reduces the mixed venous P_{O_2}. The consequent reduction in pulmonary end-capillary P_{O_2} (and therefore Pa_{O_2}) is greater for lung units with normal $\dot{V}/\dot{Q}$ ratios than in those with high or low $\dot{V}/\dot{Q}$ ratios.[167] Although the mixed venous P_{CO_2} also increases when the cardiac output is low, the rapid diffusion of carbon dioxide across the alveolar membrane means that the Pa_{CO_2} is not normally increased by a reduction in cardiac output.[168]

Reduction in cardiac output also decreases the pulmonary pressure, decreasing the perfusion to the uppermost parts of the lung and increasing the alveolar dead space. In practice, this is only important in the upright position. As previously described, a decrease in respiratory muscle blood flow as a result of low cardiac output contributes to respiratory muscle fatigue when the work of breathing is increased. If the decrease in cardiac output is predominantly caused by left ventricular failure, then the pulmonary artery occlusion pressure will be elevated and pulmonary edema may develop, as discussed in the previous section. It must be noted that the cardiorespiratory interactions are highly complex and do not follow a linear pattern, implying that more sophisticated nonlinear mathematical analysis may be superior for their evaluation.[169]

Effects of High Cardiac Output

In severe exercise, the cardiac output is very high, and pulmonary transit time is reduced. Diffusion limitation reduces the pulmonary end-capillary P_{O_2} and increases the $P_{AO_2} - Pa_{O_2}$. During short bursts of severe exercise in trained athletes, the Pa_{O_2} falls below 75 mm Hg.[170] The high cardiac output found in septic shock is associated with reduced oxygen extraction and a high mixed venous P_{O_2}, so the effect on Pa_{O_2} of diffusion limitation as a result of high cardiac output is not as pronounced in these patients. In the presence of lung disease, inotropic drugs that increase the cardiac output tend to increase the $P_{AO_2} - Pa_{O_2}$ and reduce the Pa_{O_2} by increasing the perfusion of unventilated alveoli and of low $\dot{V}/\dot{Q}$ lung units.[84]

ACUTE RESPIRATORY DISTRESS SYNDROME

ARDS is a clinical syndrome with multiple etiologies.[171] The hallmark is an acute change in lung function characterized by pulmonary edema resulting from increased alveolar-capillary permeability. This results in severe hypoxemia, decreased lung compliance, and the appearance of bilateral pulmonary infiltrates on chest radiograph. Inflammation plays a part in the pathogenesis, and fibrosis occurs in the lung parenchyma during resolution. Alveolar injury is diffuse but not uniform throughout the lung.[171] ARDS can be considered the pulmonary manifestation of the systemic inflammatory response syndrome (SIRS).[172]

ARDS may occur after direct or indirect lung injury. Septicemia, near-drowning, hypovolemic shock, and closed-space burn injury were the most common antecedent illnesses in children reported by Pfenninger and colleagues.[173] ARDS is also seen in immunocompromised children after treatment for malignancy[174]; in association with respiratory infections, including mycoplasma,[175] respiratory syncytial virus,[176] and herpesvirus[177] infections; and after major head injury,[178] multiple trauma,[179] asphyxia,[180] and chemical aspiration.[181] Studies of adults indicate that patients with multiple predisposing conditions (e.g., trauma, multiple transfusions, disseminated intravascular coagulation) are at a much greater risk of developing ARDS than those with a single risk factor.[182] The lung injury associated with cardiopulmonary bypass and ECMO support has the pathophysiologic features of ARDS.[183]

Disease Mechanisms

The pathology of ARDS has been extensively reviewed by Bachofen and Weibel,[184] and more recently by the American-European Consensus Conference on ARDS.[171] In the initial stage, there is damage to and edema of the interalveolar septa. There is extensive destruction of type I alveolar epithelial cells. Although on electron microscopy, the endothelial cell basement membrane appears relatively intact, this barrier becomes permeable to plasma proteins, and interstitial edema results. Proteinaceous fluid first collects within the peribronchial and perivascular connective tissue, then within the alveolar septa, and later in the alveoli. Edema fluid contains erythrocytes, leukocytes, fibroblasts, macrophages, cell debris, albumin, globulins, and amorphous material comprising strands of fibrin. Hyaline membranes form along the inner surface of the alveoli. As the alveoli and interstitium fill with exudate, the gas-exchanging and mechanical properties of the lung deteriorate. There are reduced lung volumes and poor compliance with $\dot{V}/\dot{Q}$ mismatching, intrapulmonary shunting, and increased dead space.[185,186]

Microthrombosis of pulmonary vessels occurs as a result of intravascular coagulation, pulmonary vascular congestion,

and the sequestration of neutrophils and platelets that plug the pulmonary capillaries. This further exacerbates endothelial damage, high pulmonary vascular resistance, and $\dot{V}/\dot{Q}$ mismatching.

In the first days of ARDS, the capillary endothelial and alveolar epithelial barrier are reduced in thickness by cellular necrosis. By the end of the first week, there is regeneration of the endothelium, and the destroyed type I pneumocytes that line the alveoli are replaced by the marked proliferation of thicker, cuboidal, type II pneumocytes. This phase of ARDS may result in complete resolution of the process or may progress to interstitial fibrosis. Fibrosis commences after the first week and particularly involves the alveolar walls. Pulmonary fibrosis rapidly and progressively obliterates the alveoli, alveolar ducts, and pulmonary interstitial space, which also is expanded by edema fluid and inflammatory cells. The apposition between the alveolar epithelium and capillary endothelium is then separated by bulky type II pneumocytes and fibroblasts in the alveolar septum and interstitium. In advanced cases of ARDS, when thickening of the alveolar wall is extensive, gas exchange is too impaired to support life. Intra-alveolar hemorrhage may be focally present in some cases but is generally not severe. Although alveolar damage is widespread in ARDS, the lung is not uniformly affected. Computed tomography of patients with ARDS shows the distribution of lung collapse to be mainly in the dependent regions.[187]

Although the predisposing causes of ARDS are known and the histopathologic changes well characterized, there is still uncertainty as to the exact role and timing of the mediators involved. Neutrophils probably have a central role in the genesis of endothelial injury[188] and lung injury associated with ARDS.[189] They are sequestered early into the lung, drawn to the lung by chemotactic components of the complement cascade (C5a), prostaglandins, tumor necrosis factor, leukotrienes, and platelet activating factor (PAF). Neutrophils release interleukin-1 and toxic oxygen radicals that cause cell destruction. Oxygen-derived free radicals, such as hydrogen peroxide and the hydroxyl radical, are bactericidal agents, which may produce host membrane damage by causing lipid peroxidation or by making target proteins more susceptible to proteolytic cleavage. Oxygen radicals also inhibit the action of α_1-antitrypsin, allowing unopposed activity of elastase and other proteolytic enzymes, which are capable of degrading elastin, collagen, proteoglycans, fibronectin, and structural components of basement membranes and the intercellular matrix. The role of oxygen radicals in ARDS has been recently reviewed by Zhang and coworkers.[190] Neutrophils stimulate the production of arachidonic acid metabolites—prostaglandin, thromboxanes, and leukotrienes—some of which cause increased capillary permeability, vasoconstriction, and platelet aggregation and are chemotactic for neutrophils.[191] Leukotriene levels in plasma and bronchoalveolar lavage have been associated with the inflammation and the risk of mortality from ARDS.[192,193]

Large numbers of platelets are present in pulmonary capillaries in ARDS. They aggregate, causing increased microvascular hydrostatic pressure, and release arachidonic acid metabolites. The number of alveolar macrophages increases greatly. These cells produce cytokines such as tumor necrosis factor and the interleukins, which cause tissue damage.

The role of PAF in acute lung injury has been reviewed by Anderson and associates.[194] PAF is produced by endothelial cells, type II pneumocytes, marginating neutrophils, and alveolar macrophages. PAF causes microvascular leakage and margination of leukocytes and contributes to the development of intravascular coagulation in lung capillaries. PAF seems to be essential in the macrophage response to endotoxin.[195] The levels of PAF and those of the enzyme that metabolizes it, PAF-acetylhydrolase, are increased in the bronchoalveolar lavage fluid of patients with ARDS.[196,197]

Role of Pulmonary Hypertension

Zapol and Snider[186] found pulmonary artery hypertension and elevated pulmonary vascular resistance in 30 patients with ARDS associated with increased right ventricular stroke work. In adults[186] and children[185] with ARDS, pulmonary artery pressure and vascular resistance gradually fall after several days in survivors but increase progressively in those who die. Severe pulmonary hypertension can result in right ventricular failure and a low cardiac index. Right ventricular dilation leads to a leftward septal shift, impairing left ventricular diastolic filling. Coronary blood flow to the right ventricle decreases, producing myocardial ischemia and further compromising right ventricular function.

Inhaled nitric oxide administered by inhalation to children with ARDS causes a significant fall in pulmonary artery pressure and intrapulmonary shunting and an increase in the cardiac index, up to a dose of 20 ppm.[198] Intrapulmonary shunting decreases because inhaled nitric oxide preferentially dilates the pulmonary vessels that supply ventilated alveoli, increasing their blood flow at the expense of less well ventilated parts of the lung. Above 20 ppm, there was no further increase in oxygenation or beneficial effect on pulmonary hemodynamics. A randomized controlled trial in adults with ARDS revealed that nitric oxide, at doses of 5 ppm, did not improve the outcome, either in terms of survival or duration of mechanical ventilation, although there were short-term improvements in oxygenation.[199]

Role of Secondary Infection and Multiple Organ Failure

ARDS may be associated with organ failure of other systems as a result of the same insult (e.g., brain failure and ARDS after the hypoxic-ischemic injury of near-drowning). Renal failure, gastrointestinal hemorrhage, disseminated intravascular coagulation, impaired liver function, bone marrow suppression, and altered cerebral function are commonly associated with severe ARDS,[200] especially during the late stages. In the initial description of the sepsis syndrome by Bone and colleagues,[201] 25% of 191 patients developed ARDS. Pfenninger and associates[173] described 20 children with ARDS, of whom 60% had coagulation failure, 40% had renal failure, 40% had brain dysfunction, and 30% had hepatic or gastrointestinal failure. Nonsurvivors had more organ systems failing than those who survived. Interventions aimed to decrease the inflammatory impact of noxious stimuli, such as lung protective strategies or tight glucose control, may be associated with a decreased incidence of both ARDS and multiple organ failure in at-risk patients.[202]

Infection may occur in children with ARDS as part of the manifesting illness, or it may be nosocomially acquired from indwelling catheters or endotracheal tubes or endogenously

acquired secondary to gut ischemia or the use of broad-spectrum antibiotics. Bacteremia was present in 45% of Bone's patients but did not influence the patient's outcome.[201] In Pfenninger's study,[173] 15% of the children with multiple organ dysfunction developed culture-proven septicemia and died. Although culture-proven bacterial infection is common in patients with multiple organ system failure, it is not a prerequisite. The lung is the most common source of sepsis at autopsy in adults with clinical sepsis but negative blood cultures. The high risk of secondary infections in the ARDS patient may stem from a functional immunodepression, likely caused by the up-regulation of anti-inflammatory mediators after the acute phase of injury.[203,204]

The roles of gastrointestinal tract mucosal ischemia and loss of barrier function in the development of multiple organ failure are yet to be fully elucidated, but there is evidence that gut ischemia is associated with the translocation of bacteria, endotoxin, and other bacterial toxins and the activation of neutrophils, which may affect distal organs, including the lungs.[205,206] This has been sometimes called the *gut hypothesis*. Gut mucosal ischemia may occur in ARDS secondary to hypoxemia or inadequate cardiac output with redistribution of blood flow away from the gut and toward other vital organs such as the brain and heart. The gut hypothesis has been recently modified to emphasize the role of gut-derived factors in the intestinal lymph, more than in the portal blood. This is now called the *gut-lymph hypothesis*.[207,208]

CLINICAL MANIFESTATIONS

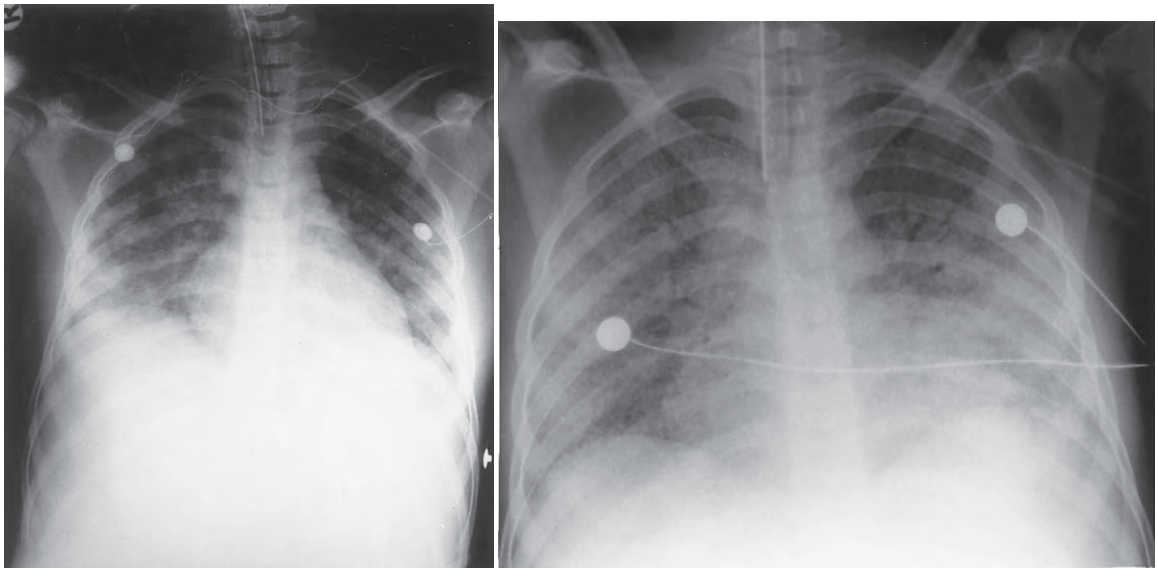
After the event or illness that precipitates ARDS, there may be clinical signs of respiratory distress, or the signs may develop later, commonly in the first 48 hours. Tachypnea is the first sign, at which stage the chest radiograph is often normal. Chest retractions, expiratory grunt, alar flaring, and cyanosis may also be present. Initially, there is respiratory alkalosis. Later, there is severe hypoxemia with a large $P_{AO_2} - P_{aO_2}$ difference and a rising P_{aCO_2}. The lungs become noncompliant with diffuse bilateral infiltrates on the chest radiograph (Fig. 19-10). The final phase involves widespread bilateral consolidation with hypoxemia in 100% oxygen and severe hypercarbia as well as respiratory and often metabolic acidosis. Multiple organ failure often ensues. Not all patients progress at the same rate or to the same extent. The condition may partially or completely resolve at any stage.

MANAGEMENT

The prevention of ARDS should be one aim of the treatment of all critically ill children. The principles of management are to treat the underlying cause if possible, ensure adequate tissue oxygenation, and prevent complications.

Investigating for Treatable Causes

Many factors cause a child's ARDS. For some children, there is no specific treatment. Treatable causes such as infection should be identified and treated. The search for primary or secondary lung infection may require culture of tracheal aspirates, bronchoalveolar lavage (BAL) fluid, or lung biopsy specimens. Lung biopsy may be clinically useful in adults with ARDS who are on ventilators, but lung biopsy has not been compared with less invasive methods in prospective trials.[209] BAL can be performed safely in such patients.[210] The most common finding in BAL fluid in patients with ARDS is increased numbers of polymorphonuclear leukocytes, making up nearly 80% of the total cell population (normal, <5%). The one type of ARDS that may respond to corticosteroid therapy is characterized by an increased number of eosinophils in BAL fluid or by peripheral eosinophilia.[211] Prophylactic antibiotics are not beneficial in ARDS, but potential bacterial pathogens found in BAL fluid should be treated. Lung fluid should also be cultured for viruses.



A B

Figure 19-10 Chest radiographs of a 12-year-old girl with acute respiratory distress syndrome (ARDS) associated with acute hepatic failure. **A,** Radiograph 2 days after onset. There are widespread alveolar opacities, mostly in the lower zones. **B,** Radiograph 4 days after onset. There is widespread consolidation with air bronchograms and alveolar and interstitial opacities.

Herpes simplex virus was identified in the tracheal aspirates of 30% of 46 adults with ARDS, in whom it was associated with the need for more prolonged respiratory support and an increased mortality rate than was the case in patients in whom the BAL fluid did not grow the virus.[177] Herpes simplex virus has also been found in the lungs of patients with burn injury.[212] The role of reactivation of this virus in ARDS is unclear, and prophylactic antiviral agents are not indicated, but acyclovir may be useful if the virus is present. BAL fluid may also have other opportunistic pathogens, such as *Pneumocystis jiroveci*, which may present with acute respiratory failure in children with known or unsuspected impaired immunity.

Ensuring Adequate Tissue Oxygenation

The therapy for ARDS is based on support for the cardiorespiratory system to maintain adequate P_{AO_2}, P_{ACO_2}, and tissue perfusion. This involves attention to ventilation strategy as well as cardiac output and tissue oxygenation. Ventilatory support maintains arterial oxygenation at a safe level while preventing pulmonary oxygen toxicity and additional lung trauma resulting from excessive ventilatory volumes or pressures. PEEP was first used successfully to treat pulmonary edema in 1938[213] and has since improved the outcome in ARDS.[214] Despite this initial success in a controlled trial of adults at risk of ARDS, the early application of PEEP at 8 cm H_2O did not reduce the incidence of the syndrome.[215] PEEP is applied to increase lung volume, keep alveoli open, and recruit collapsed alveoli and small airways. It improves arterial oxygenation in ARDS. The theoretically optimal level of PEEP would be one that allows a reduction in F_{IO_2} to a safe level (less than 0.5), does not impair venous return to the heart or reduce cardiac output, does not impair cerebral venous drainage or increase intracranial pressure, and optimizes arterial oxygenation.

PEEP may reduce cardiac output in children[216] and adults[217] with ARDS. The mechanism is likely to be both a decrease in systemic venous return and an increase in right ventricular pressure load. The latter causes a leftward shift of the interventricular septum with a reduction in filling[217] and an impaired systolic ejection function of the left ventricle. By increasing alveolar volume, PEEP increases the resistance to flow through the alveolar capillaries and thereby increases right ventricular afterload. PEEP of at least 15 cm H_2O reduces the cardiac index in adults.[217] In children without cardiorespiratory disease, Clough and coworkers,[216] using Doppler measurements of cardiac output, found a fall in cardiac output of 3.7% at 5 cm H_2O of PEEP, 6.7% at 10 cm H_2O, and 15.9% at 15 cm H_2O. There was a wide variation in subjects studied, but there was a trend toward a greater fall in cardiac output for a given level of PEEP with increasing age. Ideally, the level of PEEP chosen would be based on the measurement of cardiac output and calculated oxygen delivery. PEEP levels should be gradually increased to achieve acceptable arterial saturation with nontoxic F_{IO_2} levels (<0.5), and the effect of PEEP on hemodynamics should be monitored clinically, if measurement of cardiac output, mixed venous P_{O_2}, or oxygen consumption are unavailable.[218] Titration of PEEP against clinical measures is inexact. Hypotension often does not become apparent until cardiac output substantially falls.[219] A recent large trial in adults with ARDS found no differences in mortality with high and low PEEP while using low tidal volumes.[220]

PEEP improves compliance by opening collapsed alveoli. If PEEP levels are too high, however, overdistention of already opened alveoli may lead to a reduction in compliance. According to Sivan and associates,[221] in children with acute respiratory failure, the level of PEEP that normalized the functional residual capacity was within 4 cm H_2O of the PEEP at which static respiratory compliance was maximal; in most cases, this was the same value. Their data also showed that the best compliance was not achieved when the PEEP level was chosen by clinical judgment alone. In addition to an assessment of optimal tissue oxygen delivery, an assessment of maximal static compliance may be helpful in choosing the level of PEEP. Despite intensive research, the PEEP goals and the methods for titrating to that goal remain unclear.[222]

PEEP may increase cerebral venous pressures and intracranial pressure by increasing the intrathoracic pressure and impairing cerebral venous drainage. This is particularly important in children with brain injury. In an animal model,[223] when a lesion causing raised intracranial pressure is associated with diffuse lung injury, the rise in intracranial pressure and reduction in cerebral perfusion pressure with increasing levels of PEEP are not as great as when the lungs are normal.[224] However, the high levels of PEEP that reduce cardiac output and require blood volume expansion may lead to reduced cerebral perfusion pressure with resultant cerebral ischemia as well as volume overload, which may cause cerebral edema.

Other strategies of ventilation include a control-assist mode of ventilation, intermittent positive-pressure ventilation (IPPV) with or without paralysis, intermittent mandatory ventilation, permissive hypercapnia, inverse ratio ventilation, and high-frequency oscillatory ventilation (HFOV). Some form of synchronized, triggered, pressure-limited ventilation has been advocated[218] (e.g., pressure support, synchronized intermittent mandatory ventilation). The potential benefits of these modes of ventilation are limitations of acute rises in intrapulmonary pressures that occur with unsynchronized patient breaths, improved patient comfort, and avoidance of adverse effects of muscle relaxant medications, such as prolonged muscular weakness after the medications have been ceased. Many children with severe ARDS are unable to achieve adequate oxygenation at safe levels of F_{IO_2} and peak pressures without muscle relaxation, in which case, pressure-limited IPPV is required. Inverse-ratio ventilation increases the mean airway pressure by prolonging the inspiratory time.[225] This type of ventilation can enhance oxygenation after conventional ventilation has failed in some patients with ARDS[226] but may require heavy sedation and paralysis.[218]

HFOV has been used as an alternative to conventional ventilation in ARDS. In a randomized trial of HFOV versus conventional ventilation in children with ARDS, Arnold and collaeagues[227] found that HFOV produced greater increases in oxygenation with less barotrauma. There was no difference in other outcomes, including survival. Other studies in adults with ARDS also suggest that although high-frequency forms of ventilation may achieve preset ventilation criteria for oxygenation and gas exchange at lower inspired oxygen concentrations and lower peak pressures, there is no beneficial effect

on survival.[228] HFOV may be more likely to improve outcome if instituted as an early, rather than a late, rescue therapy.[229,230] The use of high-frequency ventilation in pediatric respiratory disease has been recently reviewed by Froese.[231]

Ventilation in the prone position in infants and children with ARDS has resulted in improved oxygenation at lower levels of inspired oxygen.[232] This strategy is based on the findings of Gattinoni and coworkers[187] that atelectasis occurred mainly in dependent parts of the lung. Regular turning from the supine to the prone position may reduce dependent atelectasis and intrapulmonary shunt. In older children who need mechanical ventilation, the lateral decubitus position can be used; this position has been advocated for patients with hypoxemia unresponsive to other medical interventions.[218] However, a well-designed randomized controlled trial using prone positioning in pediatric patients with ARDS found no improvement in any of the outcomes.[233]

Large tidal volumes, high peak airway pressures, and inspired oxygen concentrations above 0.6 have been implicated as causes of lung injury. Because of the smaller lung volume available for gas exchange in ARDS, the use of tidal volumes as small as 6 mL/kg is likely to be associated with fewer pulmonary and hemodynamic complications.[234] These small, relatively normal areas of lung are overinflated and are exposed to high positive inspiratory pressures unless low volume and pressure-limited ventilation are used. The now famous ARDS Network trial demonstrated an improvement in the survival of patients treated with low tidal volumes (6 mL/kg of predicted body weight), leading to an early stop of the trial and widespread recommendation to adopt this "protective lung strategy."[235] Although the study has been criticized for having too high tidal volumes in the control group, it stands as the best evidence in favor of using low tidal volumes. Low tidal volumes have been combined with relatively low ventilatory rates to produce controlled hypoventilation with permissive hypercapnia. Permissive hypercapnia (accepting a $PaCO_2$ up to 80 mm Hg and arterial pH above 7.15) is aimed at avoiding barotrauma and volutrauma. It is now an established and widely recommended strategy.[218]

The fluid management of patients with ARDS has also been a matter of controversy. A recent randomized controlled study compared two strategies, liberal and conservative, in the fluid management of adult patients with ARDS. There was no improvement in the survival at 60 days, but the conservative strategy was associated with shorter duration of mechanical ventilation and intensive care stay.[236]

OUTCOME

The mortality rate from ARDS in adults was about 50%,[237] and the morbidity in survivors is substantial. The new published trials have shown reductions in the mortality to 25% to 31%, reflecting the cumulative effects of improvements in critical care over the last 10 to 15 years.[238] The most recent trial in pediatric patients with ARDS reports a mortality rate of 21%.[233]

At long-term follow-up of respiratory function in nine children who survived ARDS,[239] three had recurrent respiratory symptoms consisting of moderate exertional dyspnea and cough, two had radiographic evidence of pulmonary fibrosis, and all had abnormal pulmonary function tests. The abnormalities consisted of ventilation inequalities in eight patients. The ventilation inequalities shown by multiple-breath nitrogen washout curves and obstructive airway disease were found in two patients. One child had residual restrictive lung disease. There was a mild degree of hypoxemia in seven of the children. The results were more favorable in a more recent series of pediatric long-term survivors of ARDS, with normal or near-normal pulmonary function, albeit the number of patients studied is still very small.[240]

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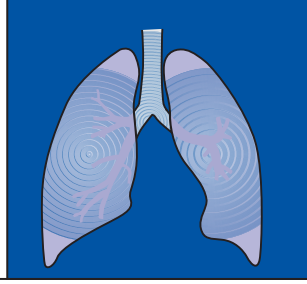

CHAPTER 20 Cardiopulmonary Resuscitation

Robert A. Berg and Vinay M. Nadkarni

TEACHING POINTS

- Cardiac arrests in children are uncommon, but not rare.
- Ventricular fibrillation occurs in ~25% of pediatric cardiac arrests.
- There are four phases of cardiac arrest: pre-arrest, no flow (untreated arrest), low flow (CPR), and post-resuscitation.
- Excellent advanced life support depends on excellent basic life support.
- PUSH HARD, PUSH FAST, minimize interruptions, allow full chest recoil, and avoid overventilation.

Pediatric cardiopulmonary resuscitation (CPR) has a rich history. For example, Kouwenhoven and colleagues first described closed chest cardiac massage in small dogs with compliant chest walls, and then established that this technique could provide circulation and result in resuscitation from cardiac arrest in children.[1] Only later did they extend the technique to adults.

CPR in children differs from that in adults.[2,3] Infants and children are anatomically, physiologically, and developmentally different from adults. In particular, the chest wall configuration and compliance of an infant are quite different from that of an adult. Perhaps more important, the etiology and pathogenesis of cardiac arrests in children are different.[2-21]

In contrast to adults, children rarely suffer sudden ventricular fibrillation (VF) cardiac arrest from coronary artery disease. Cardiac arrests in children are typically precipitated by progressive respiratory insufficiency or circulatory shock.[2-21]

Coping with a sudden unexpected death is always difficult; however, when the victim is a child, the loss tends to be more devastating. Although we know that each life is temporary, we do not expect children to die and thus are not prepared for it. Therefore, health care providers who are otherwise able to deal with most devastating problems often become emotional, and occasionally dysfunctional, when faced with a dying child. The experience for the family is naturally more intense and longer lasting. Children are the family's future. Many families never overcome the grief associated with the premature death of a child.

Definition of Pulseless Cardiac Arrest

Pulseless cardiac arrest is typically defined as the documented cessation of cardiac mechanical activity, determined by the absence of a palpable central pulse, unresponsiveness, and apnea. Differentiating severe hypoxic-ischemic shock with poor perfusion from the nonpulsatile state of cardiac arrest can be challenging at any age. This differentiation can be especially difficult in babies because of smaller size and lower blood pressures. A rescuer's ability to determine cardiac arrest by a pulse check is neither sensitive nor specific in adults.[22-29] Not surprisingly, the pulse check is even more problematic in children.[27-29] In adults, pulses can typically be palpated until the systolic pressure is <50 mm Hg. Because the normal systolic blood pressure in neonates is generally 60 to 70 mm Hg, a decrease in blood pressure to "nonpalpable pulse" may occur earlier in the continuum from hypoxic-ischemic shock to nonpulsatile cardiac standstill. Furthermore, the best arterial pulse to palpate in an adult is the carotid pulse; however, the short, fleshy neck of a baby with potential to compress the airway and impede respiration limits the effectiveness of carotid pulse palpation in infants. Therefore, palpation of the brachial, femoral, or axillary pulse may be easier.[3,27-29]

EPIDEMIOLOGY

Pediatric In-Hospital Arrests

Cardiac arrests were reported in 3% of children admitted to one children's hospital,[5] in ~2% of children admitted to pediatric intensive care units (PICUs) in the United States, in 6% of children admitted to one PICU in Finland,[6] and in 4% of children admitted to a pediatric cardiac intensive care unit.[8] The most common causes of the arrests were progressive respiratory failure and progressive shock.

Several well-designed, relatively small single institution in-hospital pediatric CPR investigations with long-term follow-up have established that pediatric CPR and advanced life support can be remarkably effective.[4-10] Almost two thirds of these cardiac arrest patients were initially successfully resuscitated (i.e., attained sustained return of spontaneous circulation). Most of these arrests/events occurred in PICUs after progressive life-threatening illnesses that had not responded to treatment despite critical care monitoring and supportive care. The 1-year survival rates of 10% to 44% are substantially better than reported outcomes following out-of-hospital pediatric CPR. Almost three quarters of survivors to discharge have good neurologic outcomes.

The largest published reports of in-hospital pediatric cardiac arrests (880 patients and 1005 patients, respectively)

emanate from the American Heart Association's multicenter National Registry of Cardiopulmonary Resuscitation (NRCPR).[11,12] Most of these arrests occurred in children with progressive respiratory insufficiency and/or progressive circulatory shock.[11] These children often had progressive underlying critical illnesses and suffered cardiac arrest despite aggressive critical care monitoring and therapy. Therefore, 95% of these arrests were witnessed and/or monitored, and only 14% occurred on a general pediatric ward. Before the arrest, 57% of these children were mechanically ventilated, 38% had continuous vasopressor infusions, and 29% had continuous direct arterial blood pressure monitoring.

Despite the diverse and complex clinical circumstances leading to their arrests, 52% attained sustained return of spontaneous circulation, 36% survived for 24 hours, and 27% survived to hospital discharge. Outcomes for these children were substantially better than reported outcomes for adults in this registry (adjusted odds ratio, 2.3 [95% CI, 2.0 to 2.7]).[11] Approximately two thirds of the patients had relatively good neurologic outcomes. Interestingly, the better survival rate compared with adults is primarily because of better survival rates among infants and preschool children, presumably in part because their compliant chest walls allow for more effective blood flow during external chest compressions.[13]

Pediatric Out-of-Hospital Arrests

Outcomes following pediatric out-of-hospital arrests are much worse than in-hospital arrests.[4,14-21] Survival to hospital discharge typically occurs in less than 10% of these children, and many have severe neurologic sequelae. Two diseases have especially poor outcomes: traumatic arrests and sudden infant death syndrome (SIDS). Traumatic cardiac arrests typically result from either severe, prolonged hypoxic episodes or exsanguination. SIDS patients are often "long dead" before resuscitation is attempted. In most series of out-of-hospital pediatric cardiac arrests, more than one third of the children have the diagnosis of SIDS. For other pediatric cardiac arrests in the prehospital setting, CPR and advanced life support from EMS providers are typically applied after prolonged periods of profound hypoxia and hypoperfusion of vital organs.

Pediatric Ventricular Fibrillation

Ventricular fibrillation is an uncommon, but not rare, electrocardiographic rhythm during out-of-hospital pediatric cardiac arrests, generally occurring in ~10% of cases.[4,21,30-33] The incidence of VF varies by setting and age. In special circumstances, such as tricyclic antidepressant overdose, cardiomyopathy, postcardiac surgery, and prolonged QT syndromes, VF is a more likely rhythm during cardiac arrest. Another special circumstance, commotio cordis, or mechanically-initiated VF because of relatively low-energy chest wall impact during a narrow window of repolarization, occurs predominantly in children 4 to 16 years old.[34,35] Out-of-hospital VF cardiac arrest is uncommon in infants, but occurs more frequently in children and adolescents. The variance of VF by age was highlighted in a study documenting VF/VT in only 3% of children in cardiac arrest 0 to 8 years old versus 17% of children 8 to 19 years old.[32]

Although the initial ECG rhythms during most pediatric in-hospital cardiac arrests are asystole and pulseless electrical activity (PEA), in approximately one quarter of arrests the rhythms are VF or pulseless VT.[11,12] Among the first 1005 pediatric in-hospital cardiac arrests in the American Heart Association's National Registry of CPR, 10% had an initial rhythm of VF/VT, an additional 15% had subsequent VF/VT (i.e., some time later during the resuscitation efforts), and another 2% had VF/VT but the timing of the arrhythmia was not clear.[12] Therefore, 27% of children with in-hospital cardiac arrests had VF/VT—not an uncommon phenomenon. Even in the setting of progressive respiratory failure and shock with an initial ECG of asystole or PEA, a substantial number of these children developed subsequent VF/VT during CPR. After initial VF/VT, 35% survived to hospital discharge.[12] Surprisingly, the subsequent VF/VT group had worse outcomes than children with asystole/PEA who never developed VF/VT during the resuscitation: 11% survival to discharge with subsequent VF/VT during resuscitation from asystole/PEA versus 27% with asystole/PEA alone.[12] Traditionally, VF and VT have been considered "good" cardiac arrest rhythms, resulting in better outcomes than asystole and PEA. However, these data have resulted in a paradigm shift: outcomes after initial VF/VT are "good," but outcomes after subsequent VF/VT are substantially worse, even when compared with asystole/PEA rhythms.

THE PHASES OF CARDIAC ARREST AND CPR

There are at least four phases of cardiac arrest: (1) pre-arrest, (2) no flow (untreated cardiac arrest), (3) low flow (CPR), and (4) post-resuscitation. Interventions to improve outcome from pediatric cardiac arrest should be targeted to optimize therapies according to the timing, duration, intensity, and "phase" of resuscitation as suggested in Table 20-1. The prearrest phase represents the largest potential opportunity for

Table 20-1
Phases of Cardiac Arrest and Resuscitation

Phase	Interventions
Pre-arrest (Prevention)	Community education regarding child safety Patient monitoring and rapid response teams Recognize and treat respiratory failure and/or shock
No-flow	Minimize interval to BLS and ACLS (organized response) Minimize interval to defibrillation, when indicated
Low-flow (CPR)	PUSH HARD, PUSH FAST Allow full chest wall recoil Minimize interruptions in compressions Avoid overventilation Titrate CPR to optimize coronary perfusion pressure Consider ECMO if standard CPR/ACLS is not promptly successful
Post-resuscitation	Optimize cardiac output and cerebral perfusion Treat arrhythmias, if indicated Avoid hyperthermia, hyperventilation, hyperglycemia Consider induction of post-resuscitation systemic hypothermia

ACLS, advanced cardiac life support; BLS, basic life support; CPR, cardiopulmonary resuscitation; ECMO, extracorporeal membrane oxygenation.

patient survival by preventing pulseless cardiopulmonary arrest. Interventions during the prearrest phase focus on prevention. Infant safety seats and safe driving to prevent traumatic arrests, water safety programs to prevent drowning arrests, medication safety caps to prevent drug poisoning arrests are well known, highly effective efforts to prevent cardiac arrests. Because many pediatric cardiac arrests are due to progressive respiratory failure and shock, the main focus of the Pediatric Advanced Life Support (PALS) course is the early recognition and treatment of respiratory failure and shock in children (i.e., prevention of cardiac arrest in the prearrest phase).[36] Increasingly, medical emergency teams (or rapid response teams) are utilized in hospitals to recognize and treat respiratory failure and shock before cardiac arrests occur.

Interventions during the no-flow phase of untreated pulseless cardiac arrest focus on early recognition of cardiac arrest and prompt initiation of basic and advanced life support. When there is insufficient oxygen delivery to the brain or heart, CPR should be initiated. The goal of effective CPR is to optimize coronary perfusion pressure and blood flow to critical organs during the low-flow phase.[2,3] Basic life support with continuous effective chest compressions is the emphasis in this phase. The focus should be to *PUSH HARD, PUSH FAST, allow full chest wall recoil, minimize interruptions, and don't overventilate.*

The post-resuscitation phase is a high-risk period for brain injury, ventricular arrhythmias, and other reperfusion injuries. Overventilation is frequent and can impede blood return to the thorax during and following CPR.[37,38] Induced hypothermia (32° to 34° C) can improve outcome for comatose adults after resuscitation from out-of-hospital ventricular fibrillation cardiac arrest.[39,40] In addition, myocardial dysfunction and fatal hypotension are common during the post-resuscitation phase.[41-46] Thoughtful attention to management of temperature, glucose, blood pressure, myocardial function, coagulation, and optimal ventilation may improve outcome in this phase.

Interventions During the Low Flow Phase: CPR

AIRWAY AND BREATHING

One of the most common precipitating events for cardiac arrests in children is respiratory insufficiency. Adequate oxygen delivery to meet metabolic demand and removal of carbon dioxide is the goal of initial assisted ventilation. Effective bag-mask ventilation skills remain the cornerstone of providing effective emergency ventilation. Effective ventilation does not necessarily require an endotracheal tube. In one randomized, controlled study of children with out-of-hospital respiratory arrest, children who were treated with bag-mask ventilation did as well as children treated with prehospital endotracheal intubation.[47] During CPR, cardiac output and pulmonary blood flow are approximately 10% to 25% of that during normal sinus rhythm.[3] Consequently, much less ventilation is necessary for adequate gas exchange from the blood traversing the pulmonary circulation during CPR in contrast to normal sinus rhythm with a normal cardiac output. Animal and adult data indicate that overventilation during CPR is common and can substantially compromise venous return and cardiac output because of increased intrathoracic pressure.[37,38] Most concerning, these adverse hemodynamic effects from overventilation during CPR, combined with the interruptions in chest compressions typically necessary to provide airway management, rescue breathing, vascular access, and rhythm analysis, can inadvertently contribute to worse survival outcomes.

CIRCULATION

Basic life support with continuous effective chest compressions is generally the best way to provide circulation during cardiac arrest. Basic life support is often provided poorly or not provided at all.[3,48-53] The most critical elements are to PUSH HARD, PUSH FAST (100 compressions/minute). Because there is no flow without chest compressions, it is important to minimize interruptions in chest compressions. To allow good venous return in the decompression phase of external cardiac massage, it is important to allow full chest wall recoil, and to avoid overventilation. The American Heart Association recommends compressing the chest of an infant or child one third to one half of the total depth of the chest.[3] When the rescuer can reach his/her hands around the infant's chest, the American Hospital Association (AHA) recommends the two thumb-encircling hand technique (Fig. 20-1). For a larger child, the rescuer can use the one-hand or two-hand technique to compress the chest.

The effectiveness of chest compressions can be monitored in several ways. If direct monitoring of arterial pressure is being performed, the aortic relaxation, or diastolic, pressure should be maintained at more than 20 to 30 mm Hg.[54-56] If direct monitoring of arterial and central venous pressure is being performed, the coronary perfusion pressure can be calculated. The coronary arteries are perfused during the relaxation phase of CPR (diastole).[57] The coronary perfusion pressure is the aortic diastolic pressure minus the right atrial diastolic pressure. Data from adults and young animals suggest that maintaining a coronary perfusion pressure of more than 15 to 25 mm Hg is important for effective resuscitation.[55,56]

For most patients, direct arterial and central venous pressure monitoring is unavailable at the time of cardiac arrest. Traditionally, the presence of a palpable pulse during CPR has been used to determine the effectiveness of CPR. Data from

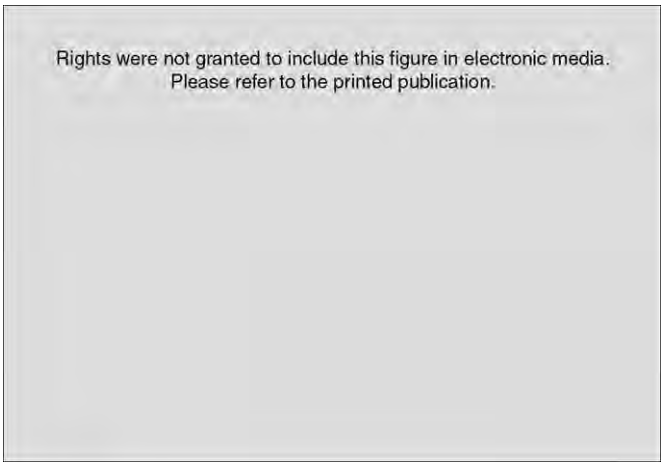

Figure 20-1 Infant CPR using the two thumb-encircling hand technique. (Reprinted with permission from the American Heart Association.)

animal studies and children demonstrate that pulsations may result from retrograde flow in the venous system as well as antegrade flow in the arterial system.[58] Nevertheless, the strength of peripheral pulsations may reflect the force and therefore the effectiveness of chest compressions.

Data from animal models and adult cardiac arrest victims suggest that measurements of end-tidal carbon dioxide (CO_2) are useful predictors of coronary perfusion pressure, cardiac output, and effective resuscitation.[59-63] During the low-flow state of CPR, the major determinant of end-tidal CO_2 level is pulmonary blood flow. Pulmonary blood flow, in turn, reflects the cardiac output produced by chest compressions. When the end-tidal CO_2 concentration is less than 10 mm Hg, CPR is inadequate, and the victim almost never survives.[62,63] End-tidal CO_2 monitoring can also verify appropriate endotracheal tube placement.[64]

Capnometry during CPR after asphyxial cardiac arrest is somewhat different from that after VF. Experimental data suggest that the end-tidal CO_2 value may be very high during the first few breaths after an asphyxial cardiac arrest. During asphyxia, alveolar CO_2 may rise, thereby resulting in high end-tidal CO_2 levels for several breaths.[65] After the first few breaths, capnometry reflects pulmonary blood flow and cardiac output and is a useful monitor of the effectiveness of CPR; however, the administration of sodium bicarbonate during cardiac arrest may spuriously increase the end-tidal CO_2 concentration without reflecting any increase in pulmonary blood flow because of increases in the level of pulmonary venous CO_2.[3]

CIRCULATION: ECMO-CPR

Dalton and colleagues[66] first reported the use of emergency extracorporeal membrane oxygenation (ECMO) during CPR for 11 children who suffered intractable cardiac arrest in their pediatric intensive care unit. Six of these 11 survived to hospital discharge.

More recently, Morris and coworkers reported 66 children who were placed on ECMO during CPR at Children's Hospital of Philadelphia over a 7-year period.[67] The median duration of CPR prior to establishment of ECMO was 50 minutes, and 35% (23 of 66) of these children survived to hospital discharge. It is important to emphasize that these children had brief periods of "no flow," excellent CPR during the "low flow" period, and a well-controlled post-resuscitation phase. Moreover, most of the survivors had reversible cardiac etiologies for their arrests. Many pediatric centers now provide ECMO-CPR for selected patients who fail to respond to initial advanced life support techniques. In addition, there is growing evidence that provision of ECMO in the post-resuscitation phase may also improve outcome from in-hospital cardiac arrests.[68]

VASCULAR ACCESS

Establishing vascular access during pediatric cardiac arrest is difficult, yet necessary, for the administration of medications and fluids.[3] Theoretically, vascular access into a large vein that drains into the superior vena cava is optimal for the delivery of medications during CPR. The lack of valves in the inferior vena cava results in to-and-fro blood flow during external chest compressions. Valves in the superior vena caval system tend to minimize this problem. Therefore, medications infused into the inferior vena caval system can take longer to reach the heart and systemic circulation. In some models, medication administration via the central venous route results in a more rapid onset of action and higher peak concentrations than administration via the peripheral route.[69] Any potential minor benefits of central venous or superior vena caval drainage on medication administration are probably less important than the rapid and safe administration of intravascular medication. Inferior venal caval access via the saphenous vein, tibial bone marrow, or femoral vein may be easier and safer than venous access near the head or neck while ventilation and chest compressions are being provided. Medication administered via the peripheral or femoral vein during CPR should probably be followed by a fluid flush to more rapidly move the medications into the central circulation.[3]

Physicians and prehospital personnel can usually attain intraosseous access for pediatric arrest victims in less than 1 minute.[70,71] Intraosseous vascular access should be strongly considered for any child in cardiac arrest without vascular access, allowing not only medication delivery but also rapid volume infusion when indicated.[3] The technique for intraosseous access is relatively easy and safe. The bone marrow cavity is effectively a noncollapsible vein, even in the presence of shock or cardiac arrest. Although almost any needle can be used, a bone marrow needle with a stylet is recommended to prevent needle obstruction from a core of bony cortex. The proximal tibia, distal femur, and anterior superior iliac spine are all acceptable sites that are easily accessible during resuscitation. The needle should be twisted into, rather than shoved through, the bone marrow. Evidence of successful entry into the bone marrow includes the lack of resistance (or "give") after the needle passes through the cortex, the needle's ability to remain upright without support, aspiration of bone marrow into a syringe, and free flow of the infusion without significant subcutaneous infiltration.[70,71]

Almost any medication that can be administered into a vein can be safely infused into the bone marrow. All medications recommended for pediatric advanced life support can be safely and effectively administered via the intraosseous route. The onset of action of medications and plasma concentrations is similar after intraosseous and peripheral venous administration during CPR.[3,70,71]

Even this relatively safe procedure can result in rare complications. Osteomyelitis, fractures, extravasation of toxic medications (e.g., epinephrine, calcium, sodium bicarbonate), and compartment syndrome with resultant amputation have been described.[3] Microvascular pulmonary fat and bone marrow emboli have been demonstrated but do not appear to be clinically significant.[72]

ACUTE FLUID VOLUME RESUSCITATION

As noted in the "Definition of Pulseless Cardiac Arrest" section, differentiating severe hypoxic-ischemic circulatory shock with poor pulses from the nonpulsatile state of cardiac arrest can be challenging. The initial treatment of choice for the former is rapid intravascular fluid volume resuscitation with 20 mL/kg of isotonic crystalloid (e.g., normal saline or

Ringer's lactate solution).[36] For hypotensive circulatory shock, the 20 mL/kg volume bolus should be provided as rapidly as possible (in less than 5 minutes). The child should be immediately reassessed and a repeat volume bolus should be provided if the circulatory shock has not resolved. In fact, a second volume bolus is nearly always needed for hypotensive circulatory shock (and often a third and fourth volume bolus). If the child has a less severe fluid deficit, volume resuscitation can be provided with a 10 mL/kg isotonic fluid bolus (especially if significant myocardial dysfunction is suspected).

Some experts recommend colloid solution fluid resuscitation (e.g., 5% albumin) rather than crystalloid; however, colloid fluid resuscitation did not improve outcome in adults compared with crystalloid resuscitation in a large randomized controlled trial or in meta-analyses of other smaller studies.*Nevertheless, because of excellent outcomes with the use of 20 mL/kg volume boluses of 5% albumin for children with meningococcemia, some leaders recommend colloid resuscitation for initial treatment of pediatric septic shock.†

Volume resuscitation may also be lifesaving for some children in cardiac arrest. CPR is unlikely to be effective when preload is insufficient (e.g., when septic shock or other hypotensive circulatory shock states progress to cardiac arrest). Importantly, hypotensive shock is the immediate precipitating factor for more than one half of in-hospital cardiac arrests in children.[11] Perhaps there should be greater emphasis on intravascular volume resuscitation during CPR for children in cardiac arrest.

ENDOTRACHEAL MEDICATION ADMINISTRATION

Endotracheal intubation may be easier to obtain than vascular access during pediatric CPR. Lidocaine, epinephrine, atropine, and naloxone (mnemonic: LEAN) are common resuscitation medications that have been successfully administered via the endotracheal tube.[3] On the other hand, sodium bicarbonate and calcium are poorly absorbed and may be very irritating to the airways and lung parenchyma, so they should not be administered via the endotracheal route. Absorption of medications into the circulation after endotracheal administration depends on dispersion over the respiratory mucosa, pulmonary blood flow, and matching of ventilation to perfusion.[73] Droplets of medication that remain on the endotracheal tube obviously do not help the patient's condition. Poor cardiac output with inadequate chest compressions results in inadequate pulmonary blood flow and, therefore, poor delivery of the medication to the heart and systemic circulation. Pulmonary edema, pneumonitis, and airway disease also affect the pharmacokinetics of endotracheally administered medications. The vasoconstrictive effects of epinephrine may limit local pulmonary blood flow and thereby diminish medication uptake and delivery.[74-76]

Case reports and the authors' clinical experiences have indicated that endotracheal administration of epinephrine can be effective and lifesaving.[77,78] However, in animal studies, plasma epinephrine concentrations and physiologic effects vary widely after endotracheal administration.[73,75,79,80] An endotracheal epinephrine dose approximately 10 times higher than that reached during intravenous administration is generally needed to obtain peak plasma concentrations. This higher dose is not without danger. After resuscitation, a prolonged depot effect occurs and may result in profound hypertension and tachycardia. After an asphyxial episode, the extra myocardial oxygen demand resulting from tachycardia and the increased afterload may not be well tolerated. On the other hand, the usual intravenous dose of epinephrine is generally ineffective via the endotracheal tube in asystolic adults.[74]

Based on these data, the AHA recommends that any route of vascular medication administration, including intraosseous or peripheral access, is preferable to endotracheal administration.[3] If, however, epinephrine is to be administered via the endotracheal tube during the resuscitation of children, the suggested initial dosage is 10 times the usual intravenous dose. However, for neonates the recommended endotracheal epinephrine dose is the same as the intravenous dose, 0.1 mL/kg of 1:10,000 solution, because (1) the depot effect can result in prolonged severe hypertension, (2) severe hypertension can lead to intracranial hemorrhage in neonates, (3) most neonatal resuscitations are successful with the present recommendations, and (4) there are limited data regarding the safety or efficacy of high-dose epinephrine via endotracheal tubes in neonates.[3]

MEDICATIONS

Medications commonly used for CPR in children are vasopressors (epinephrine or vasopressin), calcium chloride, sodium bicarbonate, and antiarrhythmics (amiodarone or lidocaine). The doses and indications for these medications are listed in Table 20-2.

Vasopressors

During CPR, epinephrine's α-adrenergic effect on vascular tone is most important.[81,82] The α-adrenergic action increases systemic vascular resistance, increasing diastolic blood pressure, which in turn increases coronary perfusion pressure and blood flow and increases the likelihood of the return of spontaneous circulation (ROSC).[81-83] Epinephrine also increases cerebral blood flow during CPR because peripheral vasoconstriction directs a greater proportion of flow to the cerebral circulation.[84] The β-adrenergic effect increases myocardial contractility and heart rate and relaxes smooth muscle in the skeletal muscle vascular bed and bronchi, although this effect is of less importance. Epinephrine also increases the vigor and intensity of VF, increasing the likelihood of successful defibrillation.

High-dose epinephrine (0.05 to 0.2 mg/kg) improves myocardial and cerebral blood flow during CPR more than standard-dose epinephrine (0.01 to 0.02 mg/kg), and may increase the incidence of initial ROSC.[85-89] Administration of high-dose epinephrine, however, can worsen a patient's

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†Pollard: Arch Dis Child 80:290-296, 1999; Carcillo: Crit Care Med (6):1365-1378, 2002.

Table 20-2
Common CPR Medications

Medication	IV Dose	Indications
Epinephrine	0.1 mL/kg of 1 : 10,000 (0.01 mg/kg) Dose via ETT: 0.1 mL/kg of 1 : 1000 (0.1 mg/kg)	Cardiac arrest: asystole, pulseless arrest; symptomatic bradycardia
Atropine	0.2 mL/kg = 0.02 mg/kg (minimum: 0.1 mg; maximum: 1.0 mg)	Symptomatic bradycardia unresponsive to effective oxygenation, ventilation, and treatment with epinephrine
Calcium chloride 10%	0.2 mL/kg = 20 mg/kg	Hypocalcemia, hyperkalemia, hypermagnesemia, calcium channel blocker toxicity
Sodium bicarbonate	1 mEq/kg = 1 mL/kg of 8.4% solution = 0.5 mL/kg of 4.2% solution	Hyperkalemia, tricyclic antidepressant toxicity, severe metabolic acidosis unresponsive to oxygenation and hyperventilation
Amiodarone	5 mg/kg bolus	Symptomatic VT or ventricular ectopy, VF/pulseless VT unresponsive to defibrillation and epinephrine
Lidocaine	1 mL/kg	Symptomatic VT or ventricular ectopy, VF/pulseless VT unresponsive to defibrillation and epinephrine

ETT, endotracheal tube; VF, ventricular fibrillation; VT, ventricular tachycardia.

post-resuscitation hemodynamic condition with increased myocardial oxygen demand, ventricular ectopy, hypertension, and myocardial necrosis.[90-92] Prospective studies in adults indicate that use of high-dose epinephrine does not improve survival compared with standard-dose epinephrine.[85-89] In addition, a retrospective study in adults suggests higher total epinephrine dose may be associated with a worse neurologic outcome.[93]

Although enthusiasm for the initial use of high-dose epinephrine waned after these studies, high-dose epinephrine was still recommended as a reasonable option if the initial standard dose failed.[36] A randomized, blinded controlled trial of rescue high-dose epinephrine versus standard-dose epinephrine following failed initial standard-dose epinephrine for pediatric in-hospital cardiac arrest demonstrated a worse 24-hour survival in the high-dose epinephrine group (1/27 versus 6/23, $P<0.05$).[94] In particular, high-dose epinephrine seemed to worsen the outcome of patients with asphyxia-precipitated cardiac arrest. High-dose epinephrine is no longer recommended for initial therapy or rescue therapy. Nevertheless, high-dose epinephrine may be considered as an alternative to standard-dose epinephrine in certain special circumstances of refractory pediatric cardiac arrest (e.g., patient on high-dose epinephrine infusion prior to cardiac arrest) and/or when continuous direct arterial blood pressure monitoring allows titration of the epinephrine dosage to diastolic (decompression phase) arterial pressure during CPR.[3]

Vasopressin is a long-acting endogenous hormone that acts at specific receptors to mediate systemic vasoconstriction (V1 receptor) and reabsorption of water in the renal tubule (V2 receptor).[3] In experimental models of cardiac arrest, vasopressin increases blood flow to the heart and brain and improves long-term survival compared to epinephrine. Vasopressin may decrease splanchnic blood flow during and after CPR. In randomized controlled trials of in-hospital and out-of-hospital arrests in adults, vasopressin had comparable efficacy to epinephrine.[95-97] Vasopressin did not improve outcome compared with epinephrine in two large trials. However, a small randomized, blinded controlled trial demonstrated that vasopressin was superior to repeated epinephrine doses in adults after the initial epinephrine dose had failed.[97] A case series of four children who received vasopressin during six prolonged cardiac arrest events suggests that the use of bolus vasopressin may result in return of spontaneous circulation when standard medications have failed.[98] Although vasopressin will not likely replace epinephrine as a first line agent in pediatric cardiac arrest, there are preliminary data to suggest that its use in conjunction with epinephrine in pediatric cardiac arrest deserves further investigation.

Calcium

For in-hospital pediatric cardiac arrests, hypocalcemia is not uncommon. Although calcium administration is recommended only during cardiac arrest for hypocalcemia, hyperkalemia, hypermagnesemia, and calcium channel blocker overdose, it is commonly used for in-hospital pediatric cardiac arrests, especially those occurring postcardiac surgery.[3] The administration of calcium has not been demonstrated to improve outcome in cardiac arrest. Animal

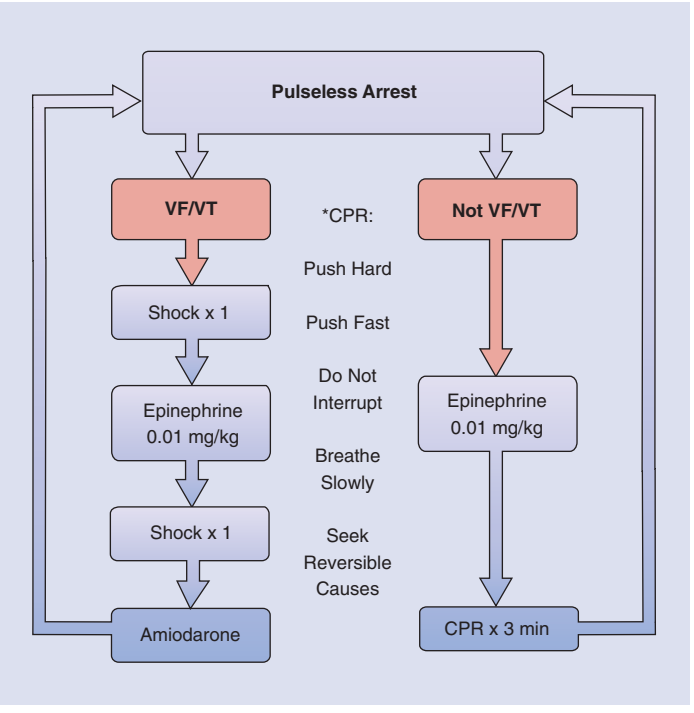

Figure 20-2 A pulseless arrest flow chart.

studies suggest that calcium administration may worsen reperfusion injury.

Buffer Solutions

Cardiac arrest results in lactic acidosis from inadequate organ blood flow and poor oxygenation. Acidosis depresses myocardial function, reduces systemic vascular resistance, and inhibits defibrillation. Nevertheless, the routine use of sodium bicarbonate for a child in cardiac arrest is not recommended.[3] Retrospective clinical series have not demonstrated a beneficial effect of sodium bicarbonate.[99] However, the presence of acidosis may depress the action of catecholamines, so the use of sodium bicarbonate seems rational in an acidemic child who is refractory to catecholamine administration. The administration of sodium bicarbonate is more clearly indicated in the patient with a tricyclic antidepressant overdose, hyperkalemia, hypermagnesemia, or sodium channel blocker poisoning.[3]

The buffering action of bicarbonate occurs when a hydrogen cation and a bicarbonate anion combine to form carbon dioxide and water. If carbon dioxide is not effectively cleared through ventilation, its build-up will counterbalance the buffering effect of bicarbonate. Other side effects with sodium bicarbonate include hypernatremia, hyperosmolarity, and metabolic alkalosis.[3,99] THAM is a non-carbon dioxide generating buffer that can be used during cardiac arrest. Note that excessive alkalosis decreases calcium and potassium concentration and shifts the oxyhemoglobin dissociation curve to the left.

An important practical matter during cardiac arrest is physicochemical medication incompatibility. Frequently the patient has only one venous access site. Administration of bicarbonate can inactivate catecholamines, and more importantly, calcium precipitates when mixed with bicarbonate. Therefore, intravenous tubing must be carefully irrigated before and after infusions of sodium bicarbonate.

Antiarrhythmic Medications: Amiodarone and Lidocaine

Administration of antiarrhythmic medications should not delay administration of a shock for a patient with VF. However, after unsuccessful attempts at electrical defibrillation, medications to increase the effectiveness of defibrillation should be considered. In both pediatric and adult patients, the first administered medication for VF is epinephrine.[2,3] If epinephrine with or without vasopressin and a subsequent repeat attempt to defibrillate are unsuccessful, the antiarrhythmic agents amiodarone or lidocaine should be considered.[2,3]

Lidocaine has been recommended traditionally for shock-resistant VF in adults and children. However, the only antiarrhythmic agent that has been prospectively determined to improve survival to hospital admission in the setting of shock-resistant VF when compared to placebo is amiodarone.[100] Furthermore, patients who received amiodarone for shock-resistant out-of-hospital VF had a higher rate of survival to hospital admission than patients who received lidocaine alone.[101] Neither of these randomized controlled trials included children. There are no published comparisons of antiarrhythmic medications for pediatric refractory VF. Nevertheless, extrapolation of the adult studies has led to the recommendation of using either amiodarone or lidocaine for shock-resistant VF in children.[2,3]

CONCLUSIONS

Outcomes from pediatric cardiac arrests were once thought to be dismal. Prompt recognition, immediate provision of excellent CPR (PUSH HARD, PUSH FAST, minimize interruptions, allow full chest wall recoil, and avoid overventilation), defibrillation of shockable rhythms, appropriate advanced life support, and excellent post-resuscitation care can result in good outcomes. More recent data indicate that ~27% of children survive to hospital discharge after in-hospital cardiac arrests.

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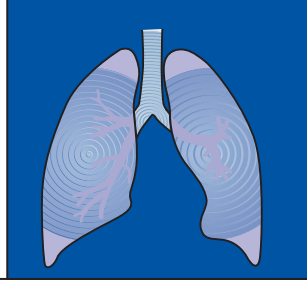

CHAPTER 21 Lung Transplantation

Trevor J. Williams*, Glen Westall, and Gregory I. Snell

TEACHING POINTS

- Donor availability is the major limiting factor to lung transplantation, thus only a small proportion of those who may benefit will be transplanted.
- Cytomegalovirus and Epstein-Barr virus (CMV/EBV) serologic mismatch is the rule in pediatric lung transplantation.
- The small airway caliber presents technical challenges at the time of surgery and follow-up bronchoscopy.
- Consent (and commitment) to the procedure of parents and child is crucial because compliance to the complex post-transplant regimen is a major issue.
- The experience can be emotionally charged and arduous but the final outcome well worthwhile.

Transplantation is one of the true miracles of modern medicine. Although the concept of exchanging severely damaged body parts dates back at least 1500 years, the 20th century saw the fulfillment of this idea. Transplantation for end-stage pulmonary and pulmonary vascular disease in children remains one of the most complex, demanding forms of solid organ transplantation. As a consequence, very few centers around the world perform pediatric lung transplantation in any substantial number. Specific issues include obtaining informed consent, compliance with complex treatment regimens, technical problems due to small size, the developing and often brisk immunologic response as well as a lack of preformed immunity to important DNA viral infections. Those factors all combine to make pediatric lung transplantation both extremely challenging and ultimately very rewarding (see Teaching Points).

HISTORY

On his return from World War II, Vladimir Demikhov, a Russian surgeon and physiologist, performed a remarkable series of experiments in the second half of the 1940s. Demikhov performed canine auto- and allogenic transplantation of heart, heart/lung, and single lung, demonstrating the technical feasibility of transplanting these organs.[1,2] Of particular note was that these procedures were performed prior to the availability of cardiopulmonary bypass. Furthermore, animals receiving heart/lung transplants died rapidly from acute respiratory failure believed to be a result of bilateral pulmonary denervation.

Demikhov's findings resulted in the first attempts at human lung transplantation utilizing a single lung transplant technique. In 1963 Hardy[3] performed a single lung transplant in an adult with obstructive lung disease and lung cancer thought to be unresectable owing to physiologic considerations. Although the patient died of sepsis and anastomotic breakdown some 18 days following transplant, the ability of the transplanted lung to participate in gas exchange was confirmed. Over the next 2 decades, approximately 40 further unsuccessful attempts at lung transplantation were made.

Important studies by the Stanford University group confirmed that in primates, bilateral denervation of the lungs did not result in the development of acute hypercapnic respiratory failure.[4] This set the stage for the first attempt at heart/lung transplantation, which was performed by Denton Cooley and colleagues at the Texas Heart Institute[5] (performed on a child) in 1968. This appears to be the first (albeit unsuccessful) attempt at lung transplantation in a child.

The first long-term survivors of any form of lung transplantation were the culmination of decades of work by the Stanford University group led by Bruce Reitz. In 1980, this group reported extended survival of primates receiving heart/lung auto- and allo-heart/lung transplantation.[6] This paralleled the meticulous work under the leadership of Norman Shumway to develop the techniques now used in heart transplantation.

The Stanford University group reported long-term survival in two patients with pulmonary vascular disease receiving heart/lung transplantation in the *New England Journal of Medicine* in 1982.[7] This landmark report began the era of modern lung transplantation. The success was based on a decade or more of meticulous basic and applied research, the newly available immunosuppressive drug cyclosporine A, and a better understanding as to what represented a suitable candidate for lung transplantation.

Heart/lung transplantation can be applied to most patients with severe pulmonary or pulmonary vascular disease. The rapid evolution of cardiac transplant programs—as well as the concern that in these combined organ transplants the likelihood of rejection of one organ would be significantly

*Financial support provided by Margaret Pratt Heart and Lung Transplant Research Trust, Ronald MacDonald House Charities, and Bennalong Foundation.

increased—led other groups, particularly the Toronto Lung Transplant group, to try to develop techniques of isolated lung transplantation.

Lung transplantation was unusual in that not all major vascular structures were routinely re-anastomosed. The bronchial circulation, providing blood supply to the large intrathoracic airways down to terminal bronchioles, was not re-anastomosed, and grave concerns for the viability of the bronchus below the anastomosis were raised.[8] This did not appear to be a problem in heart/lung transplantation where collaterals from the coronary circulation and posterior pericardium meant that anastomotic breakdown was a rare phenomenon.

Successful, isolated single lung transplant was first performed by the Toronto Lung Transplant group in 1983.[9] The patient had idiopathic pulmonary fibrosis and ultimately lived more than 6 years post transplant. The complete avoidance of corticosteroids pre- and early postoperatively, as well as wrapping of the bronchial anastomosis with a pedicle of greater omentum (bronchial omentopexy) was performed with the intention of reducing or preventing bronchial anastomotic breakdown. Initially, single lung transplantation was performed almost exclusively for patients with pulmonary fibrosis, although subsequently patients with severe pulmonary hypertension—both primary and secondary to intracardiac defects—have received single lung transplantation. In 1989, the first single lung transplant for emphysema was performed,[10,11] disproving concern that overwhelming hyperinflation of the native lung would make this procedure impossible. The first successful pediatric isolated single lung transplant was performed in a 16-year-old with familial pulmonary fibrosis in 1987.[12]

Toward the end of the 1980s, the first reports of the successful application of heart/lung transplantation in the pediatric age group,[13] particularly in patients with cystic fibrosis,[14-16] appeared. After reporting the development of an appropriate operative technique,[17] the Toronto Lung Transplant group reported the first successful double lung transplant procedure[18] in 1988. Initially this procedure was performed as an en bloc procedure with a tracheal anastomosis. This approach was associated with a very high mortality because of tracheal anastomotic breakdown.[19] Working in parallel, the Toronto group, St. Louis, and San Antonio (Texas) Lung Transplant Programs modified the procedure to the presently utilized bilateral sequential lung transplant.[20] This procedure is performed through a horizontal clam shell incision typically running below the fifth rib and transecting the sternum. One lung is transplanted with the patient generally supported on their remaining lung without the requirement of cardiopulmonary bypass.[21] Subsequently the patient is supported on the new transplanted lung allowing transplantation of the second lung—again often without the requirement for cardiopulmonary bypass.

Further improvements in the technique of bronchial anastomosis including telescoping[22] have led to a dramatic reduction in airway anastomotic complications. This is despite now almost universal pre- and perioperative corticosteroid use and discontinuation of the use of omentopexy. Worldwide, bilateral sequential lung transplantation is the most common form of double lung replacement, although some groups have continued to utilize the en bloc technique in combination with revascularization of the bronchial circulation using an internal mammary artery pedicle.[23,24]

By the early 1990s, there had been a substantial increase in the number of lung transplants performed worldwide, with more than 500 procedures having been performed. However, the International Society for Heart and Lung Transplantation/United Network of Organ Sharing (ISHLT/UNOS) Paediatric Lung Transplant Registry noted still only 30 U.S. pediatric transplants in total by the end of 1991.[25] Nevertheless, particularly in countries where a time priority organ allocation system (first come, first served system) was the system of organ allocations, children and young adults with rapidly progressive pulmonary diseases were dying without reaching a position on waiting lists where they would be realistically transplanted.

Vaughan Starnes at the University of Southern California developed a technique of utilizing the lobe from a live donor (initially a close relative) to allow transplantation, particularly of children and young adults.[26,27] The first reported successful transplant was a 12-year-old girl with bronchopulmonary dysplasia receiving a lobar transplant from her mother.[28] This procedure has now evolved to a bilateral procedure using the right lower lobe and the left lower lobe from two living donors so that bilateral transplantation can be performed. This procedure is most commonly performed for young children and adults with cystic fibrosis. Initially the donors were first-degree relatives, although more recently unrelated lobar donors have been used.[29]

In patients, particularly with cystic fibrosis, severe lung disease and end-stage liver disease occasionally coexist. Successful transplantation using en bloc heart/lung and liver or bilateral lung/liver transplants have been more recently reported.[30]

PATIENT SELECTION

Presently, the great majority of heart/lung and isolated lung transplants are performed using donors who have sustained irreversible and complete cessation of brain and/or brain stem function (brain death). Their vital organs remain ventilated and perfused because of continued mechanical ventilation and circulatory support. This is an unusual circumstance and the number of potential donors remains substantially less than the number of potential recipients.

The objective of the assessment process is, thus, not only to identify patients that might benefit from transplantation, but also to assess those who realistically will obtain a durable high quality outcome. The transplant process is onerous to the recipient and extended family and thus an assessment of the likelihood of a good outcome is an important part of the assessment process. Units vary as to precise details of their assessment process. Nevertheless, most programs have developed a process of evaluation of potential recipients that has several key features in common (Fig. 21-1). These features include an initial screening process and up-front discussion to make sure there are no absolute contraindications to lung transplantation. Integral to the process is the recognition that lung transplantation should be the last option after all other suitable treatment options have been considered. Where there are no absolute contraindications, then more detailed evaluation, typically as an inpatient, occurs. Both the

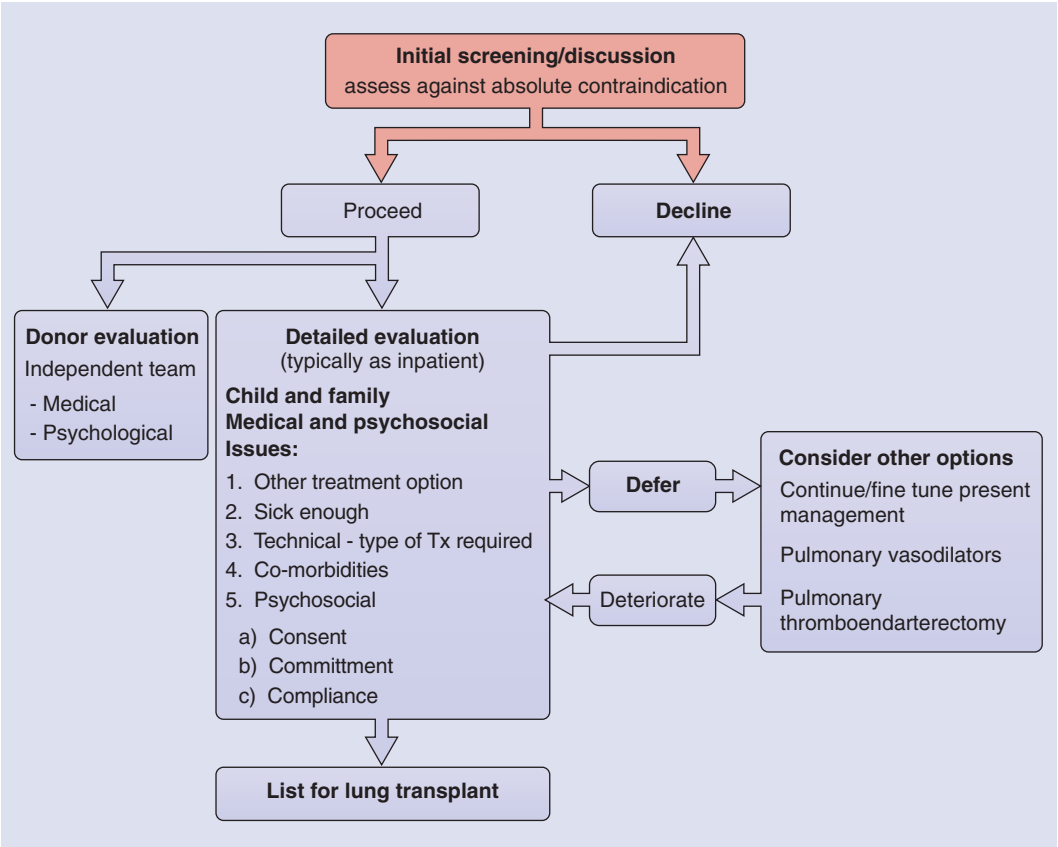

Figure 21-1 A general schema adopted by most programs outlining the process of initial screening and evaluation of potential lung transplant recipients.

child and family are evaluated as part of this process. The evaluation would typically occur with both child and family together but also with periods of separate discussion and evaluation.

The key issues that need to be addressed are the availability of other suitable treatment options; whether the patient is sick enough to warrant the risks of transplantation; technical aspects of the transplantation including which transplant procedure is most suitable; detection and evaluation of comorbidities, and detailed psychosocial evaluation of child and family to resolve issues of informed consent, commitment to the transplant procedure, and ability to comply with a complex treatment regimen.

It is evident that such an important and potentially emotionally charged decision should not be made by a single individual. It is normal practice for the details of this formal evaluation to be presented to a multidisciplinary assessment team for a final determination with respect to suitability for transplantation.

Broadly, however, patients are selected for transplantation on two grounds (Table 21-1). First, suitability may be on prognostic grounds. Lung transplantation is offered for patients with end-stage pulmonary or pulmonary vascular disease where survival is enhanced by transplantation and typically median survival is anticipated to be less than 2 years. Some patients with very poor quality of life may also be offered transplantation in the absence of a clear prognostic advantage. Those offered transplantation, however, are generally New York Heart Association Functional Class III or IV.

There continues to be evolution as to what are regarded as contraindications to lung transplantation. Generally accepted absolute contraindications[31,32] to lung transplantation are shown in Table 21-2. Important contraindications include malignancy (unless in complete remission for 5 years, the exception being non-melanotic skin cancers), serious incurable infection (e.g., HIV, which is almost universally regarded as an absolute contraindication, but in the antiretroviral era lung transplantation for pulmonary arterial hypertension may enhance prognosis for the individual). Other serious systemic illnesses and major psychiatric illness (such as uncontrolled psychosis or substance addiction) are regarded as absolute contraindications. More difficult are patients with multiple relative contraindications that would lead the assessment team to believe the likelihood of a sustained period of enhanced quality of life after transplantation

Table 21-1
General Criteria for Lung Transplantation

Prognosis	Quality of Life
End stage disease (pulmonary & pulmonary vascular) No suitable alternative treatments <2 Year median survival	NYHA Functional Class III-IV

Table 21-2
Contraindications to Lung Transplantation[31,32]

Absolute
Uncontrolled malignancy
Uncontrolled infection
- HIV
- Hepatitis B (HepBsAg +ve)
- Resistant *Burkholderia cepacia* (especially *Burkholderia cenocepacia*)
- Pan resistant organisms (especially if in vivo resistant)

Other serious systemic illness
- Liver failure
- Severe renal disease
- Other

Psychosis
Substance abuse/addiction

Relative
Previous surgery
- Cardiac repair
- Pleurectomy/pleurodesis

Infection with
- Hepatitis C
- Fungal species (especially *Aspergillus* spp.)
- Atypical mycobacteria

Comorbidities
- Chronic liver disease
- Renal impairment
- Other

Psychosocial
- Poor support
- Lack of commitment
- Demonstrated poor compliance

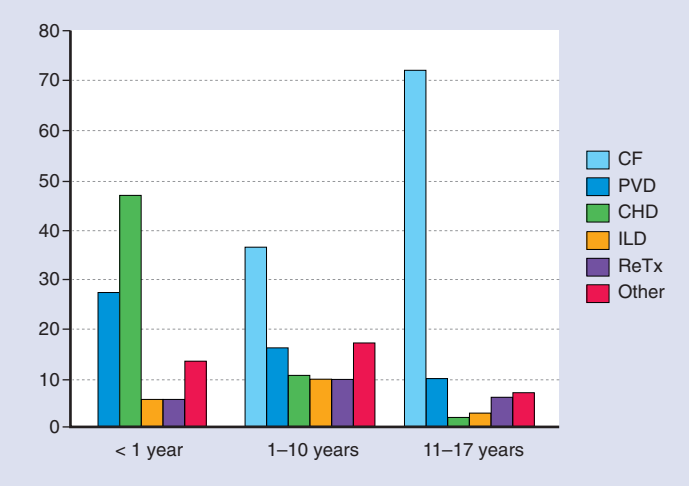

Figure 21-2 Indication for pediatric lung transplantation by recipient age. In the neonatal age group congenital heart disease is the predominant indication for lung transplantation; thereafter, cystic fibrosis is the most common indication. CF, cystic fibrosis; CHD, congenital heart disease; ILD, interstitial lung disease; PVD, pulmonary vascular disease; ReTx-repeat transplantation.

was low. Factors that would be considered include previous surgery (particularly pleurectomy or pleurodesis) but also complex cardiac repairs and infections with significant pathogens that are difficult to control post-transplant (see Table 21-2). Of particular note are *Burkholderia cepacia*,[33] atypical mycobacteria (e.g., *Mycobacterium abscessus*)[34] and fungi (such as *Aspergillus* spp.) which are of considerable concern, but colonization would not be regarded universally as a contraindication to lung transplantation. In vitro and in vivo resistance to antibiotics would be of great concern to the transplant assessment team. Other comorbidities such as chronic liver disease, renal impairment, and psychosocial aspects where there is demonstrably poor support, lack of commitment to transplantation, or demonstrably poor compliance would be considered as relative contraindications. In pediatric recipients, it is often these psychosocial aspects that require the greatest care and consideration.

The age distribution of pediatric lung transplantation is bimodal with one peak at <1 year of age and a second much larger peak at 17 years of age.[35] Each year 60 to 80 pediatric lung transplants (recipient age <18 years) from approximately 25 centers worldwide are reported to the ISHLT/UNOS international registry (compared to a yearly adult lung transplant activity of 1500 to 1600). The most common indication for lung transplantation is cystic fibrosis, which in the 11- to 17-year age group accounts for 72% of lung transplants; other indications include pulmonary vascular disease (10%) and re-transplants (6%). In the neonatal age group (<1 year old), congenital heart disease (47%) and pulmonary vascular diseases (27%) are the most common indications for lung transplantation (Fig. 21-2).

LUNG TRANSPLANT DONORS

At the outset of human lung transplantation, a very conservative approach to donor suitability was developed. In part, this came out of concerns for the cardiac allograft in heart/lung transplantation[36,37] Age (younger than 55 years), nonsmoking status, absence of history of respiratory disease, a normal chest radiograph, minimal airway secretions bronchoscopically, and a PaO_2 greater than 300 mm Hg on 100% FIO_2 and 5 cm of PEEP have conventionally been the organ-specific criteria for donor suitability. Other more general criteria for organ donation must also be fulfilled, including establishment of brain death according to the requirements of the local jurisdiction, consent from the appropriate authority (e.g., the coroner), no identifiable risk factors for serious viral infections (including hepatitis B and HIV infection) and absence of a history of malignancy, have formed part of the general donor suitability criteria. More recently this conservative approach has been progressively challenged by the use of so-called "marginal" donors.[38-40] Specific factors such as long ischemic time,[41] donor history of asthma,[42] and moderate smoking history,[43] have been investigated and found to still be compatible with good recipient outcome. It is now increasingly understood that previously defined marginal or unacceptable donors can be successfully utilized in lung transplantation.[44]

The recognition that the lungs are more resilient to prolonged periods of warm ischemia[45-47] has led to the development of lung transplantation using so-called non-beating-heart donors or donation after cardiac death. In an important recent report from Steen and coworkers from Sweden[48] successful lung transplantation was performed after a period of 4 hours of circulatory arrest, using topical cooling of the lungs through intercostal catheters inserted 2 hours after complete circulatory arrest. This raises the prospect of much more extensive use of donation after cardiac death for lung transplantation with a significant increase in rates of lung transplantation worldwide.

Programs using live donor lobar transplantation have developed protocols for detailed evaluation of the potential donors. Overall, live (lobar) donor lung transplantation accounts for 12% of pediatric lung transplantation (88% are cadaveric donors)—with the youngest recipient in the last 8 years being 7 years old.[35] Lobectomy carries a significant morbidity and mortality and so medical, surgical, and psychological evaluation are crucial in detailed evaluation of a potential live donor. Generally, a team independent of the team assessing the recipient would make a determination of the suitability of such donors.

The allocation system for organs varies quite substantially from country to country. Broadly, systems are based on time priority (a first-come, first-served approach utilized until recently in the United States) or systems based on clinical urgency and utility (as is reported in Australia), but with significant overlap in other places. The basic donor-to-recipient matching is determined by ABO and size compatibilities. The use of donor-predicted total lung capacity (TLC), recipient-predicted and measured TLC, height/weight, chest circumference, and chest radiograph-derived measurements from donor and recipient are all used in various combinations by individual programs. Generally, multiple measures are used, particularly if relying on predictive equations to determine predicted TLC in children. Where possible, matching for CMV and EBV serostatus is undertaken (although often not achievable in children). Many units routinely perform lymphocytotoxic antibody cross, matches to detect preexisting antibodies to HLA-class 1 and 2 antigens. HLA matching as performed for renal transplantation is generally not practical.

The Lung Transplant Procedure

Heart/lung, single lung, and bilateral lung transplantation have all been extensively used in pediatric recipients (Table 21-3). The trend in recent years, however,[35] has been for most pediatric recipients to receive bilateral lung transplantation—although some surgeons prefer for heart/lung transplantation to try to avoid the difficult problem of anastomotic complications in the small pediatric recipient. Particularly in the United States and Japan, live-donor lobar transplantation has also been quite extensively applied in the pediatric age range.

The time constraints around donor organ procurement often mean the patient spends no more than 1 to 2 hours in hospital before going to the operating room. Thus the patient and family need to be well prepared in advance. After arrival in the operating theater, the patient will be prepared by the anesthetic team for the surgery. This will usually include insertion of an intravenous line and epidural catheter. Once anesthetized, a central line, pulmonary artery catheter, urinary catheter, and arterial line can be inserted.

The bilateral sequential lung transplant procedure is performed through a clam shell incision which starts from the axilla, runs under the fifth or sixth intercostal space, transecting the sternum and extending along the fifth or sixth intercostal space to the contralateral axilla. This incision allows good access to the apices of the lung and appears to be well suited—particularly for transplantation of patients with cystic fibrosis.[49] Dissection of the lung is usually performed prior to initiating cardiopulmonary bypass to minimize bleeding complications. The first lung transplanted is generally the lung deemed to be most severely affected as judged on quantitated ventilation perfusion scan. Single lung ventilation is established either with a double lumen tube or bronchial blocker and the pulmonary artery is temporarily clamped to assess whether the recipient is sustainable on single lung ventilation. If hypoxia or cardiovascular instability occurs, then cardiopulmonary bypass would be used to support the recipient through the procedure. Once the appropriate anastomoses are performed, the clamps are released and perfusion to the organ is reestablished. After a period of stability, attention is switched to the contralateral lung, which is then excluded from ventilation; the pulmonary artery is then clamped and assessment is made as to whether the patient can be supported on the newly transplanted lung. Again a decision about the use of cardiopulmonary bypass will need to be made and the implantation of the second lung will then proceed. At the end of the operation at least two large drains are placed into each pleural space and the incision is closed with wiring of the ribs and sternum.

Table 21-3
Lung Transplant Options in Pediatrics

	Heart/Lung Transplant	Bilateral Lung Transplant	Single Lung Transplant	Living Donor Lobar Transplant
Potential Indication	All	All except: Severe irreversible coexisting cardiac disease	All nonseptic lung disease	All except: Severe irreversible coexisting cardiac disease
Common Indications	Pulmonary vascular disease Congenital heart disease with pulmonary hypertension	Cystic fibrosis Pulmonary vascular disease Interstitial lung disease	Rarely used in pediatrics. Interstitial lung disease	Cystic fibrosis Many rare indications
Anastomoses	Aortic Right atrial or caval Tracheal	Bilateral pulmonary arterial Left atrial Bilateral bronchial	Unilateral pulmonary arterial Left atrial bronchial	Lobar artery to pulmonary artery Lobar pulmonary vein to pulmonary vein Lobar bronchus to main bronchial
Survival (Pediatric/Adult)				
1 yr	64/62	77/76	54/76	85
5 yr	39/43	47/52	27/45	NA
Comment	Still performed where heart-lung allografts available	Most commonly performed procedure in pediatrics	Now infrequently performed	Performed particularly in U.S. and Japan

Heart/lung transplantation necessitates cardiopulmonary bypass in all recipients. Efficiency of organ utilization can be maintained by using the heart/lung transplant recipient's heart in a second recipient, the so-called heart/lung domino procedure.[50] The live donor lobar transplant procedure is generally performed using cardiopulmonary bypass and requires more difficult anastomoses between the lobar airway, artery, and vein with the main bronchial and vascular trunk on the appropriate side.

Crucial to the success of these procedures are an experienced surgical team and anesthetic team working in close cooperation with the perfusion team running cardiopulmonary bypass as required. The transplant procedure is coordinated with the donor procedure to try to minimize the period of cold ischemia. Generally cold ischemic times of less than 6 hours have been regarded as acceptable.[36]

Recipient Management

PREOPERATIVE MANAGEMENT

Once listed for transplantation, the key objectives of management are:

1. Survival through to transplantation.
2. Maintaining physical condition including optimization of weight, maintenance of physical activity, monitoring for the development of comorbidities (e.g., osteoporosis, colonization with resistant organisms).
3. Continuing to inform and educate the patient and family as to the ongoing management of the lung transplant recipient.
4. Continuing to reevaluate the patient and—if rapidly deteriorating—discussion should be undertaken addressing issues including the use of marginal or nonconventional donors.

This can be an extremely difficult and complicated time. Substantial psychosocial support is often required because the normal approach to palliative care may become inappropriate in a patient awaiting lung transplantation.

EARLY POSTOPERATIVE CARE

All patients following transplantation will be sent to the intensive care unit (ICU). The phases of postoperative management include:

- Intensive care management
- Early postoperative management
- Rehabilitation
- Long-term care of the transplant recipient

These are not mutually exclusive periods of care. In patients with severe early graft dysfunction rehabilitation may start while ventilated in the ICU.

The principal objectives of intensive care management are ventilatory support through to weaning and extubation and circulatory support—generally with an objective of keeping the recipient dry,[51] using inotropes where needed to support the circulation. Fluid management can be particularly difficult because over-generous fluid resuscitation can exacerbate primary graft dysfunction pulmonary edema[52]; conversely, hypovolemia can be associated with poor cardiac output, renal hypoperfusion, and potentially renal failure.

The most common early problem is primary graft dysfunction–related pulmonary edema which typically starts within hours of transplantation and generally reaches its peak 48 hours post-transplant.[52] If severe, advanced strategies of mechanical ventilation or support may be required, including the use of high-frequency ventilation and even periods of support using extracorporeal membrane oxygenation (ECMO).[53] In single lung transplant recipients with severe primary graft dysfunction (particularly in single lung transplantation for obstructive lung disease) differential lung ventilation through a double lumen endotracheal tube can be lifesaving—this is a rare problem in pediatric lung transplantation.

Immunosuppression can generally be discussed in three phases: induction, maintenance, and augmentation (Table 21-4). Induction therapy typically includes a calcineurin antagonist (cyclosporine A or tacrolimus) and an antiproliferative agent (mycophenolate mofetil/mycophenolate sodium, or azathioprine) as a loading dose preoperatively. Intra- and perioperatively, high-dose intravenous corticosteroids (methylprednisolone) are given, with many programs also using antilymphocyte globulins or monoclonal antibodies directed against interleukin-2 receptor (e.g., daclizumab or basiliximab). Maintenance immunosuppression is progressively introduced in the hours post-transplant. This is typically a three-drug regimen using a calcineurin antagonist (cyclosporine A or tacrolimus), an antiproliferative agent (mycophenolate mofetil/mycophenolate sodium, or azathioprine) and a corticosteroid (methylprednisolone, prednisolone, or prednisone) in a slowly reducing dose. Tacrolimus, mycophenolate mofetil, and prednisolone are the most common agents for maintenance of immunosuppression in pediatrics.[35] The more important side effects are associated with the calcineurin antagonist, and in the intensive care setting include progressive renal impairment, abnormalities of liver function tests, and neurologic complications—includ-

Table 21-4
Three Phases of Lung Transplant Immunosuppression

Induction	***Typical***	***Alternative***
	Premedication Single oral dose cyclosporine A or tacrolimus Single oral dose azathioprine/ mycophenolate High dose methylprednisolone (IV) IL2 receptor antagonist (IV)	Antilymphocyte globulin (IV) (e.g., ALG, ATGAM,OKT3)
Maintenance	***Typical***	***Alternative***
	Cyclosporine A or tacrolimus (IV then oral) AND Azathioprine or mycophenolate (IV then oral) AND (Methyl)prednisolone or prednisone (IV then oral)	Rapamycin or everolimus (oral) Cyclophosphamide or methotrexate (oral)
Augmentation	***Typical***	***Alternative***
	Methylprednisolone (IV) ALG, ATGAM,OKT3 (IV) Plus Optimize/augment baseline	Total lymphoid irradiation (TLI)

ing seizures[54] and also the rare, but occasionally rapidly fatal, progressive multifocal leukoencephalopathy.[55]

Decisions need to be made early regarding the use of antimicrobial prophylaxis. These will include antibacterial agents that will be targeted by an understanding of recipient infections pre-transplant, donor-acquired infections, and also potentially hospital-acquired organisms. Antiviral agents will be used extensively to prevent primary infection or reactivation of herpes viruses, particularly CMV/EBV. Pediatric lung transplantation is associated with higher rates of primary CMV mismatch[56] as well as high rates of Epstein-Barr–related lymphoproliferative disease.[57,58] Thus an aggressive approach to DNA virus prophylaxis is undertaken.

The requirement for prolonged ventilation in the ICU is usually associated with substantial worsening of early survival—typically because of the subsequent development of gram-negative or nosocomial ventilator-associated infection in the allograft.

Most patients, however, have good early graft function and can typically be extubated within 24 to 48 hours after transplantation. At the time of extubation, good pain relief is essential. The use of epidural analgesia has dramatically improved pain control without the substantial side effects of high-dose narcotics. Although nonsteroidal anti-inflammatories would be a useful adjunct to the pain relief regimen, these are generally contraindicated because of their substantial synergistic effect with calcineurin antagonists causing deterioration in renal function.

EARLY POSTOPERATIVE RECOVERY

Once extubated and clinically stable, patients can be moved to the general ward. Progressively, the arterial line, intercostal catheters, pulmonary artery catheter, and central venous line can be removed depending on clinical need. Typically, the epidural catheter is left in situ until 5 to 7 days post-transplant—at which time a combination of oral analgesia and intravenous narcotic including patient-controlled analgesia (PCA), can be effectively substituted. Early mobilization at this stage is encouraged within the limitations of the intercostal catheters. Patients would typically be capable of sitting on the side of the bed and transferring to a bedside chair. Progressively with removal of catheters and drain tubes further mobilization can be effected. Patients are encouraged to deep breathe and cough regularly. The denervated airways of a lung transplant recipient render the patient often unaware of accumulation of secretions in the transplanted lung. With the removal of the epidural catheter, the urinary catheter can then typically be removed.

Within the first postoperative week, the objective is typically to reach target therapeutic blood levels for the calcineurin antagonist immunosuppressive agent. Regular monitoring of bloods is often required. This has conventionally been based on predose (C_0) levels; however, recently a strategy to monitor levels 2 hours (C_2) post-dose has been adopted by some programs. This single measure best reflects the area under the curve in formal pharmacokinetic studies,[59,60] although it is less reliable in recipients with cystic fibrosis. Young patients often have intravenous access devices available (including Infusaports) which may facilitate both intravenous infusion and venesection. Early consideration of implanting a device capable of both infusion and regular venesection (e.g., a Hickman-type catheter) should be undertaken to prevent venous access being an impediment to ongoing management.

Rehabilitation

Rehabilitation of the patient should commence as soon as is practical. Severe lung disease is associated with marked structural alteration in skeletal muscle.[61-63] These changes are exacerbated by high-dose corticosteroids and the effects of calcineurin antagonist on skeletal muscle mitochondrial function.[64,65] To prevent further deterioration in functional capacity, weight bearing and ambulation is undertaken as soon as possible. The ultimate objective of this phase of therapy is to have a patient and family fully conversant with the requirements for continued rehabilitation and the drug regimen required in the long term as well as the monitoring requirements.

ONGOING MONITORING

Once discharged from hospital, patients are typically continued in supervised rehabilitation for a further 6 to 8 weeks. Regular visits and regular monitoring of their immunosuppression is required. Monitoring of the allograft through regular lung function tests and infrequent but regular bronchoscopy (with lavage and/or transbronchial biopsy) forms an integral part of patient follow-up in most transplant centers. By 3 months, most patients have improved to the point that they are capable of returning to normal activities.

OUTCOME

Survival

There is often a perception that survival in pediatric lung transplantation is inferior to that of adult lung transplantation. The International Society for Heart and Lung Transplant—United Network of Organ Sharing (ISHLT/UNOS) registry provides regular reports (regularly updated on www.ishlt.org) on the outcome for heart/lung transplantation, bilateral lung transplantation, and single lung transplantation in adults and pediatric patients.[35,66] For heart/lung transplantation, the 1-year survival is 64% in pediatric patients and 62% in adults, with a 5-year survival of 39% in pediatric patients and 43% in adults. Bilateral lung transplantation has a 77% 1-year survival in pediatric patients and 76% 1-year survival in adults, with 5-year survival of 47% and 52%, respectively. Survival in single lung transplant is inferior in pediatric patients, with a 54% 1-year survival compared to 76% 1-year survival in adults and 5-year survival of 27% in pediatric patients and 45% in adults. These poor results in single lung transplantation in pediatric patients are responsible for a substantial reduction over the years in the number of single lung transplants performed in this population.

However, it is difficult to accurately compare the figures because the mix of transplant indications is different when comparing adults and pediatric patients. From the ISHLT/UNOS registry a comparison between adult CF bilateral lung transplant recipients and pediatric bilateral lung transplant recipients (all indications, but largely CF) shows poorer survival in the pediatric group (Fig. 21-3).

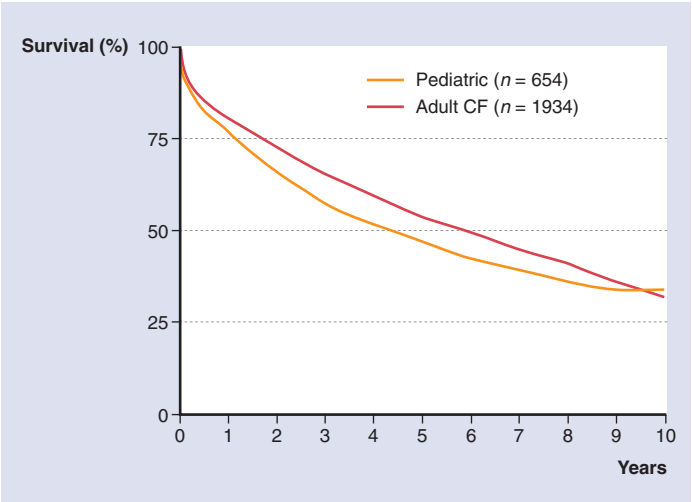

Figure 21-3 Survival following bilateral lung transplantation comparing adult cystic fibrosis (CF) bilateral recipients to all pediatric bilateral lung transplant recipients (72% of whom had cystic fibrosis). The survival is similar in both groups. Data derived from ISHLT/UNOS registry data at www.ishlt.com/, accessed December 2005.

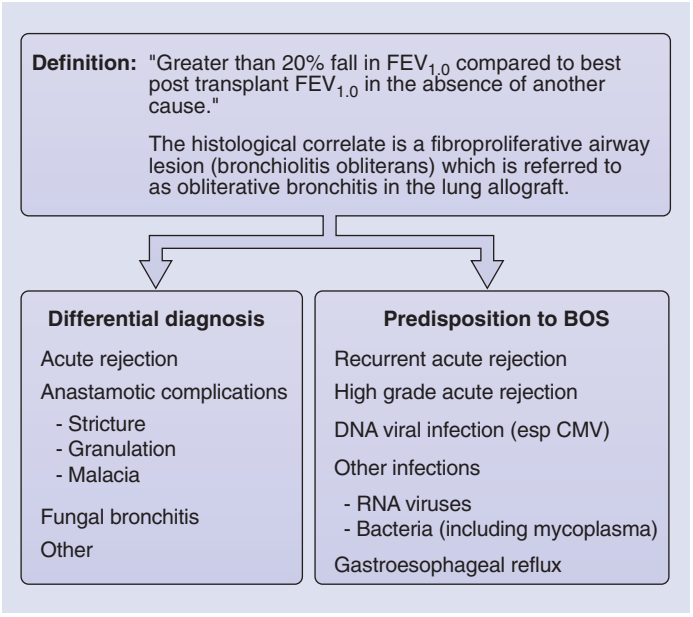

Figure 21-4 Definition, predisposing factors, and important differential diagnoses for bronchiolitis obliterans syndrome (BOS).

Comprehensive 5-year data for live donor lobar transplantation are not available at present. In pediatric patients Starnes and colleagues reported[67] 85% 1-year and 77% 2-year survival for live donor lobar transplantation. Date and colleagues reported a very impressive 100% survival in 30 patients with 1 to 66 months of follow-up following live donor lobar transplantation.[68]

Lung Function

Lung function tests have been used extensively to monitor graft function following lung transplantation. Deterioration in vital capacity or FEV_1 greater than 10% is used as a marker of significant complication[69] which requires detailed evaluation. A 20% fall in FEV_1 from best post-transplant in the absence of a clear cause is used to define established bronchiolitis obliterans syndrome (BOS)[70]—although this is graded BOS 1 to BOS 3 based on the magnitude of FEV_1 fall. More recently patients with >10% fall in FEV_1 without other identifiable cause are designated as "potential" BOS (BOS-op) to reflect the need for careful evaluation earlier in the evolution of BOS.

Patients with heart/lung transplantation and bilateral lung transplantation typically have a persistent mild restrictive ventilatory defect following lung transplantation. Interestingly, this can continue to slowly improve up to 18 months post-transplant.[71,72]

Diffusing capacity is also slightly reduced, even when corrected for the reduced lung volume and the slightly low hemoglobin seen after transplant.[71,72] Live donor lobar transplantation also results in a mild restrictive ventilatory defect and a slightly reduced diffusing capacity.[73] The development of airflow obstruction in patients with heart/lung or bilateral lung transplantation suggests significant pathology. Once bronchial anastomotic complications have been excluded, then other causes including acute rejection, infection, and BOS need to be seriously considered (Fig. 21-4).

Lung function tests following single lung transplantation are persistently abnormal in most circumstances. Patients with obstructive lung disease who have a single lung transplant have a persistent obstructive ventilatory defect, and those patients with restrictive ventilatory defects have persistent restrictive ventilatory defects following lung transplantation.[72] Diffusing capacity is inevitably reduced. Baseline spirometry is clearly important to discern early complications.

Pediatric transplantation also raises the specter of the capacity of lung to expand and fill the growing chest cavity. Initial animal studies have indicated that cut-down adult lungs transplanted into younger (smaller) recipients still have the capacity to expand but with an increase in alveolar size (not number). Conversely, transplanted immature lobes are capable of increasing numbers of functional lung units.[74] Although theoretically transplantation of immature lungs may have greater growth potential, this does not appear to be a practically significant issue.[75-77]

Functional Outcome from Lung Transplantation

Despite near normal lung function, lung transplant recipients still have quite substantial reduction in maximum exercise capacity when tested objectively. A peak oxygen consumption of 50% to 60% of predicted is typical, irrespective of pre-transplant diagnosis and transplant type.[71,72,78-83] The cardiac response in heart/lung transplant recipients is abnormal,[84] showing a blunted (denervated) response. Patients who have received single lung transplantation often approach ventilatory limitation and show desaturation at exercise termination.[85] Most patients, however, appear to have peripheral limitation to exercise. They show an early lactate threshold, but generally normal cardiac response to exercise.[80,86] The dominant problem, however, appears to be structural changes in exercising muscle with a reduction in muscle mass and a reduction in type 1 (oxidative) muscle fiber type propor-

tion.[86] Abnormalities of oxidative metabolism,[86] as well as ion channel abnormalities,[63] have now been reported in the lung transplant recipient. These changes are probably in part reflective of severe deconditioning in the pre-transplant period, as well as reflecting postoperative factors such as major surgery, sepsis, and drugs, particularly corticosteroids and calcineurin antagonists.

Despite this, at least 90% of pediatric[35] survivors of lung transplantation report no significant limitation in their activities up to 5 years post-transplant. In practice, recipients can be advised that they can do most tasks without limitation, although it is unlikely that they would perform well in endurance tasks at a high level.

COMPLICATIONS

Causes of Death

The most common cause of early deaths (less than 90 days) include sepsis and primary graft dysfunction. Acute rejection as a cause of early death is very unusual in adults, accounting for 1.5% to 2.5% of deaths in the first year post-lung transplant.[66] The situation in pediatric lung transplantation appears similar with 1.7% to 3.4% of deaths attributed to acute rejection.[35] These data should be interpreted cautiously, as typically patients who have poor early graft function have a prolonged and complicated intensive care stay. These are frequently recorded as death caused by graft failure (37% of deaths in the first 30 days in the ISHLT/UNOS registry report of pediatric lung transplantation). Often poor early graft function leads to prolonged mechanical ventilation and ultimately ventilator-associated infection due to nosocomial pathogens, which may be recorded in the registry as the cause of death. Severe early graft dysfunction is often associated with an inability to support life with conventional mechanical ventilation. Transplant centers often use high frequency ventilation and even extracorporeal membrane oxygenation (ECMO), with increasingly successful outcomes in patients who just a decade ago were unsalvageable post-transplant.[87] The ability to utilize independent lung ventilation has also proved to be potentially lifesaving. Beyond 1 year after transplant, bronchiolitis obliterans (34% of deaths) and infection (20%) are the most common causes of death in pediatric lung transplant recipients.[35]

Acute Rejection

Acute rejection can occur at any time following lung transplantation, and is diagnosed in approximately 50% of recipients within the first 3 months following transplantation. The one exception is that children in the first year of life have a significantly lower incidence and severity of acute rejection.[88] Surprisingly, despite a typically closer HLA match, living donor lobar transplant recipients have a similar incidence of acute rejection to those receiving cadaveric organs.[67] The ISHLT has developed a standard grading system for acute rejection as seen on transbronchial or open lung biopsy.[89] Grade A0 is normal appearance, grade A1 is designated minimal acute rejection. A mononuclear infiltrate may be seen around some vessels, but it is less than five cells deep. Mild acute rejection grade A2 is seen where pulmonary arteries and arterioles are surrounded with a mononuclear cell depth of more than 5 cells. Grade A3, or moderate acute rejection, is defined as extension of the inflammatory process into the pulmonary interstitium; often there are features of endothelial proliferation secondary to the lymphocytic infiltrate (endotheliitis). Severe acute rejection has features of less severe grades of rejection, but there is also evidence of diffuse alveolar damage, and this is defined as grade A4 rejection.

Many centers now perform routine surveillance bronchoscopy with biopsy, and asymptomatic rejection is not uncommon. Both a high-grade rejection[70] and recurrent low-grade rejection[90,91] are important to detect, as they appear to be risk factors for subsequent development of BOS. Typically, patients are not symptomatic unless they have high grade rejection (A3 or A4), which is often associated with pulmonary infiltrate on chest radiographs. Monitoring of lung function is normally employed and a reduction in FEV_1 or vital capacity of 10% should lead to further evaluation, including bronchoscopy and transbronchial biopsy to assess for developing acute rejection or infection.

Although the standard for detecting acute rejection and other post-transplant complications is open (or thoracoscopic) lung biopsy, these are not feasible for routine monitoring of transplant recipients. Transbronchial biopsy has, therefore, been extensively utilized. Multiple transbronchial biopsies are required to have a high sensitivity for A2 rejection (18 biopsies for 95% sensitivity).[92] In practical terms five or six 1 mm diameter transbronchial biopsies are recommended, but this probably has a sensitivity of between 85% and 90% in the diagnosis of acute rejection. Other forms of rejection have been reported. Immediate rejection owing to preformed antibodies (hyperacute rejection) has been very rarely reported.[93] The presence of a pulmonary infiltrate and bronchiolitis obliterans organizing pneumonia (BOOP) on biopsy[94] has been reported as a subacute form of rejection often requiring augmented corticosteroids for several months. BOOP is often seen as a complication of pulmonary infections,[95] but may also be part of the allo-response.

Chronic rejection is most commonly seen in the form of BOS and this is discussed in a separate section, but forms of chronic rejection including chronic vascular rejection and progressive restriction due to fibrosis are occasionally reported.

In all patients in whom rejection has occurred, particularly if repeated or severe, careful evaluation of compliance with the immunosuppression regimen is urgently needed. Compliance is one of the major issues in the management of pediatric lung transplant recipients, and a sudden development of rejection should always alert the clinician to the possibility of sudden cessation of immunosuppression.

Infectious Complications

Infections are a frequent problem in the lung allograft. The lung allograft is unique in that it is not completely revascularized (generally there is no attempt to re-anastomose the bronchial circulation), and it is the only transplanted organ directly communicating with the external environment—leading to the need to clear airborne pathogens to prevent overgrowth and overt infection.

Thus pulmonary infections represent the major infection burden following lung transplantation. Both donor-acquired and recipient-acquired organisms need to be considered. Causative organisms include community-acquired pathogens, nosocomial (hospital-acquired) pathogens, and pathogens seen in the immunocompromised host. Impaired mucociliary clearance related to the bronchial or tracheal anastomosis is a significant risk factor. If a more serious ischemic injury to the bronchial anastomosis has occurred, then sputum retention with the development of frank pneumonia is not an infrequent complication. Allograft injury or small airway injuries as seen in the bronchiolitis obliterans syndrome are also major predisposing factors to persistent and/or recurrent infection in the allograft. The use of indwelling intravenous cannulas is associated with a high incidence of line-related sepsis.

A pulmonary infiltrate with or without other features of sepsis (fever and leukocytosis) is a common clinical scenario following lung transplantation. Chest radiographs and CT scan appearances may give some information as to the differential diagnosis (e.g., a nodular infiltrate as opposed to a diffuse infiltrate), but are rarely diagnostic. The choice of antimicrobial agents will depend on which organisms are known to be present, and also organisms that are likely to be present in the individual patient circumstance. Clearly, a patient presenting in extremis requires cover for all reasonable possibilities, whereas patients presenting early on in the natural history of their infection may be given more focused antibiotic therapy and monitored carefully for response. The organism known to colonize the patient is not necessarily the pathogen at that presentation. Some patients also have polymicrobial infections requiring often complex antibiotic combinations. Notwithstanding this, patients presenting from the community are more commonly infected with community-acquired pathogens compared to more exotic opportunistic pathogens. Indeed, in the age of antibiotic prophylaxis for *Pneumocystis jiroveci*, this important opportunistic pathogen in the T cell immunosuppressed host is almost never seen. In patients presenting abruptly unwell, or those failing to respond to more simple therapy, urgent bronchoscopic sampling, with bronchoalveolar lavage and/or transbronchial biopsy, may be required. Full blood examination, renal function, drug levels, and liver function studies will guide as to the likelihood of infection with an opportunistic pathogen as well as the most appropriate antibiotic treatment. Peripheral blood should be sent for serologic examination when appropriate and cultured for relevant viruses. Diagnostic molecular assays such as polymerase chain reaction (PCR) can be used to detect CMV.

PERIOPERATIVE PNEUMONIA

This is a frequent complication of lung transplantation and may start within hours of the procedure with the patient intubated and ventilated in the intensive care. Known and potential donor pathogens, colonizing organisms in the recipient, prevalent nosocomial pathogens, as well as community-acquired pathogens all need to be adequately covered with antimicrobial agents. Generally, methicillin-resistant *Staphylococcus aureus* (MRSA) and gram-negatives such as *Pseudomonas aeruginosa* and *Stenotrophomonas maltophilia*, as well as other prevalent ICU pathogens, need to be considered at this stage. Opportunistic pathogens are rarely problematic in the first 4 weeks post–lung transplant. Occasionally fungi such as *Aspergillus* can colonize the allograft early, particularly in the absence of an established prophylaxis regimen. Prior to healing of the anastomosis, the organisms can potentially pass through the anastomosis into the mediastinum, and severe systemic infection can occur even without the patient being neutropenic.

Pneumonia Manifesting from the Community

For reasons discussed earlier, pneumonia is a frequent manifestation in the lung-transplant recipient. Pneumococcal pneumonia is prevalent; however, antibiotic choice needs to take into account recent hospital contact as well as known colonizing pathogens.

NONPULMONARY INFECTIONS

Infections in nonpulmonary sites are commonly line related[96] but otherwise related to unusual or opportunistic pathogens. These may include atypical presentations of mycobacterial infections including cutaneous nodules. Gastrointestinal infections with *Giardia* and systemic infections with *Cryptococcus* species are also regularly seen. In pediatric recipients, the high likelihood of a primary mismatch with respect to Epstein-Barr virus (donor positive, recipient negative) can be associated with the development of lymphoproliferative disease or B cell lymphoma.[97] Although these most often manifest within the lung allograft, extrathoracic sites include gastric and small bowel lymphoma. Primary infection with cytomegalovirus may be associated with viremia, pneumonitis, bone marrow suppression, or gastrointestinal manifestations (gastritis or colitis).[56]

Bronchiolitis Obliterans Syndrome

Bronchiolitis obliterans is defined as irreversible loss of lung function with a reduction in FEV_1 of 20% below best post-transplant reading in the absence of known cause. In general, the BOS criteria[70] can be used in children who can perform pulmonary function tests reproducibly (i.e., greater that 5 years of age). However, in defining functional decline, a decrease in percent predicted rather that a change in absolute value should be used to allow for the expected increase with the child's growth.[70] In small children, lung function testing by other methods, most commonly the rapid compression technique, has been used in an attempt to diagnose peripheral airflow obstruction.[98,99]

Pathologically, this is a fibroproliferative condition of small airways, the histologic lesion being bronchiolitis obliterans, which in the transplant setting is called obliterative bronchiolitis. It is not feasible to perform open-lung biopsy on all patients with deteriorating lung function on a repeated basis. For this reason, transbronchial biopsy is used as the primary histologic evaluation of the transplanted lung. This modality lacks sensitivity in the diagnosis of obliterative bronchiolitis and therefore BOS has been used to define what has generally been regarded as a form of chronic rejection. BOS is particularly prevalent in pediatric transplantation in the first 2 years following transplant (Fig. 21-5), where rates exceed that seen in adults—although after the first 2 years new cases seem to occur at about the same rate as in adults.[100] The exception may be in children younger than 3 years of age, in whom the

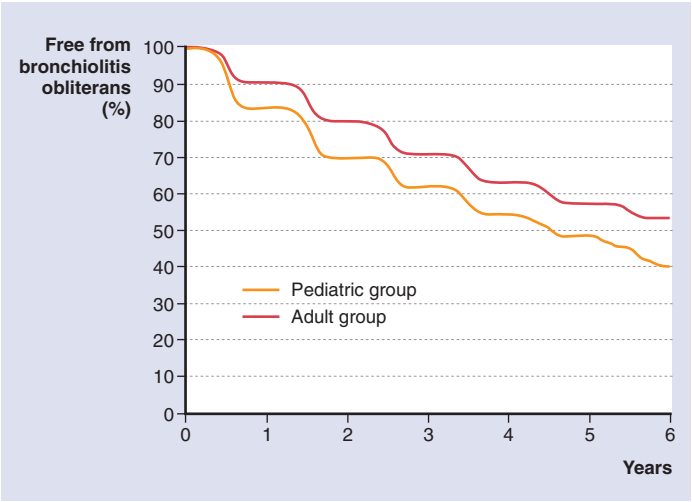

Figure 21-5 Survival curves showing freedom from bronchiolitis obliterans syndrome in adults compared to pediatric lung transplant recipients. Initially higher rates of BOS in the first 2 years post-transplant are evident in the pediatric group (yellow) as compared to adults (red line). Data derived from ISHLT/UNOS registry data at www.ishlt.com/ accessed December 2005.

incidence of BOS may be lower.[70,101] Nevertheless, by 5 years in the ISHLT/UNOS registry 50% of pediatric patients and 40% of adult patients will have BOS.[35,102]

Our understanding of the etiology of BOS has evolved dramatically over the last decade. Initially this was thought to be a manifestation of alloimmunity. The landmark review paper by Estenne and colleagues highlights a number of potential etiologic factors that may be important in the development of bronchiolitis obliterans.[70] Classic alloimmunity remains the leading risk factor and, as noted previously, high-grade acute rejection and/or recurrent low-grade acute rejection are risk factors. Indeed, although the incidence of acute rejection appears similar in pediatric living-related lobar transplants and cadaveric transplants, the better HLA matching seen in the former appears to confer a lower BOS incidence.[67,103]

CMV pneumonitis has been an established risk factor for the development of bronchiolitis obliterans[70,101] and more recently, the presence of this DNA virus, independent of a clinical syndrome, has also been found to be a risk factor.[104] Patients often report a respiratory tract infection prior to BOS developing and it is recognized that community-acquired bacterial[105] and viral infections are associated with the development of BOS.[106] Recently, macrolide antibiotics including azithromycin have been shown to significantly reverse airflow obstruction in patients with established BOS.[107-111] Although this may be due to their antimicrobial action (recurrent bacterial pulmonary infection is a common accompaniment of BOS), it is also possible that by damping down the intensity of the innate immune response, progression is halted and lung function may even improve.

Also of considerable interest is the potential role of gastroesophageal reflux with or without aspiration in the development of BOS,[112-114] including detrimental effects of bile reflux.[115] Some investigators have proposed very early intervention with antireflux surgery[116-119] to halt progression of or to prevent the development of airflow obstruction.

Table 21-5
Potential Treatment for BOS in Relation to Potential Etiology

Recurrent acute rejection/ severe acute rejection	Increase baseline immunosuppression Augmentation Careful monitoring/biopsies
DNA viral infections	Monitoring of viral DNA load (preemptive) antiviral therapy Assess intensity of immunosuppression
RNA viral infections	? Specific antiviral (ribavirin)
Bacterial infection	Targeted antibiotics Anti-inflammatory antibiotics (e.g., azithromycin/clarithromycin
Gastroesophageal reflux	Conservative antireflux measures (not simply antacid therapy) Antireflux surgery

BOS, bronchiolitis obliterans syndrome.

The differential diagnosis of BOS includes acute rejection, fungal bronchitis, and anastomotic complications—as well as other treatable infections. For this reason, careful evaluation including bronchoscopy, bronchoalveolar lavage, and/or biopsy is important is the attempt to exclude these important treatable causes (Table 21-5).

PSYCHOSOCIAL ISSUES

Generally patients are considered for lung transplantation when their anticipated survival is less than 2 years. In the pretransplant era, palliative care supporting both patient and extended family was the focus of the therapeutic team. In many ways, transplantation has complicated this. Patients often hold out in the hope that a suitable donor will become available, well beyond the point that previously they would have accepted palliative care with a focus on symptomatic relief. Patients almost inevitably are in progressive decline once listed for lung transplantation. Deaths on the waiting list are frequent.[39,120,121] Regular review of the patient and family on the waiting list reinforces the transplant unit's determination to offer transplantation. It also allows an assessment as to the urgency of transplantation and perhaps the desirability of using marginal or nontraditional donors for lung transplantation. The transplantation often occurs in a different hospital than the hospital that provided care for many years of the chronic respiratory illness. The ability of the patient and, particularly, the family to become familiar with the transplant hospital becomes important.

Psychosocial evaluation of the child and family is a key part of transplant assessment. Children usually have different priorities than their parents and complying with a complex drug regimen (particularly medications that have substantial toxicities) requires continued sustained effort. Even in seemingly compliant children with well-motivated families, sudden deterioration in graft function may reflect a discontinuation of antirejection medication. This is a frequent occurrence and although it is important not to directly blame anyone, a high index of suspicion for poor compliance must remain in all transplant recipients, especially in children.

The aim of transplantation is to return the recipient to a normal quality of life. On the waiting list for transplantation it is essential to attempt to maintain children whenever possible in educational programs and continuing social contact

with their peers. After transplantation, there is normally a 3-month period of intensive rehabilitation, but after this time it would be realistic for most recipients to return to full-time education.

Patients may prove unsuitable for lung transplantation. This issue requires very careful counseling and support because transplantation often represents the last available option for the potential recipient. Notwithstanding this, some patients have poor chance of success and the most likely outcome is that transplantation will extend their suffering, not improve their quality of life, which is its objective.

CONCLUSION

Lung transplantation has now become standard therapy for patients with severe end-stage lung disease and pulmonary vascular disease. Donor shortages, however, mean that only a small proportion of patients who may benefit will ultimately be offered transplantation. Transplantation in the pediatric age group is complicated by potential growth issues in the recipient, psychosocial issues including poor compliance with complex drug regimens, as well as a high likelihood of primary infection with DNA viruses such as cytomegalovirus and Epstein-Barr virus. Lung transplantation is still far from being a perfect solution; however, in highly selected individuals it can lead to substantially increased survival and improved quality of life.

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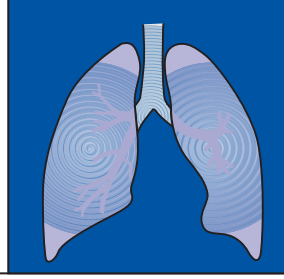

CHAPTER 22 Home Ventilation and Respiratory Support

Stephen M. Stick, Andrew Wilson, and Howard B. Panitch

TEACHING POINTS

- The goals of home mechanical ventilation are to extend life, enhance its quality, and to reduce morbidity in a cost-effective way.
- Children managed at home requiring home ventilation or positive pressure support are best managed by a multidisciplinary team.
- The decision to ventilate or provide positive pressure support for a child at home will depend on locally available resources, access to appropriate technology, and the attitudes of physicians, caregivers, patients, and other health care staff.
- An appropriate care-plan must be developed with the patient and caregivers before discharge from hospital and should include an assessment of locally available health care resources; access to working utilities and telephone service; access to emergency and respite care; and technological support.
- A wide variety of machines that support ventilation is available. The type of machine and settings should be tailored to the patient's characteristics, goals of ventilation, and the experience of the center managing the child. Flow-generators used for noninvasive positive pressure (NIPP) support might not be suitable for home ventilation in some children.
- Regular follow-up including the assessment of adequacy of ventilation during sleep improves outcomes for children managed at home with ventilatory and positive pressure support.
- Outcomes of children receiving home mechanical ventilatory support are generally good. Mortality typically is most dependent on the prognosis of the underlying disease for which ventilation is being used.
- Quality of life for the patient receiving home mechanical ventilation is also generally good, but this may be at the expense of the family's quality of life.
- Home mechanical ventilation remains an extraordinary undertaking on the part of family caregivers, and must be supported by the medical team and appropriately resourced.

Home mechanical ventilation (HMV) is a treatment option that is becoming increasingly available and one that is being chosen by families with increasing frequency as an alternative to prolonged hospitalization and institutional care. Despite the rapid uptake of this technology, there are relatively few data in children that describe outcomes, and the complex psychosocial, community, and ethical issues associated with HMV are only beginning to be explored in attempts to aid, what can be, difficult clinical decision making. There are few published guidelines concerning the selection of patients for and initiation of HMV. In 1990, the American Thoracic Society (ATS) published Home Mechanical Ventilation in Children, a statement that has not been updated despite dramatic changes in technology and the number of children being treated.[1] In this chapter we will discuss the currently available technology, patient demographics and selection, initiation of HMV, treatment outcomes, patient monitoring, and some of the issues that affect clinical decisions.

ETHICAL CONSIDERATIONS

The goals of home mechanical ventilation in children include extending duration of life and enhancing its quality. Additionally, the use of home mechanical ventilation should reduce morbidity, improve the child's physiologic function, help to achieve normal growth and development whenever possible, and also reduce overall health care costs.[2] The ethical and moral issues surrounding long-term mechanical ventilation are complex. We can only point the reader to relevant reviews and highlight some of the general considerations that can guide good clinical practice. A useful starting point is to have a methodologic framework to help analyze specific situations to arrive at a morally justifiable end point that allows for intercultural and cross-cultural differences and lacks bias. Such a framework based on principles of respect for autonomy (the obligation to respect the decision making capacities of autonomous persons); nonmaleficence (the obligation to avoid causing harm); beneficence (obligations to provide benefits and to balance benefits against risks), and justice (obligations of fairness in the distribution of benefits and risks) has recently been reviewed.[3] Nonetheless, a recent publication notes that for families, when deciding what is right or wrong for their ventilator-dependent children, choices that have life or death implications can be perceived as virtual choices and thus somewhat removed from reality.[4]

For most clinicians the most challenging patients are those with severe neuromuscular weakness such as spinal muscular atrophy (SMA) and Duchenne muscular dystrophy (DMD). Most clinicians would agree that decisions should be reached mutually by the family/patient and medical team and should

favor the child's best interests. The ramifications of that decision need to be viewed from the perspective of the affected individual, the family, and society as a whole. Some of the ethical issues that affect the decision to commence HMV in patients with neuromuscular diseases have been systematically reviewed.[5] Simmonds emphasizes the need for full disclosure of information if a truly informed decision is to be made. The review of the relevant literature by Simmonds revealed that HMV can prolong life, is associated with acceptable quality of life for patients and families, and that in general decisions regarding the initiation of HMV are influenced by local resources, cultural and religious factors, and physician attitudes. Clearly, these factors will have a marked influence on practices in different centers and this makes general management guidelines difficult to develop. A recent Canadian survey showed that 25% of physicians did not offer long-term mechanical ventilation to patients with DMD, most commonly because of the physicians' perception of poor patient quality of life.[6] However, clinicians have a responsibility to help patients and families arrive at ethically and morally justifiable decisions regarding treatment. In our experience, such negotiated care plans are best developed electively, not at times of acute medical crisis and with patients and families having options supported by available evidence presented in an unbiased, nonjudgmental way. In cases where a negotiated care plan cannot be agreed on, further independent medical opinion might be required and in some cases legal intervention is needed to facilitate an appropriate outcome that is underpinned by the principles of autonomy, nonmaleficence, beneficence, and justice.

TECHNOLOGY

The 1990 ATS statement dealt almost exclusively with children ventilated at home via tracheostomy. At that time, the ventilators that were suitable for home use were either simple portable machines that delivered volume-controlled mandatory breaths without continuous flow, or stationary pressure-controlled hospital ventilators that required a separate air compressor to run. Currently available ventilators have benefited from advances in computer-controlled flow and pressure generators, miniaturization, battery design and control algorithms. Furthermore, the advent of noninvasive positive pressure ventilation (NIPPV) via mask (nasal or oronasal) has revolutionized the management of children with a wide range of disorders from neuromuscular disease to obstructive sleep apnea and hypoventilation. However, a note of caution with regard to flow generators designed primarily for use to treat obstructive sleep apnea and that deliver user-defined inspiratory and expiratory pressures with a varying degree of sophistication with regard to modes of control. These machines are not primarily designed for use as home ventilators and their limitations include low maximum back-up rates, rudimentary trigger algorithms, high flows, and inability to accurately set or determine F_{IO_2}. Most flow generators do not have built-in alarms that are sufficiently sophisticated for patients who are ventilator dependent.

PATIENT DEMOGRAPHICS

The prevalence of home mechanical ventilation in Europe in 2001 was estimated at 6.6 users per 100,000 population.[7] The vast majority of these patients were receiving ventilation noninvasively. In 1993, Downes and Pilmer estimated that 4000, or 1.5/100,000 children in the United States were chronically ventilator dependent.[8] Although there are no recent prevalence figures for the pediatric population, it is clear that home ventilation is becoming increasingly common. There have been a number of reports from individual centers[9-15] describing the use of home ventilation in children. There is considerable information about the diagnostic groups into which children receiving home ventilation fall. The underlying diseases can be classified in four main groups: disorders of the respiratory pump (including neuromuscular diseases, diseases of the chest wall and spinal cord injury); obstructive diseases of the airways (including those associated with craniofacial anomalies); parenchymal lung diseases (particularly cystic fibrosis and bronchopulmonary dysplasia); and disorders of the control of respiration (notably congenital central hypoventilation syndrome). In the above series, neuromuscular diseases are the largest single group, accounting for between 28% and 51% of cases. Although parenchymal lung disease is a common indication for home ventilation in adults, accounting for 34% of cases in Europe,[7] this is a much less common underlying disorder in children.

COMMENCING HOME VENTILATION

Generally, children are commenced on home ventilation by one of two pathways. First, mechanical ventilation may be started as a result of an acute illness in which the child is unable to be successfully weaned from ventilation. Alternatively, a decision may be made in a child with chronic respiratory failure to electively commence ventilation. There are no published consensus statements regarding the elective initiation of home ventilation. In general, but not exclusively, mechanical ventilation via tracheostomy is commenced following an acute illness, whereas noninvasive ventilation (NIV) can be commenced either acutely or electively. Even in conditions such as neuromuscular disease, where there is clearly an opportunity to introduce home ventilation electively, these opportunities are often missed. In one series of 73 children and young adults with neuromuscular disease requiring home ventilation, 79% had commenced ventilation acutely following an episode of acute respiratory failure related to a pneumonia.[16] The authors identified nearly 200 missed opportunities to discuss elective initiation of mechanical ventilation during office visits, previous hospitalizations, or after polysomnography. This is despite excellent evidence that nocturnal hypoventilation precedes daytime respiratory failure in neuromuscular disease and that institution of nocturnal ventilation can prevent or ameliorate daytime respiratory failure.[17,18]

In most cases noninvasive ventilation would be the treatment of choice for children requiring long-term ventilation; however, there are certain circumstances in which NIV is contraindicated or in which ventilation via a tracheostomy would be preferred. Ventilation via tracheostomy should be considered if ventilation is required for more than 16 hours per day because of the difficulty in maintaining mask ventilation for this period of time and the level of respiratory insufficiency that this amount of support indicates. Application of NIV is also more difficult in infants because of the limited

number of well-fitting interfaces available, especially in places where custom mask fabrication is not employed. With current technology NIV is also difficult when supplemental oxygen is required. As oxygen must be added to either the ventilator circuit or the mask, it is difficult or impossible to monitor F_{IO_2}. Because flows generated by the ventilator are high, there is a marked dilution of the supplemental oxygen, necessitating high oxygen flows to significantly increase F_{IO_2}. Higher flows of supplemental oxygen bled into the system will also contribute to patient-ventilator dyssynchrony, especially in small children. Here, the additional flow of supplemental oxygen can mask the change in circuit flow generated during a spontaneous inspiration, which is used as a trigger signal for pressure support, assist control, or synchronized intermittent mandatory ventilation. From a practical viewpoint, it is inappropriate to consider home ventilation in a child who requires an F_{IO_2} of greater than 0.4 because of the limitations in supplying such high amounts of oxygen in a home setting. Furthermore, consideration should be given to pulse oximetry for children receiving NIV who have a requirement for supplemental oxygen oximetry—given the uncertainties inherent in oxygen delivery in this situation.

Initial Titration of Ventilation

Patients ventilated via tracheostomy are usually stabilized in the intensive care unit either during an acute episode of respiratory failure or following an elective tracheostomy. In either case, the ventilatory requirements can be relatively easily assessed because of the stable patient interface and the use of versatile ventilators with a range of modes that further facilitate stabilization.

Often, children who receive chronic ventilatory support via tracheostomy for airway or parenchymal lung disease are provided with a minimum back-up mandatory rate, and pressure support ventilation is used to support a portion or all of each spontaneous breath. Because the pressure-supported breath is triggered (initiated) by patient effort and also cycled (terminated) by the physiologic characteristics of the patient's lungs, it is a more natural and therefore often a more comfortable supported breath for the patient than is a mandatory breath that is cycled based on characteristics set by the physician or therapist. In this scheme of synchronized intermittent mandatory ventilation with pressure support (SIMV+PSV), the SIMV breaths can be set to deliver volumes slightly higher than the patient's usual tidal volume breaths, and so act as periodic sigh breaths.

There are several other strategies for determining ventilator settings, and these are based on the equipment available, the underlying disease being treated, and the goals that ventilatory support is intended to achieve. For instance, if a home ventilator that provides pressure support is not available, and one of the goals is to enhance the patient's growth by reducing the caloric expenditure of breathing, the operator might choose to use a relatively high (12 to 15 mL/kg) tidal volume and moderate mandatory breath rate to provide ventilation adequate enough to reduce the child's spontaneous efforts.[19] Patients with neuromuscular disease who often have no underlying parenchymal lung disease should not require supplemental oxygen. They should be given a minute ventilation high enough to avoid hypoventilation and its attendant hypoxemia. Often, these patients can be supported in Assist/Control mode with a minimum set rate that can be superseded by the patient, while still receiving full support during each additional breath. Patients who receive mechanical ventilatory support by a mouthpiece (sip or sip and puff ventilation) can receive breaths in either pressure- or volume-control mode. If used in the volume-control mode, however, the patient can be taught to breath stack and use the ventilator to assist with cough, thereby enhancing autonomy.

However, for patients requiring noninvasive ventilation by nasal or oronasal mask, the situation is more complex. For example, the patient interface is less stable and prone to leaks and the flow generators commonly used for inspiratory and expiratory support ventilation are relatively unsophisticated.

The nature of noninvasive ventilation is such that it is most usually used either during sleep for treatment of chronic sleep-disordered breathing or for short periods during acute illnesses. For patients requiring long-term NIV, the establishment of ventilation is best done in hospital with careful attention paid to mask fitting and titration of ventilatory variables. Initially a crude titration can be performed at the bedside—but a formal titration polysomnogram should be performed at discharge or alternatively, soon after discharge, for stable patients with straightforward ventilation requirements. Recent evidence supports regular six to twelve monthly titration polysomnograms for most patients requiring long-term NIV,[20] and more frequent assessment in patients with evolving conditions, complex respiratory diseases, or difficult interface issues. Prior to titration, care should have been previously taken to fit an appropriate and comfortable mask and then a time is chosen for titration when the child is likely to sleep. A typical example of a formal polysomnogram titration algorithm for hypoventilation that is used in our laboratory is shown in Figure 22-1. Some institutions use a split-night polysomnogram to diagnose the extent of any sleep disordered breathing and establish NIV (Fig. 22-2). The success of this approach will depend on the nature of the breathing disorder, compliance of the child, and expertise available during the study. Approximate bedside titration during the initial establishment of NIV can be effectively achieved using the algorithm in Figure 22-1 prior to a formal polysomnogram.

During titration the commonest problems encountered are air leaks (either from around the mask or through the mouth) and failure to synchronize the ventilator with the child's spontaneous breathing pattern. Spending time choosing an appropriate mask and having a range of masks available can help solve problems with leaks due to a poorly fitting mask. Occasionally, it is necessary to use a custom-made mask, particularly for children with unusual facies and craniofacial abnormalities. In order to reduce leakage of air through the mouth, it is important to ensure that the nose is clear, thus reducing the likelihood of oral breathing. Sometimes changing a mask and headgear to allow for a different sleep-ing posture can help and in young children a pacifier can also reduce airflow through the mouth. However, for some children the use of a chin-strap to elevate the mandible in order to close the mouth is unavoidable.

Air leak is an important cause of failure to synchronize the ventilator with the patient's spontaneous breathing pattern

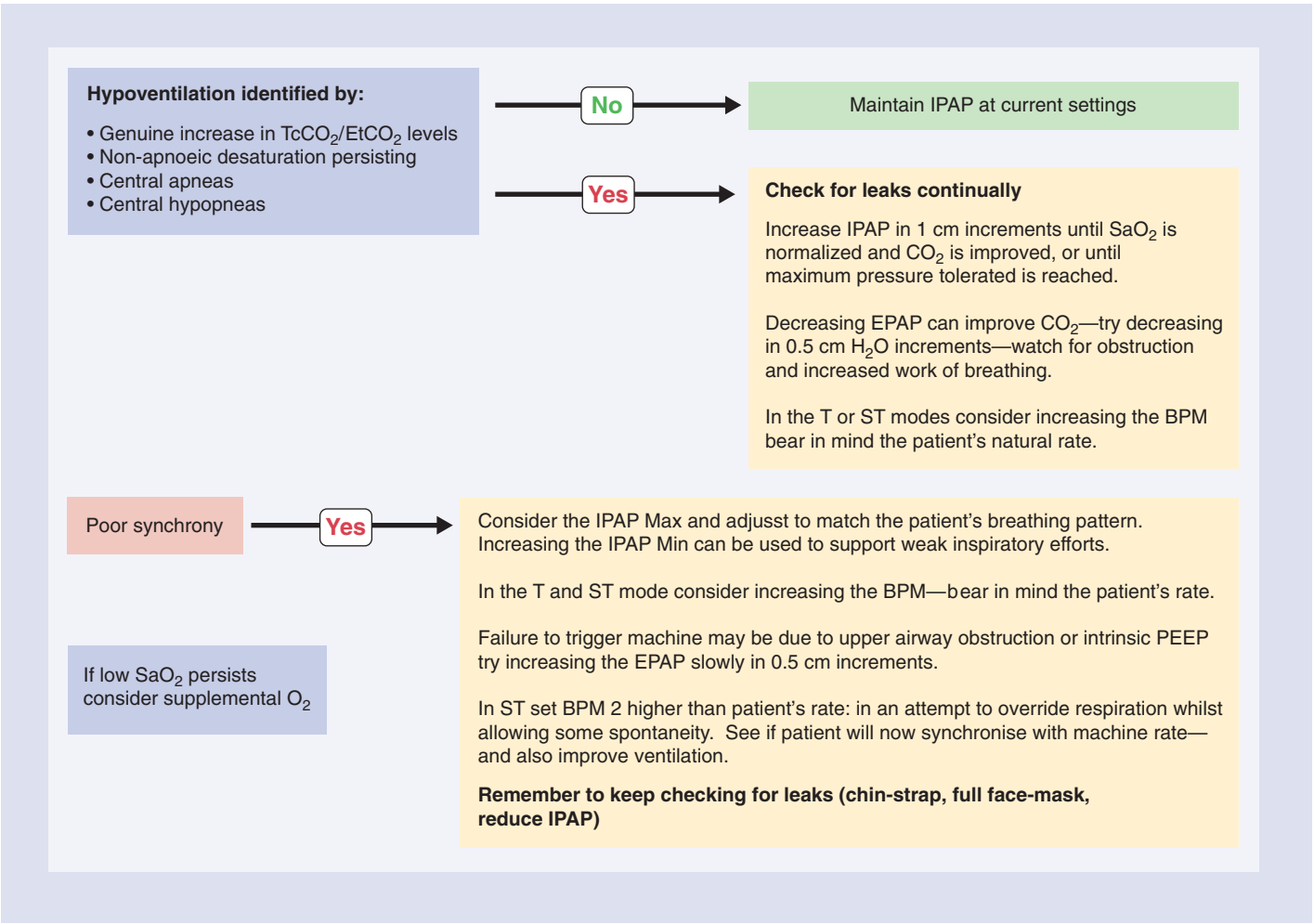

Figure 22-1 Titration algorithm for determining ventilator settings for hypoventilation treated with noninvasive mask ventilation.

and should always be checked first in patients that are difficult to ventilate. Other causes include inappropriate ventilator settings, failure to trigger because of airway obstruction or intrinsic positive end-expiratory pressure—these factors should be methodically assessed using the steps suggested in Figure 22-1.

Equipment Requirements

VENTILATORS

Mechanical ventilatory support can be provided by positive- or negative-pressure body ventilators, and by devices that deliver positive pressure to the airway opening noninvasively via nasal, oronasal, or oral interfaces, or invasively by a tracheostomy tube. Newer positive pressure ventilators suitable for home use also have the capability to provide continuous flow and pressure support ventilation. Portable systems are now available that can be used in volume- or pressure-targeted modes. Bi-level pressure generators deliver pressure pre-set ventilation and continuous flow for noninvasive ventilation, but they are not considered portable and at present, most do not have intrinsic alarm systems. Traditionally, ventilators designed for invasive use have included a greater range of monitoring and alarms and have been equipped with internal batteries. Increasingly, these features are being incorporated in ventilators designed for noninvasive use. There is an ever-enlarging range of devices marketed for the provision of home ventilation. Detailed description of individual machines is inappropriate here, and such a description would soon be obsolete. A description of the more commonly used machines has been produced recently.[21]

There is no single ventilator that is suitable for use in all home-ventilated children. A ventilator should be selected that best suits the needs of the child. Consideration should be given to whether the ventilator is designed for invasive or noninvasive use. In general, machines designed for noninvasive use should not be used via tracheostomy. When invasive ventilation is used, particularly when the child is ventilated for a significant period during the day, portability is a major issue. A ventilator that is of a sufficiently small size (for example to fit beneath a pram or stroller) and has a long battery life is necessary. Other desirable attributes for a pediatric ventilator include a selection of ventilator modes, adjustable trigger, capability to deliver raised FIO_2, and low dead space.

There are significant differences in the consistency of performance of commercially available devices.[22-25] Inconsistencies can be the result of mode of ventilation or ventilator design,[22] and can be exacerbated by extreme patient loads (high resistance, low compliance) imposed on them. Each

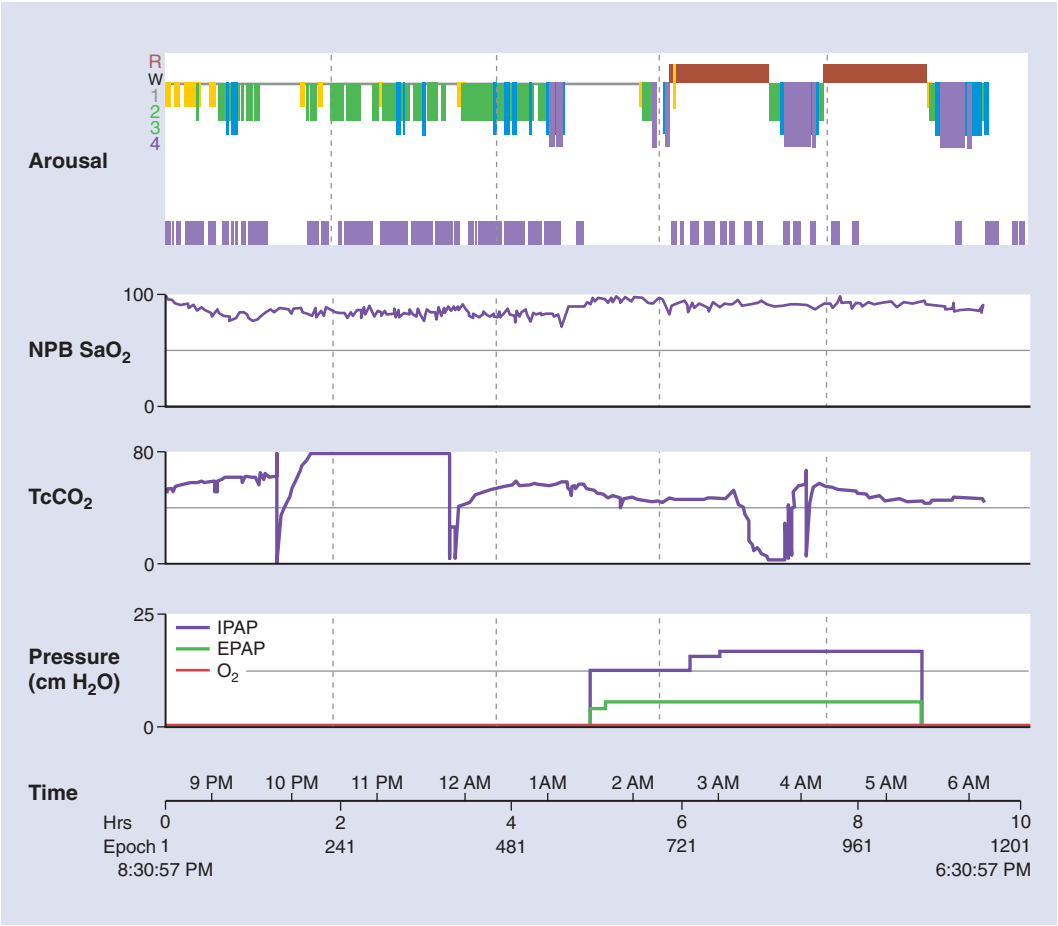

Figure 22-2 A split-night sleep study performed in a 16-year-old boy with Duchenne muscular dystrophy. In the first part of the night he is spontaneously breathing in room air; noninvasive ventilation (NIV) via nasal mask is commenced just before 2 AM. In the first part of the night, there is severe sleep fragmentation, oxygen desaturation, and hypercarbia. Once NIV is commenced, both oxygenation and ventilation improve as does sleep quality. Particular note is made of the phenomenon of rapid eye movement (REM) rebound where an increased percentage of time is spent in REM sleep once adequate ventilation is restored.

company creates its own method for turning on its machine and adjusting ventilator settings and alarms in a way that is often not intuitive—even to health care professionals.[26] Because there is no standardization of ventilator design, consideration of user friendliness must be made not only for families, but also for the center to which the child will be admitted for planned or emergency care. For this reason, many home ventilation programs limit the variety of devices used in their population, to reduce iatrogenic complications when children require rehospitalization.

The equipment needs of children supported at home with mechanical ventilation have been previously described,[27,28] and will vary depending on the interface used (noninvasive versus tracheostomy), number of hours per day the child requires support, and the distance the child resides from the health care facility or home equipment provider. Children who cannot sustain adequate ventilation without mechanical support for >4 hours or who live more than 1 hour from the health care facility or durable medical equipment (DME) provider require a second complete ventilator and circuit as back-up.[27-30]

ALARMS AND MONITORING

Although patients selected for home ventilation are, by definition, clinically stable, their dependence on technology leaves them vulnerable if this technology fails. It is, therefore, important to consider potential problems that the child may encounter and plan for these accordingly. Whereas some children will cope if deprived of their ventilatory support, others are dependent on such support and are at risk of mortality in this situation. A child who has electively commenced ventilatory support via nasal mask for nocturnal respiratory failure has very different requirements from those of a child with a high spinal cord injury who is continuously ventilated via tracheostomy.

Ventilator alarms, both internal and external, are particularly important for the patient who is dependent on ventilation. Positive pressure ventilators made for home use have intrinsic high- and low-pressure alarms. These are critical for detecting possible tube obstruction, inadvertent ventilator circuit disconnection, or accidental tracheostomy decannulation. Importantly, the use of small tracheostomy tubes with inside diameters <4.5 mm can provide enough resistance at

the end of the ventilator circuit to cause low inspiratory pressure alarms to fail to sound in the event of an accidental decannulation.[31] Thus, in smaller children, additional types of monitors are used to identify emergency situations.

External monitors such as oximeters may be indicated in some circumstances, but should not be used as de facto ventilator alarms. Rather than providing each patient with all possible alarms and monitors, it is appropriate to consider each child, the problems that may be encountered, and the child's likely response to each situation. In fact, the use of other types of monitors beyond those associated with the mechanical ventilators is a subject of controversy. Some authors advocate for the use of impedance cardiorespiratory (apnea) monitors,[27,32] whereas others think they are redundant and unnecessary.[33] Such monitors, however, will not alarm in the event of an obstructed tracheostomy tube or displaced nasal mask until hypoxemia has occurred long enough to cause bradycardia. Similarly, some groups feel that continuous monitoring of oxyhemoglobin saturation by pulse oximetry or of carbon dioxide levels by capnography have little or no place in home care.[32,33] Others rely heavily on oximetry both for weaning supplemental oxygen and also as an earlier warning to detect life-threatening events.[34] In one study, a reduction in the incidence of death or hypoxic brain damage related to airway accidents was reduced by the use of pulse oximetry in the home.[8] Oximetry can be used not only as a supplemental alarm for potential airway obstruction, but also as a tool for weaning ventilator support. It is also an early warning for the detection of an acute lower respiratory illness that may require an increase in ventilatory support. Hypoxemia as detected by pulse oximetry is also a sign that more aggressive airway clearance and possible escalation of other therapies are required for children with neuromuscular weakness who are not hypoxemic at baseline and who normally have no underlying parenchymal lung disease.[35] Similarly, intermittent capnography can be used during and after weaning trials to detect changes in adequacy of ventilation. Continuous capnography is typically not indicated for home care of ventilator-dependent children.

In general, potential risks for each patient should be considered prior to discharge, and a risk management strategy devised.[36] In summary, the provision of further home monitoring, such as pulse oximetry and capnography, should be considered on a case-by-case basis. Although pulse oximetry may be useful for assessment purposes, particularly in a child with a supplemental oxygen requirement, it is seldom indicated continuously. Again it should be stressed that an oximeter should not be used as a surrogate for an appropriate ventilator alarm. It should not be the aim of the home ventilation program to provide an intensive care unit in the home; furthermore, the provision of unnecessary monitoring devices has the potential to increase rather than decrease anxiety in caregivers and to add to the overall burden of care.

HUMIDIFICATION AND AIRWAY CLEARANCE

Children with tracheostomies (especially infants) receiving continuous mechanical ventilation require heated humidifiers (active humidifiers) to prevent drying of secretions.[29,37] Heat moisture exchangers (HMEs, passive humidifiers) can be used for short periods of time, but are not reliable for long-term use, especially in infants and small children.[33] Those patients best suited for HME use produce minimal secretions.[38] They are useful for transport, and enhance portability of patients by reducing the amount of equipment needed. Hygroscopic HMEs provide a higher output of humidity than hydrophobic HMEs.[37,38] Care must be taken to avoid excessively increasing dead space and resistance, by using an HME appropriately sized for the patient. The special equipment, supplies, and training required for care of children with tracheostomies has been detailed in a recent statement of the ATS.[38] Both stationary and portable suction equipment should be available for children with artificial airways so that they are not confined to home. Children with impaired cough require either equipment to aid with airway clearance (e.g., a mechanical in-exsufflator), or the family must be taught methods of manual airway clearance.[39]

Humidification may also be desirable for patients supported by noninvasive ventilation. This is especially true if the patient's climate is already dry, during winter months, or for those using lip seal or mouthpiece (sip) ventilation.[29] Both hot and cold passover humidifiers increase the humidity of delivered gas, although hot passover systems are more effective than cold in improving humidification of inspired air and reducing respiratory water loss with nasal continuous position airway pressure.[40]

MASKS AND INTERFACES

The most important consideration when establishing a child on noninvasive ventilation is the provision of an appropriate facial appliance. An increasing range of products are commercially available; in addition the use of custom-made masks has been described.[15]

The three most commonly used appliances are (1) nasal mask, (2) oronasal mask, and (3) nasal pillows. Where NIV is commenced electively, the child is often sent home for a period to become familiar with the mask. For young children, this is particularly important. In some situations incorporation of the mask into play, including the parent, or a doll or stuffed toy wearing the mask may help to reduce the child's anxiety. Because there are potential short- and long-term consequences from the use of a facial appliance for NIV, it may be useful to fit more than one device to assist in preventing and managing these problems. When a child is not tolerating NIV, the appropriateness and fit of the facial appliance is the first factor to be considered. An appropriately fitting interface is necessary not only for the child's comfort, but also to ensure that leak is minimized. Minimization of leak is particularly important in children with neuromuscular disease to ensure patient triggering, synchrony, and hence adequacy of ventilation.

Discharging a Child on Home Ventilation

Much of this discussion will focus on the process for discharging a child on invasive ventilation via tracheostomy. The principles are, however, applicable to the child on noninvasive ventilation. It is first useful to consider the barriers that may exist to discharging the child. When a child has been identified as being suitable for home ventilation, a formal discharge planning process must begin. By means of this process, potential barriers to discharge can be addressed, and transition to home care can occur as safely and promptly as possible.

Regardless of the underlying cause for respiratory failure, medical stability must be demonstrated before the child is deemed fit for discharge to home.[29] Clinically, the child should be free from frequent infection, have adequate stamina for periods of play or therapies, and ideally demonstrate a positive trend on the growth curve. From a physiologic standpoint, the child must have a stable airway (natural or artificial), and should not require excessive support. In this regard, general guidelines include the need for supplemental oxygen that does not exceed an FIO_2 of 0.4, and for children with underlying lung disease, a $PaCO_2$ less than 50 torr on current support. Those with neuromuscular disease should have a normal $PaCO_2$. Importantly, there should be a period of 1 to 4 weeks before discharge—during which time no changes are made to the medical regimen—to ensure that the patient is in fact stable on the proposed home regimen.

The family must demonstrate both willingness and an ability to learn all the care that is necessary to maintain the child safely at home. Children who have tracheostomies require two adults to learn care because many aspects related to tracheostomy care require the involvement of two people. In general, having two adults learn care is desirable even for children with natural airways, in the event that one adult becomes ill or is unavailable. These adults need not necessarily be the child's biological parents. Children from single-parent homes have successfully and safely been discharged on mechanical ventilator support, with another family member, a neighbor, or friend acting as the back-up caregiver. Depending on funding sources and limitations, the family may be responsible for, or at least included in the process of, selecting home care nursing and durable medical equipment companies.

The home must have adequate space to permit all of the necessary equipment as well as health care personnel that will be required for safe care of the patient. There must be adequate heat, electricity, and running water. Most importantly, there must be telephone access so that the family or home care nurse or therapist can contact appropriate medical personnel in the event of an emergency. For children who also require the assistance of a wheelchair, the home may have to be adapted to provide adequate access and egress. If the child lives a substantial distance from the discharging institution, a local emergency room and ambulance service must be identified in case of emergency to stabilize the patient before subsequent transfer.

Although home care of ventilator-assisted children substantially reduces the cost of their care,[41] it is still expensive. Thus, funding of nursing salaries, durable medical equipment rental or purchase, and purchase of disposable supplies must be guaranteed. Local resources need to be clearly identified and appropriate funding arrangements defined and implemented before discharge from hospital. Some costs of care that are typically covered during a hospital stay often subsequently become out-of-pocket expenses for the family. These would include purchase of prescription medications and special formulas. Additionally, utility bills and telephone charges should be expected to increase.

Finally, for long-term home mechanical ventilation to be successful, a multidisciplinary team of health care professionals must be available for periodic reevaluation and immediate feedback and support. Professional services represented on the team include case management and coordination, primary medical care, subspecialty medical care, home nursing services, home respiratory care, social work intervention, nutrition counseling, and input from speech, occupational, physical and developmental therapists.[13,28,29,42-45] Case managers coordinate care and services to maximize the potential of the child by overseeing the distribution of adequate and appropriate services while simultaneously containing costs. Absence of a case manager was identified as one risk factor predictive of increased stress among family members of ventilator-assisted children cared for at home.[46]

Once a child is medically stable and ready to go home on ventilatory support, there are many factors that can conspire to delay discharge. Delay in discharge is particularly apparent for those children requiring invasive ventilation via tracheostomy—indeed the delay in discharge in this situation was reported in one study to average 513 days!.[47] A number of publications have specifically addressed the barriers to discharging a child on home ventilation.[48,49] A formal discharge planning process is necessary to address these barriers and prevent delays in discharge. The most important elements of this process are the identification of a discharge planning team and a discharge planning coordinator. The coordinator needs to ensure that the team meets regularly and that progress toward discharge continues. Particular issues that the team needs to address include equipment requirements and funding sources, the identification and training of caregivers, appropriateness of housing and required modifications, community services, respite arrangements, and multidisciplinary follow-up. It is important that parents be involved at all stages and be able to actively participate in the discharge planning process. It is equally important, however, that the parents not bear inappropriate responsibility for arranging their own child's discharge.

OUTCOMES

Although the long-term outcome of a child on home ventilatory support is clearly dependent on the underlying medical condition, in general the outlook for these children is surprisingly good. When assessing the outcome of home ventilation, however, it is important to consider not only mortality and morbidity, but also quality of life and perhaps most importantly the impact of home ventilation on the child and the family. In addition, there are potential complications of home ventilation that warrant further discussion.

Mortality and Morbidity

Although the primary aim of home ventilation is to improve quality of life for children with respiratory failure, survival obviously remains a very important outcome variable when assessing the success of this intervention. Because NIV is a relatively new modality, there are much more data regarding the mortality of children invasively ventilated via tracheostomy. Prolonged survival of these children is well documented, and survival rates are probably improving. Frates in 1985[50] reported a 5-year survival of 65%; more recently survival rates of up to 71% at 10 years have been reported.[10,51,52] It is important to note that in most cases mortality relates to progression of the underlying condition, and that death from

ventilator or other equipment failure is uncommon. In fact, the greatest predictor of long-term survival in children with chronic respiratory failure is the prognosis of the underlying condition.[53]

Some causes of mortality, however, are directly related to tracheostomy tube obstruction, ventilator circuit disconnection, or inadvertent tracheal decannulation. Downes and Pilmer found that the incidence of life-threatening airway accidents was 2.3/10,000 patient-days in the home compared with 0.9/10,000 patient-days in the hospital.[8] Among a group of 101 infants with chronic respiratory failure cared for over 18 years, 20 died while still being mechanically ventilated and another 10 died after having been weaned.[27] Six of the deaths were caused by airway-related accidents, but only one of these occurred while the child was still in the hospital. Of the five deaths occurring at home, three were in children who had weaned from mechanical ventilation but remained tracheostomy-dependent because of subglottic stenosis. Two other children sustained severe hypoxic encephalopathy resulting from airway-related accidents.

In Frates' retrospective review of 54 patients cared for at home over 20 years, nine patients were weaned from ventilatory support, but 17 died.[50] Of those, four deaths were ventilator-related. Three children died as a result of unwitnessed ventilator disconnections. In each case, the low-pressure alarms failed to sound because the end of the circuit was obstructed by the patient's soft tissues. A fourth child died in a tank ventilator (iron lung) as a result of an overnight power failure. The authors speculated that at least three and perhaps seven deaths might have been avoided if the child had been monitored either visually or electronically. Of 22 children followed in a Canadian home ventilation program, 14 (64%) had neurologic disorders, whereas eight (36%) had primary pulmonary disorders.[45] Seven patients died, three in the neurologic group and four in the pulmonary group. No death was the cause of equipment malfunction, disconnection, or obstruction. One child died of acute bacterial tracheitis, and another died shortly after he presented in septic shock. All other deaths were related to progression of the underlying disease.

Many would expect that a child discharged on tracheostomy ventilation is likely to require frequent rehospitalization. This is actually not the case—these children have been reported to average less than one hospitalization per patient per year.[51] Some children will improve at home, and will be able to cease ventilation or be weaned to noninvasive ventilation. Such outcomes also appear to be related to the child's underlying disease. Infants and young children with parenchymal lung disease, such as bronchopulmonary dysplasia or airway anomalies such as tracheomalacia, have a high likelihood of discontinuing ventilator support. Of 27 children discharged to home successfully on ventilator support from one program, 15 were able to come off all ventilation successfully.[49] Of these, 12 had a combination of chronic lung disease and an upper airway abnormality. In another series, 8 of 12 ventilator-dependent children with chronic lung disease or congenital anomalies were able to be weaned completely from ventilator dependence, and there were no deaths in those groups.[54] In contrast, only 1 of 16 children with neuromuscular disease or central nervous system disorder was able to wean from ventilator support, but five died. Overall up to 40% of children discharged on home ventilation will eventually be able to be decannulated.[49,54]

As mentioned earlier, there are limited data on the long-term survival of children receiving noninvasive ventilation at home. NIV has been reported to significantly reduce morbidity in children with respiratory failure. After commencing NIV, children with neuromuscular diseases have reduced hospitalizations, and reduced days spent in intensive care units.[55] As well as correcting nocturnal respiratory failure and improving sleep parameters, NIV also has been shown to improve daytime respiratory function, and to delay the onset of daytime respiratory failure.[17,18]

Complications

VENTILATOR FAILURE

Failure of the ventilator, or of the power supply, is a particular concern for those children who are dependent on ventilatory support, that is, those who are at risk of mortality without such support. Thankfully, such equipment failure is relatively uncommon, with one incident expected per patient every 1.25 years.[30] Importantly adverse events and hospitalizations are very unlikely to occur as a result of these failures. The provision of appropriate power and ventilator alarms, and back-up power supply has been discussed; these measures minimize patient risk in the event of equipment or power failure. Perhaps the most reassuring evidence of the impact of ventilator failure comes from the Hanshin-Awaji earthquake in Japan.[56] Nineteen children of home ventilation were affected by this disaster, which interrupted water, gas, and electricity supplies. All of these children survived the disaster. By anticipating potential equipment and power problems, potentially catastrophic events can be overcome.

TRACHEOSTOMY-RELATED COMPLICATIONS

Detailed discussion of the risks and complications of tracheostomy is beyond the scope of this chapter. Complications are discussed in detail in the ATS consensus statement on the care of a child with a chronic tracheostomy.[57] Because the tracheostomy is the interface between the child and the ventilator, decannulation and blockage are particularly relevant to children on home ventilation. Again, provision of appropriate ventilator alarms is necessary to minimize these risks. Care should be taken in children with small, uncuffed tracheostomy tubes because standard low-pressure alarm settings may be insufficient to detect accidental decannulation.[31]

The issue of lower airway colonization and infection with microorganisms secondary to tracheostomy is of particular relevance to children receiving home ventilation. Colonization of the lower airways with potentially pathogenic organisms is almost inevitable in these children.[58] Fortunately, symptomatic infection is less common. Despite best attention to hygiene and airway toilet, however, lower respiratory tract infection remains a significant risk.

MASK-RELATED COMPLICATIONS

Local complications such as pressure sores are common, particularly over the nasal bridge, or, depending on the mask, over the forehead. These can be prevented or treated. Appropriate mask selection and education about mask fitting, par-

ticularly avoiding over-tightening, are paramount. If necessary, local skin dressings can be used. On occasion, an alternative mask may be provided to rotate potential pressure sites. Of more concern, there are increasing reports of midface hypoplasia in children receiving long-term NIV by nasal mask.[59,60] Prolonged daily use, commencement of NIV before 8 years of age, and facial muscle weakness have been identified as risk factors for this problem.[60,61] The optimal methods for prevention and management of facial growth complications of NIV are yet to be determined; however, regular evaluation of maxillary growth is recommended, particularly in the presence of the risk factors just described.

Quality of Life

When using physiologic indicators to gauge the impact of long-term mechanical ventilation, it is clear that mechanical ventilation is beneficial. The use of positive pressure ventilation is associated with fewer hospitalizations, better sleep quality, and improved daytime function in patients with neuromuscular disease.[55,62] Daytime ventilation also improves in those subjects with diurnal hypoventilation who begin nocturnal ventilation.[63] When examining more global issues, quality of life of children who receive chronic mechanical ventilatory support at home is at least as good as that of children with other chronic diseases.[63] Older ventilator-dependent patients, including those with progressive neuromuscular weakness, are reported to have a positive outlook regarding their quality of life and look to the future with regard to life plans.[6,64,65] However, a recent study suggested that adolescent ventilator-dependent children may be less satisfied with their daily activities than are younger ventilator-dependent children, and overall satisfaction correlated with a greater degree of activity.[66] The amount of support patients receive through skilled professionals or trained caregivers and assistive technologies has also been found to relate directly to a better quality of life.[67]

The practice of caring for a ventilator-dependent patient at home is stressful for families, and that stress increases with the duration of home mechanical ventilation.[64,68] Caring for a ventilator-dependent child also has adverse impacts on the health of the caregivers, including interrupted sleep, and limited time for the caregiver to pursue health-promoting activities.[69] Mental health of caregivers is more likely to be adversely affected than physical health.[70] Although family quality of life may suffer, parents typically express a preference to have their child at home instead of in a hospital.[4,71] Children, when given the opportunity, express the same desire to be at home.[72] Some factors that have been associated with greater caregiver stress include limited financial resources, absence of a nurse case manager and fewer services provided at the time of discharge, and an unstable family environment.[4,46]

It is important to stress that the child and the family's assessment of the child's quality of life may well be very different from what is perceived by medical staff. Indeed, health care practitioners are likely to assess a child's quality of life as markedly lower than the child's caregivers.[73]

CONCLUSION

Home mechanical ventilation of infants, children, and adolescents has become a widely accepted treatment option for many who survive but do not completely recover from acute life-threatening illnesses or those who have diseases that result in chronic respiratory failure. Significant advances have been made over the last half century, and particularly over the last 20 years, in the equipment used to support these children, in monitoring capabilities, and in our understanding of the underlying processes that lead to pediatric respiratory failure. Challenges remain, however, and include ways to provide this resource-intensive care in the most cost-effective way, how best to support families so as to avoid caregiver fatigue/burnout and disruption of the family structure, and how to resolve ethical dilemmas associated with conditions for which this type of care is considered futile by some. For those adolescents with chronic conditions that result in permanent respiratory compromise, programs for transition to adult care will have to be created, as will social programs to guarantee access to public transportation, housing, and employment opportunities.

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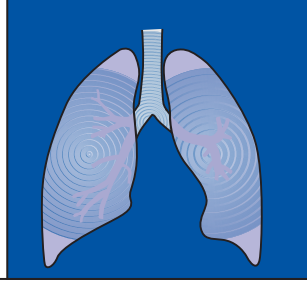


CHAPTER 23 Lung Trauma: Near-Drowning and Toxin Inhalation

Robert Henning

TEACHING POINTS

- In a burned child, intubate early if there are any signs of airway obstruction.
- Consider carbon monoxide and cyanide poisoning in any closed space fire.
- In burn inhalation or near-drowning, consider early bronchoscopy for diagnosis, removal of casts, or if lobar or segmental atelectasis is present.
- Use microbiologic surveillance only if there are new or increasing signs of sepsis.
- In blast injury, the principal lung problems are alveolar edema and air embolism.
- In any traumatic or inhalation injury to the lung, avoid corticosteroids and prophylactic antibiotics.
- Use the lowest ventilator pressures and tidal volumes that are compatible with acceptable gas exchange.
- In toxic chemical injury, remove from exposure, decontaminate, support breathing and oxygenation, and consider antidotes—repeated as often as needed.
- In suspected hydrocarbon inhalation, avoid induced vomiting, nasogastric lavage, and milk gavage.

SMOKE INHALATION: RESPIRATORY BURN INJURY

Burns are a leading cause of accidental death in children in the Western world.[1-3] In 2004 in the United States, fire caused the death of 3900 people and 18,000 were significantly injured.[4] Male gender, low socioeconomic status, and membership in a minority racial group increase the risk of death or injury from burns in children.[5] Burn injuries in house fires are more likely to cause death than were burns in other situations, especially in children under age 5, principally because inhalation injury is more common in house fires[5] and because young children lack the experience and strength to escape. Smoke inhalation is responsible for twice as many deaths as skin burns.[6] Inhalation injury increases burn mortality by 20% in large (>80% body surface area [BSA]) burns, 4-fold in medium (20% to 80% BSA) burns and 20-fold in smaller (<20% BSA) burns.[5]

Causes of Lung Injury

HEAT

Inhalation of hot dry gas (at up to 1000° C within a burning building)[7] injures the mucosa of the mouth, nose, pharynx, and larynx, but subglottic injury is limited to the upper third of the trachea because the inhaled gas has a low specific heat and the large heat-exchanging surfaces of the nose, mouth, and pharynx cool the gas before it reaches the mid-trachea. Flame burns from an explosion may cause severe mucosal injury to the upper trachea but do not burn small airways or lung parenchyma. Steam, which has a high specific heat, causes severe injury to the whole tracheobronchial tree and can injure alveoli. Scalds (e.g., in a toddler who swallows hot coffee) usually injure the mouth, pharynx, and larynx, but hot inhaled liquid can also injure the trachea, especially the subglottic region, and occasionally more distal parts of the bronchial tree[8] (for causes of lung injury, see Box 23-1).

CHEMICAL INJURY

Smoke consists of carbon particles suspended in a mixture of toxic gases. The particles, 5 μm to 5 mm in diameter, are coated with toxic products of burning or pyrolysis (heat-induced, nonoxidative decomposition of organic materials) (Table 23-1).[9-11] The high specific heat of the particles causes further heat injury to the mucosa of large and small airways. The particles also combine with sloughed cells, mucus, denatured protein, and edema fluid to obstruct airways and fill alveoli.

The gaseous and particle-coating toxins may be water soluble (e.g., NH_3, HCl, ketones) or water insoluble (e.g., phosgene, nitrogen oxides). Other constituents of smoke include systemic toxins such as carbon monoxide (CO), cyanide, antimony, cadmium, chlorobenzene, and propionitrile.[7,12] The water-soluble irritants cause coughing and increased ventilation, which exposes bronchioles and alveoli to the other toxins and promotes the entry of carbon particles into small airways. Alveolar ventilation increases on initial exposure to smoke and then decreases due to central nervous system depression.[7]

PULMONARY EFFECTS OF A SKIN BURN

Cutaneous burns cause acute lung injury (ALI: see Chapter 19), with impaired gas exchange, reduced lung compliance, and diffuse pulmonary infiltrates on the chest radiograph in the absence of inhalation injury. Massive chest wall edema and eschar formation cause severe restriction of tidal volume in the hours after a circumferential burn to the thorax, requiring urgent escharotomy to relieve the restriction and permit adequate ventilation.

BOX 23-1 Causes of Respiratory System Injury in the Burned Child

- Heat
  - Dry
  - Steam
  - Hot particles
- Smoke gases
- Toxin-coated carbon particles
- Hypoxia
- Carbon monoxide
- Cyanide
- Skin burn: systemic inflammatory response syndrome and chest wall edema

Pathology of Inhalation Injury[13]

AIRWAY EPITHELIAL INJURY

Flame injury to the oropharynx causes severe edema of supraglottic structures: massive swelling of the epiglottis, aryepiglottic folds, and ventricular folds develops over the first 1 to 4 hours postinjury, causing severe supraglottic airway obstruction and making visualization of the larynx extremely difficult.[14] The absence of supraglottic edema does not rule out significant injury to small airways, alveoli, or capillary endothelium, however. Soot is visible in the trachea in up to 30% of patients with clinical evidence of burn inhalation injury,[14] and up to 85% have erythema or edema of the tracheal mucosa.[15]

Heat and toxic chemicals (see Table 23-1) cause mucosal cells to separate rapidly from the basement membrane.[16] In moderate to severe injury, live mucosal cells may only be found in crypts and mucosal folds.[17] Necrosis of mucosal cells and inhibition of ciliary action in surviving cells by smoke chemicals such as aldehydes mean loss of ciliary activity, which leads to the blockage of airways by debris, causing atelectasis and secondary infection. A pseudomembrane consisting of sloughed cells, together with mucus from stimulated mucous glands, proteinaceous exudate, and carbon particles,[18] accumulates in alveoli and small and large airways.

Bacterial colonization of the airway is detectable by 72 hours.[19] Deeper injury to the basement membrane and submucosa permits the entry of bacteria into the interstitial tissues of the lung and into blood. In the longer term, it causes fibrous scarring with narrowing of large airways, especially at the tip of an endotracheal tube.

Water enters damaged type I pneumocytes, causing them to become rounded and bulge into the alveolar lumen, and to produce intercellular gaps, through which interstitial edema fluid enters the alveolus. Necrosis of type I pneumocytes leaves a bare alveolar basement membrane. By 7 days postinjury, this is gradually covered by proliferating type II pneumocytes.

HEALING

Airway healing occurs through the proliferation of surviving mucous gland cells or metaplasia of epithelial cells.[18] If the lung's reticulin fiber framework remains intact, normal lung architecture can be restored, but fibroblast proliferation and formation of mature collagen distort or obliterate alveoli and narrow the lumens of small bronchi and bronchioles. Complete healing takes up to 4 weeks in moderately severe injury.

SURFACTANT

Smoke inhalation and steam injury of the lung reduce surfactant activity, trebling the minimum surface tension, and abolishing the normal hysteresis of the surface tension–surface area curve.[20]

BRONCHIAL BLOOD FLOW

Bronchial blood flow rapidly rises 8- to 20-fold after inhalation injury.[10] As well as increasing the delivery of activated polymorphonuclear leukocytes to lung tissue, where they mediate tissue injury, this increased blood flow promotes fluid accumulation in the lung by increasing the capillary surface area available for fluid filtration and increasing downstream intracapillary pressures (see Pulmonary Edema). The

Table 23-1
Chemical Constituents of Smoke

Constituent	Source	Role	Effects
Acetic acid	Petroleum products, wood, paper, cotton	Irritant	Cough, bronchospasm, laryngospasm, mucosal injury
Acrolein	Wood, paper, cotton, acrylics, petroleum	Irritant	Cough, bronchospasm, damages cilia and macrophages
Formaldehyde	Wood, paper, cotton, melamine, wallpaper	Denatures protein	Mucosal and alveolar injury; pulmonary edema
HCl	PVC	Irritant	Cough, bronchospasm, pulmonary edema. Damages cilia and macrophages.
NH_3	Wool, nylon, melamine	Irritant	Cough, bronchospasm, laryngospasm, mucosal cell necrosis Airway and alveolar edema.
Nitrogen oxides	Wallpaper, nitrocellulose	Denatures protein	Cell necrosis in alveoli and bronchioles. Pulmonary edema and BOOP
Phosgene	PVC	Denatures protein	Cell necrosis in alveoli and bronchioles. Pulmonary edema and BOOP
Carbon monoxide	Most organic materials	Asphyxiant	Systemic anoxia: brain and heart failure
Cyanide	Nylon, polyurethane, carpets, upholstery	Asphyxiant	Systemic failure of electron transport: brain and heart failure

BOOP, bronchiolitis obliterans organizing pneumonia; PVC, polyvinyl chloride.
From Alarie Y: Toxicity of fire smoke. CRC Crit Rev Toxicol 32:259-289, 2002; Traber DL, Herndon DN, Soejima K: The pathophysiology of inhalation injury. In Herndon D (ed): Total Burn Care, 2nd ed. London, Saunders, 2002, pp 221-253; and Wald PH, Balmes JR: Respiratory effect of short-term, high-intensity toxic inhalations: smoke, gases and fumes. J Intensive Care Med 2:260-278, 1987.

mechanism of these changes is not yet certain, but inducible nitric oxide synthetase (iNOS) and sensory nerve–mediated release of substance P and calcitonin gene–related peptide may have roles.[10,21]

PULMONARY EDEMA

Alveolar and interstitial lung edema develops rapidly after a skin burn, even in the absence of inhalation injury. In addition, about 4 hours after inhalation injury, extravascular lung water and lung lymph flow increase markedly.[16] Proteinaceous fluid accumulates in alveolar septa, interstitial extravascular spaces, and bronchial submucosa, where it contributes to the marked small airway obstruction seen in burn inhalation injury. Edema fluid also fills alveoli, contributing to intrapulmonary shunting and increasing lung elastance.

Raised pulmonary and bronchial capillary pressures and transiently (lasting 48 hours) increased capillary permeability are responsible for the accumulation of fluid in the lung.[22] Several mechanisms underlie the increase in capillary permeability, including release of proteases and active oxygen species by activated neutrophils and upregulation of iNOS by polyADP-ribose polymerase (PARP) in damaged pulmonary epithelial cells. Inhibition of each of these pathways and neutrophil depletion reduce lung water and reduce the deterioration in gas exchange in animal models of inhalation injury.[21,23]

Carbon Monoxide

CO produced by partial combustion of a variety of organic materials (see Table 23-1) impairs oxygen transport by displacing oxygen from hemoglobin, for which its affinity is 250 times that of oxygen. CO shifts the oxyhemoglobin dissociation curve to the left, impeding the release of oxygen to the tissues, so that the total effect on tissue oxygenation is much worse than that of hypoxia alone.

At a P_{CO_2} of 0.16 mm Hg, 75% of hemoglobin is combined with CO, so that an FICO less than 0.1% can sequester much of the circulating hemoglobin.[24] When carboxyhemoglobin (COHb) is present, a pulse oximeter overestimates the true oxygen content of blood and may read 96% saturation, when COHb is 44% of total hemoglobin (i.e., when *available* hemoglobin is only 56% of total hemoglobin).[25]

The main intracellular effects of CO are as follows:

1. Inhibition of cytochromes, especially cytochrome *c* oxidase, leading to cellular energy failure, especially in brain, liver, kidneys, and myocardium[26]
2. Increasing the amount of free NO radical, which combines with superoxide anion to form peroxynitrite, leading to widespread endothelial injury, especially in the brain and lungs[24]

Myocardial injury reduces the cardiac output, and the consequent reduction in oxygen delivery exacerbates the energy failure, especially in central nervous system neurons. About 14% of survivors of significant CO poisoning develop acute neurological abnormalities (disorientation, excitement, lethargy, and coma), of whom some have permanent residual neurological deficits. COHb levels of 30% to 40% cause headache, nausea, confusion and syncope, and levels of 50% to 60% cause coma.

Cyanide

Cyanide is produced by the combustion of nitrogen-containing materials such as nylon and silk and polymers such as melamine and polyurethane.[27] Cyanide reversibly inhibits cytochrome oxidase, causing failure of mitochondrial energy metabolism and a metabolic acidosis, only a small proportion of which is due to excess lactate production.

Inhaled CN^- concentrations greater than 100 ppm cause death within 60 minutes, and 180 ppm causes death within 10 minutes.[28] Symptoms occur minutes to hours into moderate exposure to CN^-. Delayed toxicity (onset of symptoms hours after removal from CN^-) does not occur.

Central nervous system dysfunction due to cyanide varies from anxiety, lethargy, and confusion to coma, convulsions, and brain death.[28] Low concentrations of cyanide at brief exposure cause tachypnea (due to metabolic acidosis), which increases the entry of other toxins into the lungs, whereas central nervous system depression in prolonged exposure leads to hypoventilation and apnea. Myocardial toxicity causes tachycardia and hypertension early, followed by myocardial depression, hypotension, and reduced cardiac output, which further exacerbates the failure of intracellular oxidation and energy supply.

Diagnosis

In fire victims, inhalation injury is likely to be present in those with facial burns, conjunctivitis, or rhinorrhea and in those rescued from fire in a closed space (e.g., a house or an automobile fire). Dyspnea, cough, stridor, wheeze, and a hoarse voice are rarely present on arrival at the hospital but may develop later, and children almost never expectorate soot-laden sputum. Inhalation injury is a little more likely with larger than with smaller BSA burns.[29]

A history of inhalation of hot steam or of an infant who swallows hot liquids should lead to suspicion of an upper airway injury, with close observation for signs of stridor or upper airway obstruction, and investigation (see later) if necessary.

The principal issues to be considered at presentation in a child who has one or more of these risk factors are those that require early intervention:

1. Is upper airway obstruction present now, or is it likely to develop in the next few hours to the point that airway protection will become necessary?

Facial burns and a history of flame or hot steam exposure (or hot liquid ingestion in an infant) mean the child is at risk of supraglottic and subglottic swelling and obstruction. The presence of stridor with or without chest wall indrawing, a barking cough, a hoarse or muffled voice, or drooling or inability to swallow means that upper airway obstruction is present *now* and is likely to progress rapidly unless the airway is protected by insertion of an endotracheal tube. The stridor is usually low pitched and may be inspiratory or expiratory or both. Frequent observation to detect these signs is the most reliable method of functional assessment of the airway.

If the clinical signs are inconclusive, awake fiberoptic laryngoscopy following topical anesthesia of the nasopharynx

with lidocaine spray may give useful information about injury to the supraglottic tissues and the need to protect the airway by tracheal intubation.[30] Reduction of supraglottic swelling seen at laryngoscopy is a useful guide to the timing of extubation.[31]

Flexible bronchoscopy via an endotracheal tube may be used to diagnose airway injury and to assess its extent. Many pediatric burn units recommend bronchoscopy of all children with suspected inhalation injury on the day of admission.[32,33] Follow-up bronchoscopy over the next 72 hours is used to detect airway narrowing and the presence of airway casts. Recurrent airway obstruction by casts may require repeated bronchoscopy over the first 2 to 3 days. Large casts, however, may require rigid bronchoscopy for their removal.

After extubation, bronchoscopy may be used routinely to detect ulceration and swelling at the level of the vocal cords (especially the anterior commissure and interarytenoid area), at the cricoid cartilage, and at the endotracheal tube tip, to which burned children are especially prone.[34] Bronchoscopy is not a sensitive predictor of parenchymal lung injury.[15]

Spirometry and meaningful flow-volume curves are generally impossible to achieve in children younger than 6 years, especially in the presence of facial burns, pain, distress, and depressed conscious state. In teenagers with inhalation injury, FEV_1 and the FEV_1/VC ratio decrease in the first 6 hours after injury due to swelling of the mucosa in the large and small intrathoracic airways.[31,35]

2. Will this child develop respiratory failure in the next 6 to 12 hours?

The key to diagnosis of incipient respiratory failure is repeated clinical examination by an experienced observer. Dyspnea, tachypnea (especially if increasing), wheezing, crackles on auscultation, and hypoxemia are late signs of injury to the parenchyma and airways and imply the need for close monitoring and for immediate consideration of examination and protection of the airway and support of breathing.[36]

Cyanosis may be difficult to detect in the presence of skin burns, especially burns of the face or oropharynx. Pulse oximetry is unreliable when skin blood flow is reduced by hypovolemia, or when the tissues are edematous. Arterial blood gas analysis is then required to assess gas exchange. In most children with inhalation injury, $PaCO_2$ is normal or low. $PaCO_2$ may be raised by impaired respiratory drive due to head injury, hypoxic brain injury, cyanide or CO poisoning, or opiate drugs. Hypercarbia may also be caused by severe upper or lower airway obstruction or by splinting of the chest wall by edema, eschar formation, or pain.

Clinical signs of lung injury may fluctuate: dyspnea and cough may disappear when the child is removed from the smoky atmosphere but may return in 6 to 12 hours, as inflammation of the lung parenchyma increases. Wheezing due to airway mucosal edema, mucus production, and separation of sloughed mucosa in large and small airways may appear a few hours after injury and may suddenly increase due to movement of airway casts, requiring urgent bronchoscopy for cast removal. Gas trapping with chest hyperinflation, pulsus paradoxus, and occasionally pneumothorax may become more severe over the next 96 hours.

Chest auscultation is difficult over extensive skin burns, but areas of reduced air entry and focal or diffuse wheezes and crackles may be detectable. In small infants, there may be few signs other than hyperinflation, wheezing, poor air entry, tachypnea, and sometimes apnea.

Most wheezing after inhalation injury is due to mucosal edema, increased mucus production, and cast formation in the large and small intrathoracic airways; smooth muscle contraction is less often a significant factor. In children with reactive airways, irritant components of smoke such as NH_3, chlorine, and acrolein may provoke wheezing by stimulating type C sensory nerves within the respiratory tract mucosa. These sensory nerve fibers then release neuropeptides such as substance P and neurokinins A and B, which increase mucus production and vascular permeability, cause bronchoconstriction, and may activate mast cells.[37]

3. Is CO or cyanide poisoning present?

The most reliable indicators of CO and cyanide intoxication are a history of fire in a closed space, unconsciousness (even brief), confusion, convulsions, cyanosis (much more common than cherry-red mucous membranes in CO poisoning), pulmonary edema, or hypotension. Children are symptomatic (syncope or lethargy) at lower levels of COHb (e.g., 25%) than are adults.[38] Kussmaul breathing due to metabolic acidosis and red venous blood (due to impaired oxygen extraction) may be present in cyanide poisoning.

In any child suspected of suffering smoke inhalation, the child should breathe, or be ventilated with, 100% oxygen and blood samples should be taken for measurement of COHb and plasma cyanide. A high COHb may indicate the need for further normobaric or hyperbaric oxygen therapy, but the history of the fire conditions and repeated assessment of mental function are better guides to therapy when the COHb on presentation is low, as COHb depends on the time elapsed since exposure and the FIO_2 breathed in the meantime.[31,39]

The result of plasma cyanide measurement often arrives too late for timely administration of an antidote. In a child with a history of smoke exposure, metabolic acidosis, and physical signs of cyanide toxicity, administration of nitrites and sodium thiosulfate is justified if the COHb is high (>25%), as CO and cyanide intoxication often occur together.[31,40,41]

Radiological Investigation (Box 23-2)

The initial chest radiograph on presentation to hospital is an insensitive predictor of the development of parenchymal lung disease, as changes are present in only 50% of patients who later develop the condition.[32,42]

Some patients (up to 38%) in whom significant inhalation injury is suspected on clinical grounds never develop radiological changes attributable to the smoke injury. In patients who develop such changes, the great majority do so in the first 24 hours, and the remainder by 48 hours (Fig. 23-1A). Radiological changes appearing after 48 hours are generally associated with positive cultures of tracheal mucus and are more typical of bronchopneumonia or of fluid overload.[43]

If gas exchange deteriorates and dyspnea and the respiratory rate increase, a plain chest radiograph may reveal a pneumothorax, a collapsed lung or lobe, pulmonary edema,

BOX 23-2 Plain Chest Radiographic Signs of Burn Inhalation Injury

Atelectasis
Local (especially perihilar) or generalized alveolar opacity
Interstitial opacity
Regional or generalized overinflation due to gas trapping
Perivascular haziness
Peribronchial cuffing

From Whitelock-Jones L, Bass DH, Millar AJ, et al: Inhalation burns in children. Pediatr Surg Int 15:50-55, 1999; Wittram C, Kenny JB: The admission chest radiograph after acute inhalation injury and burns. Br J Radiol 67:751-754, 1994; and Teixidor HS, Rubin E, Novick GS, et al: Smoke inhalation: radiologic manifestations. Radiology 149:383-387, 1983.

an endotracheal tube displaced downward into a bronchus, pneumonic consolidation, or a pleural effusion.

Thoracic computed tomography (CT) scans may reveal more detail of the extent of atelectasis or consolidation (see Fig. 23-1B) and of associated injuries such as blunt trauma or blast injury of the lung (see later) than is seen on plain chest radiographs. CT scans have been used to grade the severity of lung damage in animal models of inhalation injury,[44] but for treatment and prognosis, the important indicators of injury severity are the functional variables of gas exchange and lung mechanics.

Management of Inhalation Injury (Box 23-3)

All patients should be given high flow oxygen (>10 L/min) by mask, and the stomach should be decompressed by a nasogastric tube because acute gastric dilation with its attendant risks of regurgitation-aspiration and impairment of venous return and of diaphragmatic movement is very common in children with skin burns and inhalation injury.

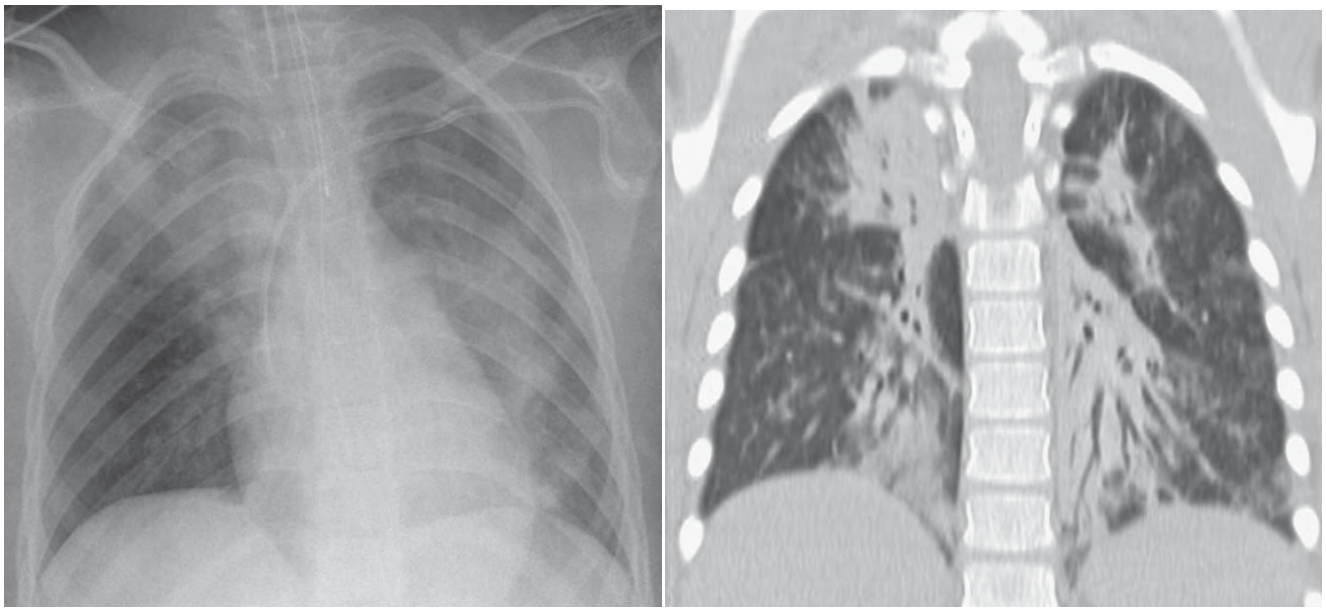
AIRWAY

If significant airway obstruction appears early after the injury, the child's trachea should be intubated immediately, because mucosal swelling and airway obstruction are likely to increase over the next 2 to 3 days. It is safer to intubate early rather than later, when mucosal edema in the mouth and pharynx and swelling of the tongue and its supporting structures make it much more difficult to visualize the larynx, identify landmarks, and enter the trachea. Inhalation anesthesia is used for tracheal intubation, as for any patient with upper airway obstruction.

Endotracheal tube fixation and patency are critically important in these patients because re-insertion of a dislodged or blocked endotracheal tube may become impossible when edema is at its maximum, and emergency tracheostomy may be extremely difficult and dangerous in the presence of neck burns. Nasotracheal tubes are more readily secured than are orotracheal tubes in small children, provided that there is no contraindication such as fractured skull base or severe coagulopathy. Adequate humidification, frequent tracheal suction, and close nursing observation are essential to the successful management of a child with inhalation injury of the airway.

BOX 23-3 Priorities in Acute Management

Maintain an adequate airway, breathing, and circulation
Establish venous access
Exclude carbon monoxide and cyanide poisoning



A B

Figure 23-1 **A,** Chest radiograph of a 3-year-old girl, 36 hours after burn inhalation injury, showing confluent airspace opacities in the right upper and left lower lobes, with loss of lung volume in the right upper lobe and some peribronchial cuffing. **B,** Coronal cut of a chest CT scan 1 month after inhalation injury (same patient), showing multiple areas of consolidation with patches of ground glass appearance.

If airway obstruction is minimal, the child should be observed very closely in a well-lit ward, with the diagnostic measures already discussed. There is no benefit from mist tents or steroids.[45] Although nebulized epinephrine may reduce the severity of large and small airways obstruction caused by edema, its use may not benefit the patient if it merely postpones tracheal intubation to a time when it becomes difficult or dangerous.

If tracheal intubation is impossible, or the laryngeal inlet cannot be seen, the safest options are (1) passage of an orotracheal tube over a fiberoptic laryngoscope and (2) needle or surgical cricothyroidotomy in a child older than 12 years and needle cricothyroidotomy in a child younger than 12 years.[45] Elective tracheostomy is rarely required, as even children who require tracheal intubation for 4 or more weeks can be safely managed with translaryngeal intubation, given meticulous attention to airway care and sedation.[46]

GAS EXCHANGE

Hypoxemia and the ($P_{AO_2} - P_{aO_2}$) difference increase progressively in the first 72 hours after inhalation injury. All patients should be given the highest available concentration of oxygen (by mask or endotracheal tube) if there is any suspicion of CO (see later) inhalation. If the P_{aO_2} deteriorates despite O_2 by mask, the child requires tracheal intubation and continuous positive airway pressure (CPAP) or intermittent positive pressure ventilation (IPPV) with positive end-expiratory pressure (PEEP) (see Chapter 19).

After 18 hours, any beneficial effect of a high partial pressure of inspired oxygen (P_{IO_2}) is outweighed by the risk of pulmonary oxygen toxicity, so every effort should be made to keep the F_{IO_2} below 0.5. This may involve permitting a P_{AO_2} of 45 to 50 mm Hg and using high levels of PEEP or high-frequency ventilation (Box 23-4).

The basic management of impaired gas exchange in inhalation injury is that of ALI (see Chapter 19). Institution of CPAP or IPPV/PEEP before hypoxemia develops will provide better long-term survival than if it is started after hypoxemia appears.[47] Noninvasive CPAP or bilevel positive airway pressure (BiPAP) delivered via face mask (see Chapter 19) can avoid tracheal intubation and its complications in many cases[48] but should be used only when airway injury has been excluded and the child is conscious and cooperative.[49] It is feasible even in the presence of facial burns[48] but may be more useful in older children and teenagers than in preschool children and infants, who have smaller faces (to which mask adjustment is more difficult) and are more irritable. Noninvasive ventilation requires close monitoring, lest the signs that bronchoscopy or intubation/ventilation are needed urgently be missed.

High-frequency oscillation with or without prone positioning (see Chapter 19) may be used when adequate oxygenation cannot be achieved by conventional ventilation without the use of excessive airway pressures.[33,50,51] Several centers have reported the use of ECMO with intact survival in children with burn inhalation injury.[52,53] Atelectasis, sputum retention, and airway casts may contribute to hypoxemia. Maintenance of gas exchange requires adequate humidification of inspired gas, regular tracheal suction, and, if necessary, bronchoscopic removal of casts. A pneumothorax caused by airway obstruction and consequent gas leak may lead to sudden hypoxia and hypotension and require urgent tube thoracostomy. Escharotomy of the chest wall is often needed to correct the restrictive lung defect and hypoventilation caused by circumferential chest burns.[45]

Bronchodilator drugs such as β_2-sympathomimetics do not improve the P_{AO_2}, P_{aO_2}, or lung mechanics when most wheezing is due to narrowing of large airways or the presence of airway casts or mucus plugs (and may increase the $P_{AO_2} - P_{aO_2}$ gradient by impairing focal hypoxic pulmonary vasoconstriction), but a therapeutic trial of nebulized albuterol is sometimes worthwhile. The use of corticosteroids for wheezing is justifiable only in patients who are known asthmatics or in patients dependent on exogenous steroids.[45] Their use in other children who wheeze after burn inhalation injury increases the risks of sepsis and gastric hemorrhage without demonstrable benefit.

SEPSIS

Secondary bronchopneumonia occurs in 30% to 50% of children with inhalation injury,[32,54,55] most commonly in the first 7 days and is a major cause of early and late (more than 3 weeks postburn) death. The principal risk factor for lung infection in children with inhalation injury is tracheal intubation, which bypasses the barriers to infection of the normal respiratory system and allows colonization of the airways by bacteria from the patient's own mouth, skin, and bowel.[11]

Routine bacteriological surveillance of tracheal aspirate and blood is likely to reveal tracheal colonization and transient bacteremias, respectively, neither of which requires antibiotic treatment. Cultures should be taken only when there is clinical suspicion of pneumonia (new fever, deteriorating gas exchange, new alveolar opacities on chest radiograph, rising white blood cell count with increasing immature neutrophils). In these circumstances, cultures of blood and bronchoscopic or blind bronchoalveolar lavage tracheal aspirate should be taken. Antibiotic therapy should cover *Staphylococcus aureus*, *Enterococcus* spp., and gram-negative bacilli including *Pseudomonas* spp.

Prophylactic antibiotics do not reduce the incidence or severity of pneumonia in children with inhalation injuries, but do increase the risk of colonization with antibiotic-resistant bacteria.[56] The evidence that drugs that suppress gastric acid secretion (e.g., ranitidine or proton pump inhibitors) are more likely to predispose a burned patient to gram-negative pneumonia than gastroprotective agents such as sucralfate is conflicting.[57,58] Experimental and nonhelpful trentments for

BOX 23-4 Ventilation Strategy to Avoid Ventilator-Induced Lung Injury

Low tidal volumes (6 mL/kg)
Moderately high PEEP (7 to 12 cm H_2O)
Permissive hypercapnia

From Smailes ST: Noninvasive positive pressure ventilation in burns. Burns 28:795-801, 2002; Sheridan RL, Schnitzer JJ: Management of the high-risk pediatric burn patient. J Pediatr Surg 36:1308-1312, 2001.

BOX 23-5 Experimental Treatments of Inhalation Injury

N-Acetyl cysteine aerosol
Heparin aerosol
Intravenous lisofylline
Intrabronchial instillation of surfactant via bronchoscope

From Desai MH, Mlcak R, Richardson J, et al: Reduction in mortality in pediatric patients with inhalation injury with aerosolized heparin/N-acetylcysteine. J Burn Care Rehabil 19:210-212, 1998; Tasaki O, Mozingo DW, Dubick MA, et al: Effects of heparin and lisofylline on pulmonary function after smoke inhalation injury in an ovine model. Crit Care Med 30:637-643, 2002; and Pallua N, Warbanow K, Noah EM, et al: Intrabronchial surfactant application in cases of inhalation injury: First results from patients with severe burns and ARDS. Burns 24:197-206, 1998.

BOX 23-6 Nonhelpful Treatments for Inhalation Injury

Corticosteroids
Mist tents
Prophylactic antibiotics
Routine microbiologic surveillance

inhalation injuries are listed in Box 23-5[59-61] and Box 23-6, respectively.

CARBON MONOXIDE AND CYANIDE

Any child who was unconscious at the fire scene or was rescued from inside a burning house or automobile may have sustained CO or cyanide poisoning and should receive high-flow oxygen by mask. The trachea of a child who has been unconscious should be intubated to allow 100% oxygen to be delivered.

The rate of COHb dissociation is proportional to the PaO_2,[62] so the use of hyperbaric oxygen (HBO_2) should be considered in any child whose COHb concentration is greater than 30% at hospital admission. The use of HBO_2 therapy remains controversial.[24] Of the six randomized trials that have assessed the outcome of its use, four found no benefit, whereas two found some benefit. All trials were flawed, and meta-analysis of the trials did not demonstrate a benefit.[63] Nevertheless, a number of nonrandomized trials and case series have found an unexpectedly good outcome in CO-poisoned patients after HBO_2 therapy, and its use is recommended in many centers,[24] provided that adequate staff expertise and facilities are available for safe transport of the child and care within the hyperbaric chamber.

Testing of blood for plasma cyanide is time consuming, so a decision to treat presumed cyanide toxicity is made on clinical grounds. Any child found unconscious or convulsing after inhalation injury and any child with severe CO poisoning should be treated for cyanide toxicity (Box 23-7).

BOX 23-7 Treatment of Cyanide Toxicity

Amyl nitrite: Inhale vapor from one amyl nitrite pearl for half of each minute until IV sodium nitrite infusion started.
Sodium nitrite 3% solution: infuse 0.33 mL/kg (maximum 10 mL) over 2 to 5 minutes
Then:
Sodium thiosulfate 25% solution: infuse 1.65 mL/kg (maximum 50 mL) over 5-10 minutes

From Curry SC: Cyanide: hydrogen cyanide, inorganic cyanide salts and nitriles. In Brent J, Wallace KL, Burkhart KK, et al (eds): Critical Care Toxicology Philadelphia, Elsevier/Mosby, 2005, pp 987-997.

Complications of Burn Inhalation Injury

Early complications include atelectasis, lung infection (discussed earlier) and barotrauma. Gas trapping due to obstruction of small and large airways by edema, slough, and carbon particles leads to air leakage from alveoli or from damaged airways. Pneumothorax, pneumomediastinum, pneumoperitoneum, and subcutaneous emphysema are especially common in patients mechanically ventilated with tidal volumes greater than 10 mL/kg but can occur with lower tidal volumes and even following coughing in nonventilated patients.[11]

Late complications include injury to the larynx and upper trachea and to small airways and lung parenchyma. Laryngeal injury by heat and smoke toxins may be exacerbated by tracheal intubation, leading to laryngeal scarring. Subglottic injury is generally found at the level of the tip of the tracheal tube or at the level of its cuff, especially when high cuff pressures are used. To avoid these injuries, the use of low cuff pressures, low ventilator airway pressures, and possibly early (within 10 days postinjury) tracheostomy should be considered.[64]

Some degree of small airways obstruction and increased airway reactivity occur commonly after inhalation injury[65,66] and may persist for 6 months or longer. In children, a combined restrictive and obstructive pattern may be found.[67] Bronchiectasis, bronchial stenosis, and bronchiolitis obliterans with progressive respiratory failure have also been reported following inhalation injury (see Box 23-8 for specific teaching points).

DROWNING

Drowning is a leading cause of death in Western countries. In the United States, approximately 850 children drown each year (1.4 : 100,000), of whom 60% are aged less than 4 years, while another 4500 sustain nonfatal immersion.[68] Boys are 4 times more likely to drown than are girls.[69] *Drowning* implies death within 24 hours after immersion, and *near-drowning* is an immersion injury with survival for at least 24 hours (Table 23-2).

Drowning causes a hypoxic-ischemic insult to the whole body. The main determinant of outcome is the severity of the hypoxic-ischemic brain injury. The lung itself suffers a hypoxic insult, as well as a direct injury from aspiration of water,

BOX 23-8 Burn Inhalation Teaching Points

- Intubate early if there are any signs of airway obstruction.
- Provide adequate humidification and tracheal tube suction.
- Early bronchoscopy is used for diagnosis and removal of casts.
- Consider noninvasive CPAP or BiPAP.
- Provide lung-protective ventilation strategy.
- Provide a trial of bronchodilator drugs for wheezing.
- Culture blood and tracheal mucus if clinical signs of sepsis are present.

Table 23-2
Aspects of Drowning and Near-Drowning in Different Age Groups

	Infant and Preschool-Age Children	Older Children and Teenagers
Site	Fresh water: Bucket Bath Backyard pool Farm pond or dam	River Lake Sea
Risk factors		
	Inexperience	Bravado
	Incoordination	Alcohol
	High center of gravity	Shallow water diving
	Unfenced pool	Epilepsy
	Lapse in adult surveillance	Cardiac arrhythmia
	Child abuse	

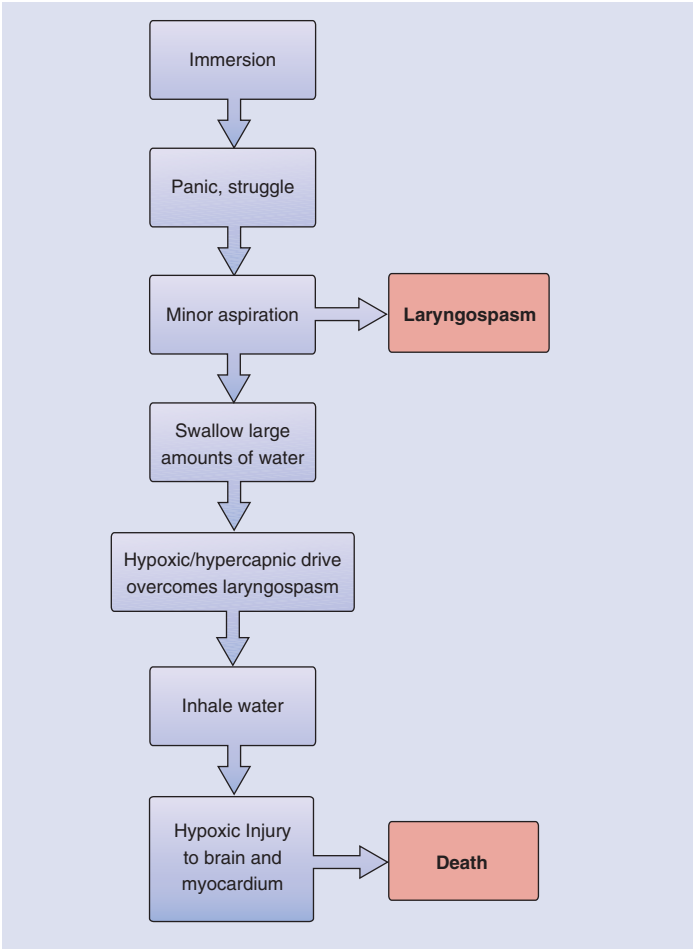


Figure 23-2 Sequence of events during immersion.

debris, dissolved toxins, microorganisms. and gastric contents. Pulmonary edema due to impaired performance of the asphyxiated myocardium and secondary septicemia further reduce lung function in near-drowned children.

Although it is often stated that 10% to 15% of drowned people do not inhale water, the evidence for this statement is in doubt, and many of these "dry-drowning" victims appear to have sustained a cardiac arrest before immersion.[70] A large study found the incidence of "dry drowning" to be less than 2%.[71] Most survivors of near-drowning have aspirated 22 mL/kg or less.[72] Gastric distention due to swallowed water leads to vomiting during resuscitation in at least half of child survivors, and aspirated gastric contents are found at autopsy in 70% of drowning victims[73] (Fig. 23-2).

Small or large bronchi may be obstructed by particles of sand,[74] mud, undigested food, or plant or animal debris, leading to atelectasis soon after rescue and to secondary infection of the obstructed lobe or segment (Table 23-3).

Table 23-3
Injurious Components of the Immersing Medium

Component	Effect
Water	Inflammation, edema, and surfactant depletion
Osmolality	Cell swelling (fresh water) or shrinkage (seawater)
Ions Ca^{2+}, Mg^{2+}	Hypercalcemia or hypermagnesemia
Gastric acid	Injury and inflammation of airways and alveoli
Gastric food particles	Airways obstruction and inflammation
Detergents	Airway mucosal injury
Oils	Lipoid pneumonitis
Industrial pollutants	Injury and inflammation of airways and alveoli
Suspended solids: sand,[74] clay, and mud	Airways obstruction and secondary infection
Phytoplankton and zooplankton	Airways obstruction; secondary inflammation and infection
Vegetable matter	Airways obstruction; secondary infection
Microorganisms	Pneumonia

Pulmonary Effects of Water Aspiration

Aspiration of sterile isotonic saline causes peribronchial and perivascular edema, thickening of alveolar septa, dilation of alveolar capillaries, and vesiculation of capillary endothelial cells and type I pneumocytes. Associated with these changes, static lung compliance decreases progressively over 3 or more hours postinsult. At 24 hours later, static compliance is still 50% of preinsult values, and focal areas of pneumonitis are present, with a peribronchial and perivascular infiltrate, mainly of mononuclear cells. Areas of atelectasis alternate with areas of hyperexpansion.[75] Removal, inactivation, and impaired production of surfactant, as well as capillary congestion and increased interstitial fluid, contribute to the reduction of static lung compliance.

Tonicity of the Aspirated Fluid

These changes are most severe when distilled water is aspirated but are almost as severe when 3% saline (similar to seawater) is aspirated.[76] Inhalation of fresh water leads to water movement into cells, and dilution of extracellular and intracellular fluid electrolyte concentrations, while inhaled seawater increases electrolyte concentrations and leads to exit of water from cells. In practice, in most cases, these electrolyte changes are very minor because of the small volume of water aspirated. The severity of pulmonary edema in survivors of freshwater drowning is very similar to that in salt water near-drowning.[77]

Injury to alveolar cells impairs surfactant production, obstructs air entry into alveoli, and impedes alveolocapillary gas diffusion. Injury to airway mucosal cells leads to increased mucus production and airway obstruction by swelling and sloughed cells and predisposes to gas trapping and to secondary infection. Acute respiratory distress syndrome (ARDS) develops within 1 to 48 hours in about 40% of survivors of near-drowning, because of a combination of direct lung injury (including a hypoxic-ischemic injury to the lung); the global hypoxic-ischemic injury, including that to the bowel; sepsis, and the host inflammatory response (see Chapter 36).

Hypoxic-ischemic injury to the myocardium impairs systolic and diastolic function, causing pulmonary congestion and edema, which exacerbates the defects in gas exchange and lung mechanics of the acute lung injury. A generalized increase in capillary permeability often follows a global hypoxic-ischemic injury, leading to pleural effusions, ascites, and edema of the lungs and chest wall. This further reduces respiratory system compliance, leading to hypoventilation, atelectasis, and impaired gas exchange.

Secondary Infection

Although lung infection complicates only a minority of near-drownings, it can be a severe, life-threatening complication. It appears more commonly in immersion in water polluted with microorganisms (e.g., sewers, drains, spas), in warm-water immersion, and when there is aspiration of gastric contents[78] or persistent atelectasis. The use of mild hypothermia for 12 to 24 hours to improve the neurological outcome in patients who have sustained a cardiac arrest does not appear to increase the risk of developing pneumonia[79,80] (Table 23-4).

Many of these pneumonias are associated with bacteremia and with a high case-fatality rate.[78]

Table 23-4
Sources of Infection

Subject's nasopharynx	*Pneumococcus; Staphylococcus aureus;* microaerophilic streptococci
Subject's bowel	Gram-negative bacilli
Immersion medium	
Spa or hot tub	*Pseudomonas aeruginosa*
Polluted pools	*Nocardia* spp.; *Pseudallescheria boydii; Aspergillus* spp., *Aeromonas* spp.; *Chromobacterium violaceum; Vibrio* spp.
Southeast Asian pools	*Burkholderia pseudomallei*

Assessment of the Near-Drowning Victim

On arrival at hospital, the airway is cleared and secured, adequate ventilation and oxygenation are achieved, independent circulation is established, and a nasogastric tube is passed. It is useful to know the duration of immersion, the nature of the immersing medium (fresh or salt water, muddy, polluted), and whether the child is known to have vomited.

Examination should address the patency of large and small airways, respiratory effort, and the adequacy of the child's breathing and gas exchange. Wheezing or asymmetry of air entry may suggest bronchial obstruction with foreign bodies. Tachypnea, expiratory grunt, alar flaring, tracheal tug, and soft tissue in-drawing are often present at the time of first assessment, and widespread crackles are commonly found on auscultation. In nonventilated children, these signs increase in prominence over the next 4 to 6 hours.

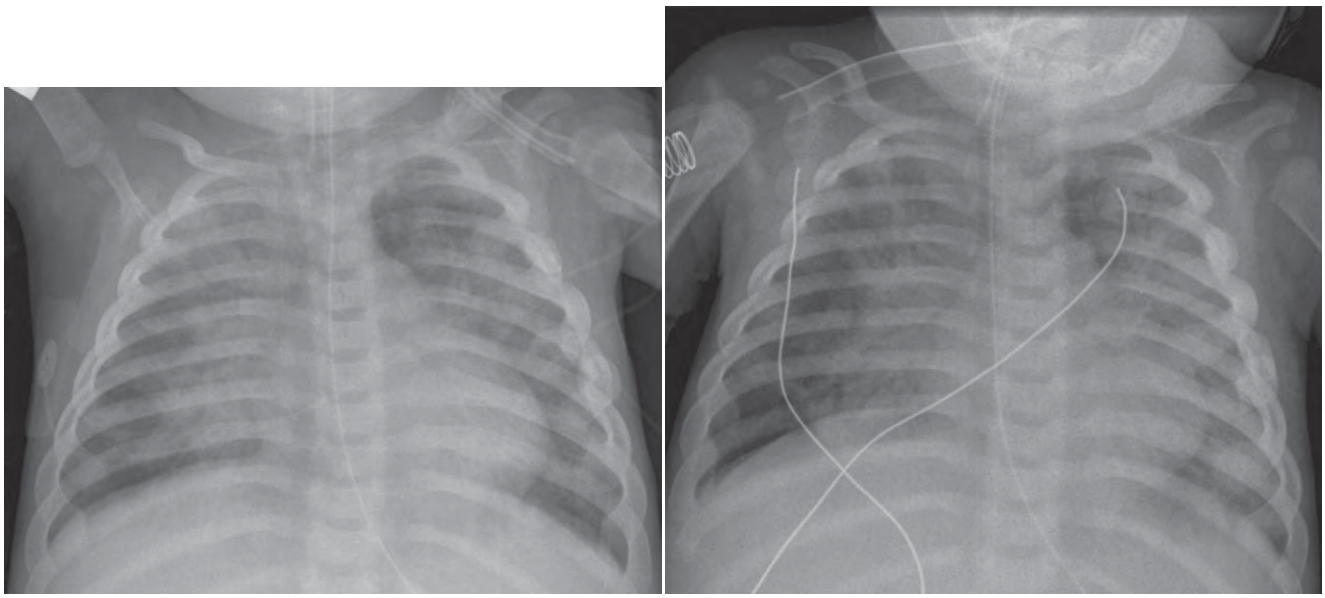
Initial assessment should include pulse oximetry and frequent arterial blood gas analysis, with calculation of the $P_{AO_2} - P_{aO_2}$. Gas exchange and lung mechanics often deteriorate over the first 12 hours in hospital, requiring increasing levels of respiratory support. A chest radiograph frequently shows patchy alveolar infiltrates (Fig. 23-3) and may show areas of atelectasis, gas trapping, or barotrauma due to obstruction of airways by foreign bodies. If the history suggests the possibility of large particle aspiration or if lobar or segmental atelectasis is present, fiberoptic bronchoscopy may be performed through the endotracheal tube. Rigid bronchoscopy may be needed for large particles.

After prolonged immersion (longer than 5 minutes) or if there is a history of asystolic cardiac arrest, or persistent hypotension, or if inotropic drugs are required, repeated echocardiographic examination is useful to monitor impaired myocardial performance as a contributor to respiratory dysfunction.

The total and differential white cell counts can indicate the development of infection in near-drowned children,[81] although the white cell count is commonly raised for 2 to 3 days (and the child may be febrile) after a global hypoxic-ischemic insult, even in the absence of sepsis.[78] Transient leukopenia due to hypoxic bone marrow depression, followed by leukocytosis with many immature neutrophils, often follows prolonged cardiac arrest. Bacteriological surveillance should include blood cultures and bronchoalveolar lavage if there are clinical or laboratory signs of sepsis. Organisms grown from cultures of tracheal mucus of near-drowned children may be upper airway contaminants, airway colonizers, or pathogens, so diagnosis of pneumonia in these circumstances depends on finding a positive blood or tracheal culture in the presence of new clinical signs of pneumonia, a secondary rise (or fall) in leukocyte count, and new radiographic changes.[78]

Management (Table 23-5)

The child's airway, breathing, and circulation are assessed and secured during primary resuscitation. The trachea should be intubated if the airway is obstructed, if the child's airway protective reflexes are inadequate, if ventilation will be required for more than a few minutes, or if the child's



A B

Figure 23-3 **A,** Chest radiograph of a 13-month-old, 2 hours after fresh water immersion, showing extensive, mainly perihilar, airspace opacities. **B,** Chest radiograph of the same patient, 24 hours later, showing some clearing of the pulmonary edema.

consciousness is impaired. All other near-drowned children should receive high-flow oxygen by mask.

In the presence of encephalopathy, the SaO_2 should be maintained greater than 96% (PaO_2 greater than 80 mm Hg) and the child should be mechanically ventilated to achieve a $PaCO_2$ of 35 to 40 mm Hg for optimal brain protection. In the absence of encephalopathy, SaO_2 should be maintained at greater than 90% (PaO_2 greater than 60 mm Hg). If this cannot be achieved by mask delivery of oxygen, CPAP 5 to 15 cm H_2O or bilevel positive airway pressure (BiPAP) may be delivered by face mask or nasal prongs. If these measures fail to maintain adequate gas exchange, the child requires tracheal intubation and mechanical ventilation. Prone positioning, high-frequency oscillation ventilation, and occasionally extracorporeal membrane oxygenation (ECMO) have been used, with a successful outcome in near-drowned children.

Table 23-5
Controversial Treatment Measures in Near-Drowned Children

Treatment Goal	Treatment Measure	Evidence of Efficacy
Maintain gas exchange	Open lung strategy: high PEEP and low tidal volume	Controlled trials suggest benefit[82]
	Prone positioning	Case reports suggest benefit[83]
	High frequency oscillatory ventilation	Case reports suggest benefit[84]
	ECMO	Case reports suggest benefit[85-87]
	Inhaled nitric oxide	Case reports suggest benefit
	Surfactant	Case reports suggest benefit[88]
Reduce lung inflammation	Pentoxifylline	Animal studies suggest benefit[89]
	Steroids	Reviews of evidence found little evidence of benefit from steroids[78,90]
Prevention of pneumonia	Prophylactic antibiotics	Not recommended. Case series did not show benefit[91,92]

Patients are usually hypovolemic from capillary leak of fluid after a significant near-drowning event.[77,93] Central venous pressure monitoring, fluid replacement, and inotropic drugs are more appropriate than diuretics, despite the presence of pulmonary edema.

Therapeutic bronchoscopy is often useful to remove obstructive debris when there is lobar or segmental atelectasis. Prophylactic antibiotics do not reduce mortality or the risk of pneumonia and should not be used. Although some recommend the use of frequent sputum cultures to direct antimicrobial therapy, the presence of colonizing organisms and upper airway contaminants makes interpretation of such cultures difficult. An alternative approach is to perform cultures only when there is new or increasing evidence of sepsis. Empirical treatment with an extended spectrum β-lactam/β-lactamase inhibitor with or without an aminoglycoside covers most bacterial causes of pneumonia in near-drowned children.[78]

Outcome

Mortality among patients who reach hospital after a near-drowning event is 10% to 20%.[93-95] Most deaths are due to neurological injury: Mortality due to acute lung injury or pneumonia occurs in 1% to 3% of patients.[93,94] About 70% of patients with cough and chest crackles develop pulmonary edema, and 15% develop pneumonia.[94]

In survivors, transient restrictive lung defects (lasting up to 4 months), and long-lasting small airways obstruction and bronchial hyperreactivity have been described[96,97] (see Box 23-9 for specific teaching points).

BOX 23-9 Drowning Teaching Points

- Early bronchoscopy is used if lobar or segmental atelectasis is present.
- Use microbiologic surveillance only if there are new or increasing signs of sepsis.

TRAUMATIC LUNG INJURY

Trauma is the principal cause of death in children in the United States. Chest trauma is second to brain trauma as a cause of death.[98] Thoracic injury is present in 5% of admissions to a pediatric major trauma center.[99] About 30% of these have an isolated chest injury,[99,100] with mortality about 5%.[99] When combined with a head injury, mortality increases to 35%.[99]

The most common intrathoracic injury is lung contusion or laceration in 50% of chest-injured children. Only 25% have rib fractures. Smaller numbers have injury to the trachea or major bronchi. From 60% to 90% of chest injuries in children are nonpenetrating (mainly to passengers or pedestrians in automobile accidents or due to falls or nonaccidental injury). The remainder are penetrating (gunshot or stabbing).[99,101,102]

Mechanism of Injury

When struck by an object (e.g., the ground or part of a motor vehicle) or a blast pressure wave, the body wall deforms. Its viscoelastic properties mean that high-velocity impacts transmit more energy to chest viscera than does lower-velocity deformation of the same or greater depth.[103] Fast impacts such as blast produce high-amplitude pressure waves in tissues: these travel at or above the velocity of sound. Slower impacts (e.g., deceleration of a moving body) cause low-velocity shear waves, which severely distort tissues and organs. This causes collision of viscera with rigid structures; stretching and tearing tissue components (e.g., bronchi and blood vessels) at points of attachment, and acceleration of tissues of different densities (e.g., alveoli and blood vessels) at different rates, causing asynchronous motion and tearing.[104]

Although rib fractures (including fractures at two sites on the same rib, producing a flail segment) may uncommonly be found in children, a more common finding is severe injuries to thoracic viscera without rib fracture,[102] as the child's less-calcified ribs can flex markedly without breaking.

Lung Contusion

Widespread disruption of alveoli and alveolar capillaries underlying the area of impact (or in the opposite lung, because of contrecoup injury) causes extravasation of blood into alveoli, small airways and interstitial spaces in the lung, obstructing air entry to injured and noninjured parts of the lung, and providing a substrate for secondary infection. Intrapulmonary shunt and ventilation-perfusion mismatch increase, leading to hypoxemia.[105] Extravasated blood, the consequent inflammatory response, and reduced surfactant production increase lung water and lung elastance, leading to increased work of breathing and hypercarbia.[106] Increased mucus production exacerbates the obstruction of large and medium-sized airways caused by the presence of blood.

Following the interstitial hemorrhage, inflammatory edema and cellular infiltrate accumulate over 48 hours[106,107]; the contusion heals over 7 to 10 days with little pulmonary scarring.[107]

At presentation to hospital, there may be few clinical signs apart from mild tachypnea and desaturation. These may become more severe over the next few hours, requiring CPAP or mechanical ventilation to maintain adequate gas exchange. Air entry may be reduced, and dullness to percussion and inspiratory crackles appear. Patchy alveolar opacity appears on plain chest radiographs in the first 6 hours and becomes more dense over the next 12 hours. On CT scan, the contused area is usually a subpleural crescent of consolidation in the posterior part of the lung. It often extends across the boundaries of lung segments and lobes[108] (Fig. 23-4).

The most common differential diagnosis is fat embolism, especially in older children and teenagers with long bone fractures. The most useful differentiating features are the presence of overlying skin injury and the localized nature of the lung contusion compared with widespread, late-appearing (24 to 48 hours postinjury) radiological opacities in fat embolus. Less reliable indicators are the presence of skin petechiae, encephalopathy, and urinary fat globules in the fat embolism syndrome.

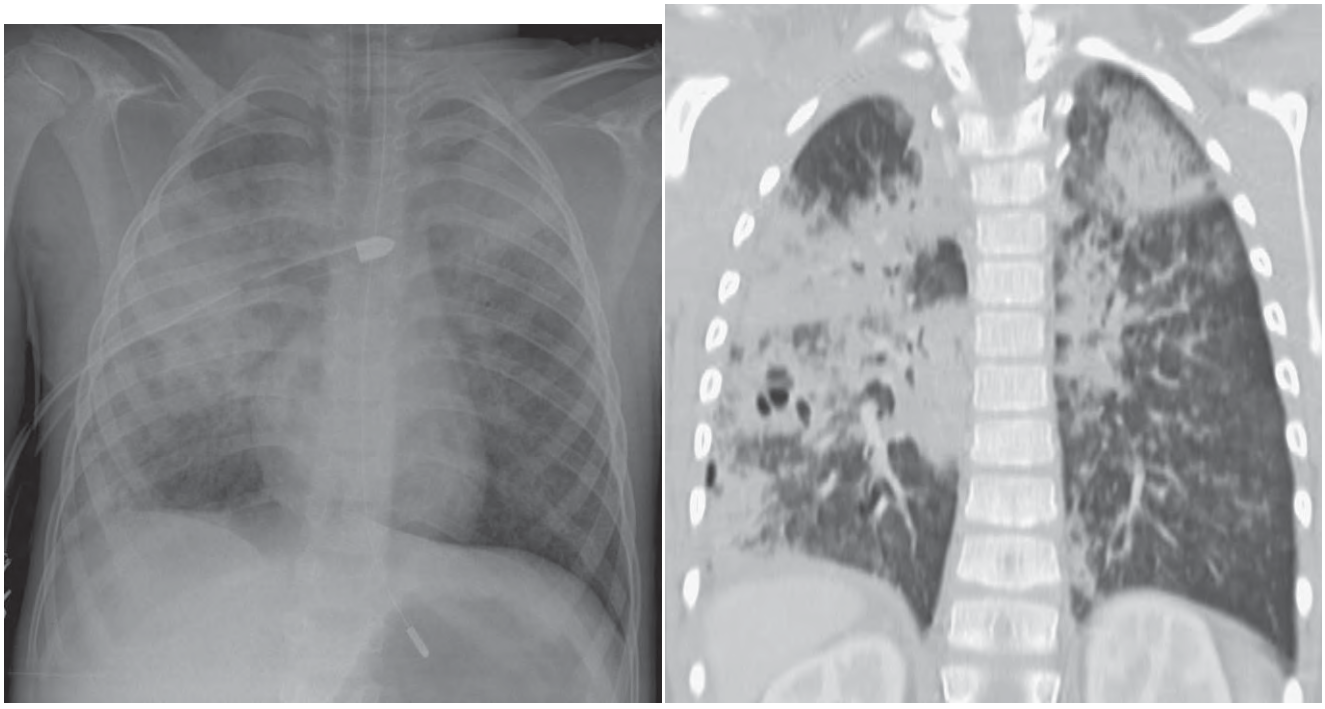
Management of lung contusion is supportive. Blood gases should be maintained in the normal range by mechanical ventilation only if required for optimum management of associated injuries (especially head injury and hemorrhagic shock). Otherwise, more conservative management goals (e.g., PaO_2 greater than 50 mm Hg and pH greater than 7.25) may be used. There is no convincing evidence to support the use of steroids or prophylactic antibiotics in lung contusion.[104]

In contrast to adults, 70% of whom have residual restrictive lung defects after sustaining lung contusion,[109] most children recover without residual abnormalities of lung function.[110]

Lung Laceration

The lung surface can be lacerated by the ends of fractured ribs or, in the absence of rib fracture, by extreme deformation of a child's flexible rib cage. Hemothorax, pneumothorax, and hemopneumothorax are often found in association with tears of the lung surface. They may uncommonly be associated with injuries to major bronchi and other mediastinal structures. A small pneumothorax found on plain chest radiograph or CT scan should be observed clinically and on follow-up radiographs but does not require drainage, even in children on mechanical ventilation,[111] unless it expands significantly or interferes with gas exchange or with venous return. Larger pneumothoraces and hemothoraces require tube thoracostomy[98] (preceded, in the case of a tension pneumothorax, by needle thoracostomy). Rarely, a large laceration causes a severe air leak and requires surgical repair, preceded by bronchoscopy to exclude tracheobronchial injury.[98]

Lung deformation and tearing can also lead to the formation of cavities within the lung that may become filled with blood (intrapulmonary hematoma) or with air (traumatic



A B

Figure 23-4 **A,** Chest radiograph of an 8-year-old, 1 hour after being run over by an automobile, showing extensive confluent airspace opacities in the periphery of both lungs, with a residual right-sided hemothorax. **B,** Coronal cut of a CT scan from the same patient, 4 hours after injury, showing widespread, mainly subpleural opacities, with some cystic areas in the right upper lobe and the apical segment of the right lower lobe.

pneumatocele). The hematoma, a rounded opacity that may contain an air pocket, appears on chest radiographs only when the surrounding area of contusion begins to fade. It generally resolves over 1 to 2 months without specific treatment.[112]

Traumatic pseudocysts may be asymptomatic or may be associated with dyspnea, cough, and hypoxemia. They appear on plain erect chest radiographs after 5 to 6 days as a round or oval air-filled cavity that may have a fluid level but may not be apparent on supine films.[113] They do not require drainage or other specific treatment unless they become infected, bleed or expand progressively, or rupture into the pleural cavity.

Tracheobronchial Injuries

Tears in the airway occur anywhere from the glottis and extrathoracic trachea (causing severe subcutaneous emphysema) to the major bronchi, where they cause pneumothorax, bronchopleural fistula, and mediastinal and subcutaneous emphysema, as well as airway obstruction and collapse of a lobe or lung. The usual cause is anteroposterior crush injury of the larynx, trachea, or chest wall or a blow-out injury by severe chest and lung compression with a closed glottis.[98] Investigation requires bronchoscopy. Small tears may be managed conservatively, but larger tears require surgical repair (see Box 23-10 for specific teaching points).

BOX 23-10 Traumatic Lung Injury Teaching Points

- Low-velocity trauma causes lung laceration and subpleural consolidation.
- Avoid corticosteroids and prophylactic antibiotics.

BLAST INJURY

Accidental blast injuries are less common in childhood than in young adults, but landmine- or terrorism-related blast injuries in children are becoming increasingly common.[114-116]

Detonation involves very rapid expansion of gases, which produces a wave of high pressure traveling faster than the speed of sound, followed by a wave of low pressure, then a longer-lasting blast wind that is strong enough to throw the human body and other objects about, causing severe injury. Blast in enclosed spaces (e.g., buses, trains, or buildings) is even more damaging, as reflection of shock waves produces very high pressure summation waves. This explains the much higher mortality rate and frequency of lung injury in closed-space explosions compared with open-air explosions.[117]

In addition to the tissue disruption caused by differential acceleration of structures of different densities,[118] shock waves due to blast cause "spalling" (shearing or bursting) at gas–liquid interfaces such as alveoli, which disrupts alveoli and alveolar capillaries. They also cause implosion due to rebound overexpansion of gas-containing spaces after the pressure wave passes.[104] Widespread damage to alveoli and alveolar capillaries leads to hemorrhage into alveoli and airways, to rapid accumulation of edema fluid in alveoli and pulmonary interstitial tissues, and to the entry of air into pulmonary vessels, with consequent systemic air embolism. Air emboli to cerebral or coronary vessels can lead to sudden

BOX 23-11 Blast Injury Teaching Points

- The principal lung problems are alveolar edema and air embolism.
- Drain any hemothorax or pneumothorax.
- Use the lowest ventilator pressures compatible with acceptable gas exchange.

death in minutes. Widespread air or fibrin emboli cause long-lasting injury to tissues and organs, including the spinal cord.[118,119]

Blast injury to the lung is very often associated with other primary injuries, including burns, traumatic amputations, and injuries to the head, abdomen, eyes, and tympanic membranes and to penetrating shrapnel injuries.[117,118,120] Patients present with dyspnea, hypoxemia, cough, chest pain, and hemoptysis. Bloodstained froth is found in tracheal or gastric aspirates. There may be signs of air emboli to brain, heart, and other organs. Most patients have alveolar infiltrates on chest radiograph, usually bilateral and perihilar, but sometimes diffuse. Pneumothorax and pneumomediastinum may also be present.[120]

Management is supportive: hemothoraces and significant pneumothoraces should be drained. The prone position or affected lung downward is used to limit the entry of air into the left ventricle.[121] All patients should receive the highest practicable concentration of oxygen by mask, or (unless basal skull fracture is suspected) by mask CPAP. Severe type II respiratory failure or severe hemoptysis requires tracheal intubation and mechanical ventilation using permissive hypercapnia and, if necessary, PEEP at 10 cm H_2O.[120] The lowest peak airway pressure that achieves acceptable PaO_2 (50 mm Hg) and pH of 7.2 is used, as high peak airway pressures increase the risk of systemic air embolism.[118] Occasionally, high-frequency oscillation or jet ventilation may be needed.[122] Hyperbaric oxygen treatment has been used to treat systemic air emboli.

Although almost all patients with pulmonary blast injury develop signs within 1 hour, it is prudent to observe blast victims without such signs, and with a normal chest radiograph and blood gases, for at least 6 hours.[121] Patients with moderate or severe injury may develop ALI and multiorgan failure, while those with milder injury begin to improve within 24 hours of injury.[122] Many survivors have complete asymptomatic recovery, while a few have a residual restrictive defect[120] (see Box 23-11 for specific teaching points).

BIOLOGICAL WARFARE AGENTS AND THE CHILD'S RESPIRATORY SYSTEM

Biological warfare is the intentional release of infective organisms or their toxic products for the purpose of killing or harming enemy military personnel or populations. In the case of biological terrorism, the target is the civilian population, and the aim is to disrupt the society by overwhelming its medical and social resources and undermining the confidence of the civilian population in the infrastructure and institutions of the society. In warfare, biological weapons are more likely to be used as strategic weapons (against populations) than as tactical weapons against troops, because their onset of effect is too slow for tactical use.[123] Therefore, either in warfare or in terrorist attacks, children are likely to be affected (Box 23-12).

BOX 23-12 Characteristics of an Effective Biological Warfare Agent

Cheap and easy to produce
Easy to deliver in an effective form (e.g., 1- to 6-μm aerosol particles)
Easy to disseminate (e.g., as aerosol rather than diluted in a water supply)
Easy to conceal and transport
Short incubation period causes mass casualties simultaneously for maximum psychological effect
Lethal effect
Highly contagious
Difficult to treat
Its name causes fear in the population (e.g., "plague" or "anthrax")

From Weinstein RS, Alibek K: Biological and Chemical Terrorism: A Guide for Healthcare Providers and First Responders. New York, Thieme, 2003.

The U.S. Centers for Disease Control and Prevention (CDC) classifies possible biological warfare agents as class A (easily disseminated or person-person transmission; high mortality; requiring intensive public health intervention and preparedness; likely to cause panic: e.g., plague, anthrax; smallpox, viral hemorrhagic fevers; botulism; tularemia); class B (moderately easily disseminated; moderate morbidity but low mortality: e.g., brucellosis; Q fever; ricin; T-2 mycotoxins) or class C (pathogens that are available and could be readily produced and engineered as bioweapons: e.g., hantaviruses; yellow fever; tick-borne encephalitis).[123] Box 23-13[125] lists reasons for the vulnerability of children to biological agents.

Adequate treatment of several of these diseases depends on early diagnosis and treatment in the incubation period or at the first manifestations: Box 23-14[126] lists possible indicators of the presence of a biological attack (Tables 23-6 and 23-7).

BOX 23-13 Vulnerability of Children to Biological and Chemical Warfare Agents

Inexperience and small size make avoidance and escape difficult.
Inability to communicate symptoms impedes timely diagnosis and treatment.
Some vaccines (e.g., plague and anthrax) are not licensed for children.
There is a reluctance to use drugs such as doxycycline and fluoroquinolones in children.

From Cieslak TJ, Henretig FM: Bioterrorism. Pediatr Ann 32:154-165, 2003.

BOX 23-14 Indicators of a Biological Attack

- Appearance of an uncommon disease (e.g., inhalational anthrax)
- Clusters of patients with an uncommon disease in a nonendemic area
- Unusual route of infection or time of year for that disease
- Unusual patient age, clinical presentation, or severity of a known disease
- Increased mortality in birds or animals
- Unusual variant of microorganism, including antibiotic sensitivity pattern
- Claim of attack by a terrorist group

From Khardori N: Bioterrorism and bioterrorism preparedness: Historical perspective and overview. Infect Dis Clin North Am 20:179-211, 2006.

Individual Diseases

ANTHRAX

Organism

Bacillus anthracis

Weapon

Aerosolized 1- to 2-μm endospores

Disease

Inhalational anthrax

Mortality

Fifty kilograms of anthrax spores spread upwind of a city of 500,000 is estimated to cause illness in 250,000 people and kill 100,000.[127]

Presentation

Fever, rigors, dry cough. After 2 to 3 days, sudden severe dyspnea, fever, profuse sweating, and shock appear. Severe mediastinal lymphadenopathy may cause stridor and superior vena caval obstruction with head and neck edema; 50% have hemorrhagic meningitis. Rapidly increasing respiratory failure and shock lead to death within 36 hours.[128]

Diagnosis

Depends on awareness and suspicion. The chest radiograph shows a wide mediastinum with pleural effusions and alveolar infiltrates. These changes and the hilar adenopathy are even more evident on CT scan and are the most sensitive and specific features that differentiate inhalational anthrax from community-acquired pneumonia or influenza-like illness. Other differentiating features are nausea, vomiting, temperature above 100.4° F, altered mental status, and cold mottled, cyanotic, or sweaty skin.[129] Blood culture is positive if taken before antibiotics are given.[128] Enzyme-linked immunosorbent assay or polymerase chain reaction testing of blood, cerebrospinal fluid, or tracheal aspirate may confirm the diagnosis.[130]

Treatment

In children, combination therapy with ciprofloxacin 10 to 15 mg/kg (maximum 400 mg) IV every 12 hours or doxycycline 2.2 mg/kg (maximum 100 mg) IV every 12 hours, *plus* amoxicillin 50 mg/kg IV every 6 hours is recommended.[130,131]

Table 23-6
Biological Warfare Agents That Cause Fever Plus an Acute Respiratory Illness (Cough, Dyspnea, and Cyanosis)

Disease or Agent	Delivery	Person-Person Transmission	Incubation Period
Inhalational anthrax	Spores/aerosol/food	No	1-5 days
Blastomycosis	Spores/aerosol	No	30-45 days
Hantavirus	Aerosol/food/water	No	1-5 weeks
Legionnaires' disease	Aerosol	No	2-10 days
Leptospirosis	Aerosol	Rare	3-30 days
Melioidosis	Aerosol/soil/water	Yes	2-400 days
Pneumonic plague	Aerosol or fleas	Yes	1-6 days
Psittacosis	Aerosol	Rare	5-15 days
Q fever	Aerosol/food/water	No	2-14 days
Pneumonic tularemia	Aerosol/ticks/food/water	No	3-14 days

From Weinstein RS, Alibek K: Biological and Chemical Terrorism: A Guide for Healthcare Providers and First Responders. New York, Thieme, 2003.

Table 23-7
Agents Causing Respiratory Failure but with a Nonrespiratory Presentation or Site of Action

Disease or Agent	Delivery	Person-Person Transmission	Incubation Period
Botulism	Aerosol/food/water	No	18-36 hr
Tricothecene (T-2) mycotoxins	Aerosol/droplets/skin absorption	Via skin contact with a victim	Minutes to hours
Tetrodotoxin	Aerosol/food/water	No	10 min to 3 hr
Saxitoxin	Aerosol/food/water	No	30 min to 10 hr
Lassa fever	Aerosol	Yes	5-14 days

Patients given antibiotics earlier than the median 4.7 days from symptom onset had a 40% mortality rate, compared with 75% mortality for those treated later than 4.7 days.[132]

Prophylaxis
Ciprofloxacin 10 to 15 mg/kg (maximum 500 mg) orally every 12 hours or doxycycline 2.5 mg/kg (maximum 100 mg) orally every 12 hours. The cell-free $Al(OH)_3$-adsorbed vaccine AVA effectively prevents inhalational anthrax when combined with post-exposure antibiotics, but requires a series of six inoculations over 18 months and is available only to individuals at high risk of exposure.[130]

BLASTOMYCOSIS[124]

Organism
Blastomyces dermatitidis

Weapon
Aerosolized spores

Disease
Sixty percent of cases develop pneumonia.

Mortality
Five percent

Presentation
Fever, rigors, cough, myalgia, arthralgia; 60% develop a productive cough, hemoptysis, pleuritic chest pain, and dyspnea. Chest radiograph may show hilar lymphadenopathy, alveolar infiltrates, nodules, and cavitation.

Diagnosis
Depends on suspicion plus culture and staining of yeast-like organisms in tracheal aspirate, bronchoalveolar lavage fluid, or lung biopsy specimens

Treatment
Treatment of pneumonia: Amphotericin B 0.3 to 0.6 mg/kg IV daily until stable, then itraconazole 4 mg/kg daily orally for 6 months; 10% to 14% relapse; review every 3 to 6 months for 2 years

HANTAVIRUS[133]

Organism
Members of the genus *Hantavirus* (especially Sin Nombre virus)

Weapon
Aerosol of virus or of infected rodent excreta

Disease
Hantavirus pulmonary syndrome

Mortality
Forty percent

Presentation
Three to 5 days of mild febrile illness: fever, rigors, myalgia, malaise, headache, nausea, diarrhea, followed by sudden onset of severe pulmonary edema due to increased capillary permeability. Tachypnea, hypoxemia, and dyspnea usually require mechanical ventilation. Severe cases have marked myocardial depression, with hypotension, metabolic acidosis, exacerbation of pulmonary edema, and tachyarrhythmias. In survivors, heart function returns to normal over 1 week, but many have residual small airways obstruction.

Diagnosis
Based on clinical suspicion plus sudden onset of pulmonary edema, with thrombocytopenia, hemoconcentration and left shift of polymorphs, together with rising titres of Hantavirus-specific IgM and IgG

Treatment
Supportive: Mechanical ventilation for respiratory failure, and management of circulatory failure using close hemodynamic monitoring, inotropic drugs, and antiarrhythmic agents as required

LEGIONNAIRES' DISEASE (see Chapter 35)

Organism
Legionella pneumophila

Weapon
Aerosolized droplets

Disease
Legionnaires' disease

Mortality
Five percent to 15%

Presentation, Treatment, and Outcome
See Chapter 35.

MELIOIDOSIS[124,134]

Organism
Burkholderia pseudomallei

Weapon
Aerosolized droplets

Disease
Acute pulmonary melioidosis

Mortality
After a bioterrorist attack, not known

Presentation
Sudden onset of high fever, rigors, headache, myalgia, cough, and chest pain. This may progress to pneumonia with lung abscesses, which may become chronic.

Diagnosis
Clinical suspicion plus chest radiographic appearance of pneumonia, miliary nodules, or lung abscess. The organism may be cultured from blood, urine, tracheal aspirate or needle aspirate of abscesses, or from skin lesions.

Treatment
Ceftazidime 50 mg/kg IV every 6 hours plus amikacin 15 to 20 mg/kg IV daily plus sulfisoxazole 75 mg/kg (maximum 4 g) stat, then 35 mg/kg (maximum 1.5 g) orally every 6 hours for 4 weeks[134]

PNEUMONIC PLAGUE

Organism
Yersinia pestis

Weapon
Aerosol of organisms or release of infected fleas

Disease
Pneumonic plague, which can develop primarily from inhalation of an aerosol or may develop from progression of bubonic plague caused by the bite of an infected flea

Mortality
Almost invariably fatal if antibiotic treatment is started more than 24 hours after onset of symptoms.[135] Fifty kilograms of dried organism released 2 km upwind of a population center of 500,000 has been estimated to cause 100,000 casualties, of whom 55,000 will die.[123] Pneumonic plague is extremely contagious via droplet spread.[124]

Presentation
Pneumonic plague: Sudden onset of fever, rigors, headache, myalgia, and malaise. Buboes are absent. Chest pain, dyspnea, and productive cough follow rapidly. Sputum (in adolescents and older children) is mucoid or frothy and blood-streaked. Respiratory failure ensues early, followed by circulatory collapse, disseminated intravascular coagulation, and multiorgan failure. Chest radiograph shows patchy atelectasis or segmental consolidation, which spreads rapidly

Diagnosis
Depends on recognition of profuse gram-negative or bipolar stained bacilli in blood or sputum, especially if the laboratory is aware of the possibility of plague[123,131]

Treatment
For 10 days: Streptomycin 15 mg/kg (maximum 1 g) IM every 12 hours or gentamicin 6 mg/kg IV daily or doxycycline (>8 years old) 2.2 mg/kg IV every 12 hours. *Exposure prophylaxis (for 7 days):* Ciprofloxacin 15 mg/kg every 12 hours by mouth

PSITTACOSIS (see Chapter 41)

Organism
Chlamydia psittaci

Weapon
Aerosol of organisms

Disease, Presentation, Clinical Course, and Treatment
See Chapter 41.

Mortality
Approximately 20% (possibly greater in a bioterrorism attack due to the high initial organism load)[124]

Q FEVER (see Chapter 35)

Organism
Coxiella burnetii

Weapon
Aerosol of organisms

Disease, Presentation, Clinical Course, and Treatment
See Chapter 35.

Mortality
Uncommon

TULAREMIA (see Chapter 35)

Organism
Francisella tularensis

Weapon
Aerosol of the organism

Disease
Pneumonic tularemia

Presentation, Clinical Course, and Treatment
See Chapter 35.

Mortality
From 35% to 45% if untreated; 5% to 9% if diagnosed and treated early[136,137]

BOTULISM

Agent
Toxin of *Clostridium botulinum*

Weapon
Aerosol or contamination of food or water

Disease
Descending paralysis, including paralysis of respiratory and bulbar muscles, leading to respiratory failure, which may last weeks to months

Lethality
LD_{50} of 1 ng/kg

Treatment
Horse serum antitoxin is most effective if given within 24 hours of the onset of symptoms.[138] Therapy is supportive and includes prolonged (weeks) mechanical ventilation.

SAXITOXIN (PARALYTIC SHELLFISH POISONING)[124,139]

Agent
Toxin produced by various marine microalgal dinoflagellate species, including *Alexandrium* spp., *Pyrodinium* spp., and *Gymnodinium* spp.

Weapon
Aerosol or contamination of food or water

Disease
Numbness and paraesthesiae of the face and limbs, rapidly progressive ascending paralysis, including paralysis of respiratory and bulbar muscles, leading to respiratory failure. Hypersalivation and sweating. Cardiac failure and arrhythmias and hypotension in severe cases. Muscle power returns in 3 to 4 days.

Treatment
Supportive: Mechanical ventilation if needed, plus support of cardiac failure and cardiac arrhythmias

TETRODOTOXIN[124,139]

Agent

Toxin of several marine species, including toadfish, puffer fish, blue-ringed octopus, xanthid and horseshoe crabs, and some newt, frog, and worm species

Weapon

Aerosol or contamination of food or water

Disease

Facial numbness and paresthesia, progressive ascending paralysis, including paralysis of respiratory and bulbar muscles, leading to respiratory failure. In severe cases, there may be hypotension or hypertension, cardiac arrhythmias, and seizures

Lethality

Up to 50% in severe cases, even with intensive supportive treatment

Treatment

Supportive care of airway, breathing, and circulatory abnormalities

TRICOTHECENE MYCOTOXINS[124,140]

Agent

Mycotoxins, including T-2, produced by various fungal species of the genus *Fusarium*

Weapon

Aerosol is inhaled or absorbed through intact skin

Disease

Rapid onset of skin and eye redness, burning and ulceration; epistaxis, wheeze, dyspnea, cough, and pulmonary hemorrhage with hemoptysis

Treatment

Supportive: Intravenous fluids, analgesia, and mechanical ventilation if necessary. Decontamination of skin by irrigation may prevent person-to-person transmission.

LASSA FEVER[124,141-143]

Agent

Several members of the Arenavirus family, including the Lassa, Junin, Machupo, and Sabia viruses, cause similar syndromes of viral hemorrhagic fever.

Weapon

Aerosol of the virus or contamination of surfaces, food, or water

Disease

High fever, rigors, sore throat, myalgia, and diarrhea. Endothelial damage and increased vascular permeability lead to a widespread petechial rash, mucosal bleeding, shock, and pulmonary edema. Facial and laryngeal edema and pleural effusions are seen in severe cases.

Lethality

From 1% to 2% overall and 15% to 20% in hospitalized patients

Diagnosis

Lymphopenia and thrombocytopenia peak at 10 days. Enzyme-linked immunosorbent assay or reverse transcription–polymerase chain reaction testing of blood, throat swabs, or urine identifies the virus.

Prophylaxis

Ribavirin 7.5 mg/kg twice daily for 8 days is suggested for high-risk contacts, but its efficacy is unproved. Several vaccines are undergoing testing in animals.[143]

Treatment

Ribavirin 30 mg/kg IV once, then 15 mg/kg IV every 6 hours for 4 days, followed by 7.5 mg/kg IV every 8 hours for 6 days. Respiratory and circulatory support may require mechanical ventilation, replacement of fluid losses, and inotropic drugs (see Box 23-15 for specific teaching points).

CHEMICAL WARFARE AGENTS AND THE RESPIRATORY SYSTEM

Chemical warfare agents are substances that can be released deliberately with the aim of causing death and disability. They may be used against a body of troops or against a population with the aim of causing fear and disruption of the function of the society. Chemical agents may be military agents such as the nerve gases, sulfur mustard, or CS gas or may be industrial chemicals such as chlorine, ammonia, methylisocyanate, or phosgene, which are stored in bulk close to population centers and can be released by military or terrorist action. Box 23-16 lists likely chemical terronism agents.

Military agents are expensive and generally difficult to clandestinely produce, store, transport, and release, whereas very large quantities of industrial chemicals can be released by a terrorist-detonated explosion at a storage facility or in a bulk-transport vehicle. The use of either type of agent causes fear, anxiety and very large numbers of mildly affected casualties, which, in turn, threatens disruption of the society's health care resources.[144]

Chlorine, phosgene, cyanide, and sulfur mustard were used in World War I. The nerve gases were developed in the 1930s to 1950s but not deployed on a large scale until the Iran-Iraq war in the 1980s. The terrorist organization Aum Shinrikyo released sarin gas on two occasions: in 1994, Sarin was released upwind of an apartment block, killing 7 and injuring 500. In 1995, sarin was released in several Tokyo subway trains, killing 12 and injuring 3800.[145]

Accidental release of a mixture of gases including cyanides and methylisocyanate in Bhopal, India, in 1984 killed at least 3000 people and injured at least another 80,000.[144]

BOX 23-15 Biological Warfare Agents Teaching Point

- Children are vulnerable because small size and inexperience increase exposure.

BOX 23-16 Chemical Warfare Agents

Military Agents	Others
Nerve gases	*Cyanides*
Tabun	*Riot control agents*
Sarin	CN (mace)
Soman	CS
VX	DS
Vesicants	Bromobenzyl cyanide
Mustard	Capsaicin (pepper spray)
Nitrogen mustard	*Respiratory agents*
Sulfur mustard	Ammonia
Lewisite	Chlorine
Phosgene oxine	Phosgene

Chemical agents can injure many levels of the respiratory system. Those that cause seizures or coma (e.g., nerve agents, cyanides, H_2S) impair respiratory drive and airway protective reflexes, while nerve agents also cause flaccid paralysis of all skeletal muscles including the diaphragm and intercostal muscles. Vesicant agents and irritants such as NH_3 and Cl_2 cause mucosal swelling and necrosis from the mouth and larynx to the respiratory bronchioles, as well as causing alveolar injury and flooding. Nerve agents and irritants also cause small and large airway obstruction due to bronchorrhea. Cyanides impair cellular utilization of oxygen.

Children are more vulnerable than adults to agents that form dense vapors lying close to the ground (chlorine and sarin).[146] They are also more vulnerable than adults to the epileptogenic effects of nerve gases.[147]

Individual Agents

NERVE AGENTS

These organophosphate compounds inhibit acetylcholinesterase, which is the enzyme that degrades acetylcholine at muscarinic (postganglionic parasympathetic and central nervous system) and nicotinic (autonomic ganglia and skeletal neuromuscular junction) sites. Enzyme inhibition causes acetylcholine to accumulate, resulting in overexcitation at these sites. Volatile agents such as sarin, tabun, and soman form vapors and may be inhaled. Less volatile agents such as VX are 10 times as potent and form droplets that are absorbed through the skin. Binding between agent and enzyme is initially reversible (e.g., by oxime compounds such as pralidoxime), but "aging" by dealkylation irreversibly inactivates the enzyme, such that oxime antidotes are ineffective. Restoration of normal function then depends on the synthesis of fresh acetylcholinesterase. Aging takes place over minutes (soman) to days (VX).[148]

RESPIRATORY EFFECTS OF NERVE AGENTS

- Increase in airway secretions: profuse bronchorrhea and sialorrhea causing widespread airways obstruction
- Bronchoconstriction
- Fasciculation, weakness, and flaccid paralysis of skeletal muscles including respiratory and bulbar muscles.
- Seizures, coma, and central apnea
- Death is usually due to obstruction of large and small airways by mucus.[148]

Diagnosis

There may be a history of exposure or a cluster of patients presenting with similar signs of dyspnea, wheezing, profuse nasal, oral and respiratory secretions, meiosis, lacrimation, sweating, diarrhea, involuntary urination, muscle fasciculation and paralysis, seizures, and coma.

Treatment

- Atropine 0.04 mg/kg (2 to 6 mg in adults) IM or IV, repeated every 2 to 5 minutes as needed to control secretions, dyspnea, and wheezing
- Diazepam 0.2 mg/kg IV repeated as needed for seizures
- Pralidoxime 20 mg/kg, repeated every 2 to 5 minutes as needed to control symptoms
- Tracheal intubation, suction, and mechanical ventilation
- Consider inhaled salbutamol.
- Intravenous fluids
- Remove the patient's clothing into sealed plastic bags. Decontaminate the skin using soap and water or sodium hypochlorite, 1 part in 9 parts of water.

VESICANT AGENTS (BLISTER AGENTS)

These are alkylating agents (the mustards) or arsenicals (Lewisite) that cause widespread cellular necrosis and basement membrane degeneration in skin and respiratory epithelium within 2 to 12 hours of exposure.[149] Although most of these agents have low volatility, respiratory injury due to inhalation of vapor is more likely when they are used in warm environments or when the more volatile Lewisite is combined with sulfur mustard.

The mustards cause blistering and epithelial necrosis of the mouth, nose, pharynx, larynx, and upper airways. These are associated with a burning sensation in the mouth and nose, epistaxis, dry cough, laryngospasm, and wheezing. In severe exposures, and especially with Lewisite and phosgene oxime, pulmonary edema and necrotizing bronchiolitis may appear and pseudomembrane formation obstructs large airways.

Early death is uncommon and is usually caused by airways obstruction or pulmonary edema. More commonly, death occurs 5 to 10 days after exposure, due to ALI or secondary pneumonia, to which leukopenia caused by bone marrow suppression make the victim more vulnerable.[124,149,150]

Management

- Rapid (minutes) decontamination: remove clothing; adsorb the agent with powders such as charcoal, flour, powdered soap or earth, then rinse with water.
- Administer oxygen by mask.
- Consider early intubation, tracheal toilet, humidification, and bronchoscopy to remove pseudomembranes.

- Consider the use of bronchodilators.
- In the presence of pancytopenia, consider the use of granulocyte colony stimulating factor (GCSF) and of cotrimoxazole (the latter as prophylaxis against *Pneumocystis jiroveci*).

RESPIRATORY AGENTS (Box 23-17)

Chlorine (see later regarding chemical and particulate injury), ammonia, and phosgene are stored and transported in bulk in populated areas, and mass release of these agents by terrorist action against storage or transport containers is the most likely source of intentional inhalational exposure.

On contact with water within the airway, phosgene hydrolyses to form HCl, chlorine forms HCl, HOCl, and free oxygen radicals, and ammonia forms the highly alkaline NH_4OH. Each causes cell membrane damage and denaturation of cytoplasmic proteins.

Phosgene, which is less irritant and therefore less likely to evoke airway protective reflexes, penetrates more deeply into the respiratory tree, mainly affecting bronchioles and alveoli, where it causes pulmonary edema and bronchiolitis obliterans. Chlorine and ammonia, being highly irritative, cause cough, laryngospasm, and bronchoconstriction, but with greater exposure (e.g., in a small child who is unable to escape the low-lying cloud of denser-than-air chlorine), alveolar injury with pulmonary edema appears in 2 to 4 hours.[151] With all of these agents, the greater the inhaled dose, the earlier do the symptoms appear.

Treatment[151]

- Removal from exposure
- In the case of Cl_2 and NH_3, copious irrigation of skin, eyes, and mucous membranes
- Close observation for signs of desaturation or respiratory distress
- Supportive respiratory care
  - Oxygen by mask
  - Consider the use of bronchodilators with or without steroids for severe wheezing
  - Consider noninvasive CPAP or BiPAP for severe wheezing or pulmonary edema.
  - Intubation and mechanical ventilation with high PEEP if needed for pulmonary edema.
  - Consider the use of nebulized lidocaine 1% for pain and severe coughing.
  - Consider flexible bronchoscopy to locate and remove pseudomembranes if wheezing is persistent and unresponsive to bronchodilators.

BOX 23-17 Examples of Industrial Chemicals Capable of Causing Lung Injury

Anhydrous ammonia
Sulfur dioxide
Hydrogen chloride
Hydrogen fluoride
Phosgene
Nitrogen oxides
Chloropicrin
Perfluoroisobutylene (PFIB)
Benzene
Methylisocyanate

RIOT CONTROL AGENTS (see Box 23-16)

Children may be exposed accidentally or as hostages, or by terrorist action. The agents can be dispersed as powders, droplets, or vapor from cannisters, projectiles, or via the air conditioning system of public buildings. The effects of these agents are of relatively short duration (minutes to 2 to 4 hours after removal from exposure).

Respiratory effects are mainly confined to the upper airways (cough; burning sensation in the throat; laryngospasm) but bronchospasm is sometimes seen, and noncardiogenic pulmonary edema may rarely occur when the agents are used in confined spaces, or when exposure is prolonged (e.g., the victim is unconscious or is too young and inexperienced to escape).[152]

Treatment[152]

- Remove from exposure.
- Decontaminate skin by irrigation with water plus soap or a very dilute solution of $NaHCO_3$.
- Administer oxygen by mask.
- Support oxygenation and ventilation by noninvasive CPAP or BiPAP if necessary.
- Victims of severe exposure may require mechanical ventilation with PEEP.
- There are no specific antidotes for these agents.

INCAPACITATING AGENTS

Analogues of fentanyl and benzodiazepines with a very short time of onset and duration of action have been used against groups of people, notably in the Moscow theatre siege. The principal respiratory effects of such agents are central respiratory depression or apnea, and upper airway obstruction due to unconsciousness. Severe exposure is most likely when the agents are used in a confined space (e.g., via the ventilation system of a building), and its outcome is severe hypoxic injury to the brain and heart, leading to death.

Treatment

- Remove from exposure.
- Provide conventional management of the unconscious patient with attention to airway maintenance and to the adequacy of breathing.
- Mechanical ventilation via endotracheal tube may be required.
- Specific antidotes to opioids (e.g., naloxone) or to benzodiazepines (e.g., flumazenil) may have to be given repeatedly or by infusion until full consciousness and adequate spontaneous ventilation return and remain stable.[152,153]

CHEMICAL AND PARTICULATE LUNG INJURY

Major lung injury resulting from the inhalation of noxious gases, chemicals, and particulates is less common in children than in adults, in whom chemical pneumonitis is most commonly associated with industrial accidents. The most common causative agents are hydrogen sulfide, phosgene,[154] sulfur dioxide,[155] nitrogen oxides,[156] cadmium, nickel, and other metal fumes,[157] although damage to the respiratory system can be caused by a very wide range of industrial and domestic chemicals.[158] The epidemiology of inhalation in children predominantly reflects the availability of noxious substances within the home. Pulmonary injury in children has been reported after the inhalation of chlorine, talcum powder, detergent powders, and mercury and the aspiration of activated charcoal. Children with asthma are particularly susceptible to respiratory irritants; chlorine, NH_3, nitrogen dioxide, and sulfur dioxide have been reported as precipitants of airway obstruction.

Chlorine

Chlorine is an irritant gas that can damage the tracheobronchial tree and lung parenchyma. Its use in households as a component of cleaning agents and swimming pool disinfectant[159,160] means that it is frequently encountered by children. Pulmonary toxicity from chlorine inhalation has been reported in children of all ages.[161-163] Voluntary chlorine inhalation has been reported in adolescents.[161,164]

DISEASE MECHANISMS

Chlorine gas is more dense than air and dissipates slowly, leading to prolonged exposure. Chlorine is estimated to be 20 times more toxic as an oxidizing agent and irritant than HCl. It is irritating to the eyes and skin and causes bronchoconstriction, airway inflammation, and alveolar injury. Inhalation of 40 to 60 ppm can produce pneumonitis and pulmonary edema. Cellular toxicity results from the reaction of molecular chlorine with water, forming reactive oxygen species plus HCl and HOCl, which cause denaturation of proteins and cell necrosis. Because the formation of toxic products requires water, damage is most severe in tissues with a high water content, such as the mucosa of the conjunctival sac and the respiratory tract. Pathological examination of the lungs of patients who have died after chlorine gas exposure shows denudation of alveolar and bronchial epithelium, alveolar edema, hyaline membrane formation, and pulmonary intravascular thrombi.[165]

CLINICAL PRESENTATION

Symptoms begin within minutes of exposure to more than 5 ppm. They include irritation of the eye, nose, and upper respiratory tract. Wheezing develops early. Paroxysmal cough, dyspnea, lacrimation, chest discomfort, mucus production, palpitations, dizziness, headache, and nausea are the major symptoms at presentation.[163,166] Wheeze and tachypnea are early signs. Stridor caused by laryngeal edema may be present. Cough with frothy sputum, cyanosis, and crackles on auscultation usually develop within the first 24 hours after exposure[159] and indicate severe lung injury with pulmonary edema. The onset of pulmonary edema may be rapid. Respiratory alkalosis is most common in mild exposure, but persistent hyperchloremic metabolic acidosis may occur.[159,163,167] The presence of hypercarbia or hypoxemia with an increased $P_{AO_2} - P_{aO_2}$ indicates severe respiratory involvement. A depressed conscious state, most probably caused by hypoxemia, has been reported in severely affected children.[159] Spirometry in the acute stages shows an obstructive pattern with a fall in the FEV_1 and the FEV_1/VC ratio[166,168] Reduction of the functional residual capacity indicates pulmonary edema.[169,170] Lung compliance is reduced, and there is intrapulmonary right-to-left shunting. The chest radiograph may be normal at presentation or may show evidence of airflow obstruction with hyperinflation or pulmonary edema with interstitial markings and perihilar alveolar opacities. Ventricular arrhythmias[161] and poor tissue perfusion requiring the infusion of plasma expanders[159] have been reported.

MANAGEMENT

- Most cases require only supplemental oxygen.
- Consider β_2 sympathomimetics and corticosteroids for wheezing.
- Consider noninvasive CPAP or BiPAP.
- Provide tracheal intubation if needed for upper airway obstruction.
- Intubation plus mechanical ventilation with high PEEP may be needed for severe respiratory failure.
- Consider the use of HFOV and ECMO.
- Restrict fluid intake to 70% maintenance to limit lung water accumulation.
- Monitor arterial blood gases and cutaneous oximetry.
- Avoid prophylactic antibiotics
- Experimental: nebulized $NaHCO_3$ to prevent pulmonary edema[171]
- If hypoxemia resulting from pulmonary edema persists despite oxygen therapy, CPAP (delivered by mask, nasopharyngeal catheter, or endotracheal tube) or IPPV with PEEP may be needed. PEEP may not be advantageous if the predominant pulmonary abnormality is airflow obstruction and air trapping resulting from bronchospasm, rather than pulmonary edema, although a trial of CPAP or IPPV with PEEP is justified if gas exchange is deteriorating despite conservative therapy. Patients with airflow obstruction may generate their own "auto-PEEP," and this may be an indication for positive-pressure support. Tracheal intubation and assisted ventilation are required when hypoxemic or hypercapnic respiratory failure, a depressed conscious state, or severe upper airway obstruction occurs. Serial blood gases and continuous cutaneous oximetry should be used in all children with respiratory signs. Observation for 24 hours is indicated for all children who have had significant exposure.

PULMONARY SEQUELAE

Several studies have documented persistent obstructive pulmonary abnormalities in adults after acute chlorine exposure.[166,168] Some 2 weeks after minimally symptomatic exposure, 18 adults had diminished FEV_1 and a maximum mid-expiratory flow rate. Those with the greatest reduction from predicted values were those with the most severe symptoms after exposure and those with a past medical history of

smoking or asthma.[166] Airway reactivity may persist for many years after exposure.[168,172] It is not known whether preexisting bronchial hyperreactivity accounts for the apparently high prevalence of persistent airflow obstruction after chlorine exposure. Residual volume may be reduced for years after exposure, possibly due to peribronchial fibrosis.[168] Recurrent episodes of wheezing and cough, with airflow obstruction that was responsive to bronchodilators and that resolved over 2 years, have been reported in a child exposed to chlorine.[163] Children who have significant exposure to chlorine require follow-up for the assessment of pulmonary function and treatment if symptomatic airflow obstruction develops.

Ammonia

Liquid NH_3 is a component of household cleaning products, but exposure to NH_3 gas with inhalational injury is rare in childhood. NH_3 is highly water soluble and in aqueous solution forms strongly alkaline NH_4OH. Exposure to high concentrations of NH_3 causes liquefactive necrosis of the mucous membranes and submucosal tissues of the upper respiratory tract. This leads to laryngeal edema and inflammation, mucous hypersecretion, mucosal sloughing, tracheitis, and bronchoconstriction. Pulmonary edema may result from massive exposure or may develop after the relief of upper airway obstruction.

Severe lacrimation, pharyngeal irritation, cough, and stridor may develop within minutes of exposure. Upper airway obstruction may be severe and require endotracheal intubation. Treatment is supportive and is similar to that for chlorine inhalation. Bronchodilators are indicated for airflow obstruction. Corticosteroids have not been shown to be of definite benefit but probably should be given for symptomatic upper airway obstruction. Nebulized epinephrine may reduce laryngeal edema and maintain a patent airway without tracheal intubation. Although most patients recover, long-term pulmonary function abnormalities and bronchiectasis have been found in adults after acute NH_3 gas inhalation.[173,174]

Alkaline Laundry Detergents

Via a mechanism similar to that of NH_3, sodium carbonate–containing laundry detergents have caused upper respiratory tract obstruction.[175] Children drool and experience stridor 1 to 5 hours after ingestion of the powder. Most vomit after ingestion. One child reported to have inhaled detergent developed symptoms immediately. At endoscopy, there was edema of the pharynx, epiglottis, and larynx. Tracheal intubation may be required for airway management.[175] Caustic burns may be associated with corneal injury.

Talcum Powder

Talc inhalation is a common problem that affects primarily infants up to the age of 2 years. Exposure occurs most commonly at times of diaper changes. Some reports have suggested that the similar appearance of baby powder containers to nursing bottles is an etiological factor.[176] Aspiration of talc has caused severe respiratory distress and death in young children.[177,178] The mortality rate may be up to 20% in cases severe enough to require assisted ventilation.[178]

DISEASE MECHANISMS

Talc is a powder of hydrous magnesium silicate ($Mg_3Si_4O_{10}H_{20}$). It consists of a layer of magnesium hydroxide between two silica sheets that slide past each other, giving the slippery feel. The mean particle size is less than 5 mm. Inhaled talc causes airway obstruction, drying of the respiratory mucosa, impairment of the ciliary clearing mechanism, and inflammation.[179] Inflammatory infiltrates in biopsy and autopsy specimens consist of mononuclear and giant cells filled with crystalline doubly refractile bodies.[180] Hyaline membrane formation, obliteration of small bronchi and alveoli, and fibrotic changes are also seen.

Children usually develop cough and respiratory distress immediately after inhalation. Sometimes the onset of symptoms is delayed for several hours.[181] Cardiorespiratory arrest due to obstruction of large airways has been reported after massive aspiration.[178] Many children have minimal or transient symptoms. Wheezes, crackles, and tachypnea are common. A chest radiograph may show hyperinflation with patchy infiltrates. Hypoxemic respiratory failure should be treated like other causes of severe respiratory distress syndrome: with supplemental oxygen, PEEP, fluid restriction, and assisted ventilation (see Chapter 19). Sedation and paralysis may be required. Barotrauma has been reported in talc inhalation.[179] Corticosteroids have been used to modify the inflammatory response. Bronchoalveolar lavage has been used therapeutically to clear debris obstructing large airways, but whether the benefit of this procedure outweighs the risks is unknown.

Complete resolution of pulmonary lesions with normal lung function at follow-up has been reported in survivors even after massive aspiration, although a combined restrictive and obstructive pulmonary function defect may occur.

Activated Charcoal

The use of activated charcoal has become widespread in the treatment of toxic ingestions and overdoses, and there has been substantial morbidity and several reports of deaths resulting from aspiration pneumonia associated with its use. Some clinical aspects of drug intoxication make the nasogastric administration of charcoal particularly hazardous. The patient may have a depressed conscious state or have seizures with poor airway protection or may be combative and uncooperative, resulting in malpositioning or dislodgment of the nasogastric tube. The ingested poison may cause vomiting by a central effect or from gastric irritation, gastric stasis, or intestinal ileus. Gastrointestinal obstruction may be caused by a solid charcoal bolus.[182] Multiple doses of charcoal in patients with impaired bowel motility[183] or even a single dose after the administration of ipecac[184] is likely to be especially dangerous.

DISEASE MECHANISMS

When aspirated, the thick charcoal suspension may cause obstruction of the large[184] and small[185] airways. Gas trapping and barotrauma are common features. Pneumonitis with all the features of ARDS may develop. This may be exacerbated by the aspiration of gastric contents. Autopsy findings have shown lung parenchymal scarring with bronchiectasis, bronchiolectasis, and bronchiolitis obliterans. Large amounts of

residual charcoal are found in the airways and alveoli associated with an inflammatory reaction that includes giant cells,[185] alveolar macrophages, and histiocytes. Regional lymph nodes also show charcoal deposition within histiocytes. Diffuse pulmonary thromboembolism has also been reported.

CLINICAL FEATURES AND MANAGEMENT

Charcoal aspiration produces severe respiratory failure. Tachypnea, dyspnea, wheezing, and cyanosis may increase in severity in the 48 hours after aspiration. Wheezes and crackles are audible widely over the chest, and areas of reduced air entry may be found in the presence of obstruction of the large airways. Radiological findings of lung infiltrates (Fig. 23-5) may underestimate the extent of lung affected. ARDS may develop despite relatively normal early chest radiographs.[186] Bronchoscopy and tracheobronchial toilet may be useful.[184,185] Copious charcoal-laden secretions may be aspirated from the trachea for many days after the inhalation episode. β-Sympathomimetic agonists have been used to treat wheeze after aspiration, but the reversibility of airflow obstruction is probably minimal. After charcoal aspiration, bacterial colonization of endotracheal tube secretions may be associated with systemic evidence of sepsis.[183,185,186] Management should include bacteriological surveillance of blood and tracheal aspirate and appropriate antibiotic treatment if infection is likely.

Activated charcoal should be used very cautiously in childhood ingestions. In many cases of suspected poisoning in children, the lung disease that may be induced by aspiration carries a far higher risk of mortality and morbidity than the ingested poison.

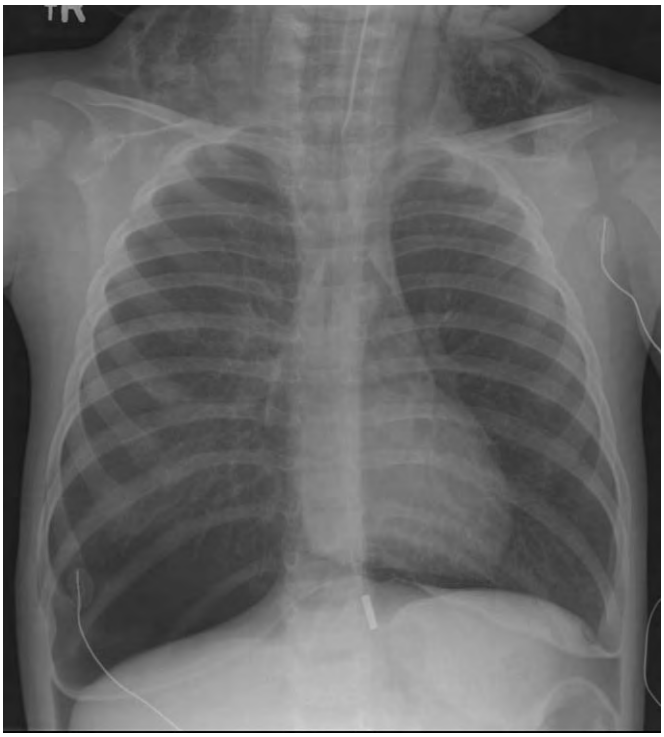


Figure 23-5 Chest radiograph of a 15-month-old, 12 hours after aspiration of activated charcoal, showing gas trapping on the left, with a right-sided pneumothorax, mediastinal gas, and subcutaneous emphysema.

Mercury

Mercury vapor inhalation is a very rare condition in childhood but causes severe acute respiratory distress and is commonly fatal.[187] The heating of mercury has been used to separate gold from gold ore and form a gold-mercury amalgam. Children have developed progressive pulmonary failure within hours of exposure; this failure is clinically and pathologically similar to other causes of ARDS. There is one report of HFOV being successfully used to maintain gas exchange in an infant with this condition.[188]

Hydrogen Sulfide

Hydrogen sulfide (H_2S) is a widely distributed cellular asphyxiant.[189] It is produced by decomposition of organic matter in oxygen-poor environments, such as sewers, farm manure pits (into which children may fall, or around which they may play), as well as in some industrial processes and from volcanic gas vents. Olfactory detection of H_2S fatigues rapidly, increasing the risk of prolonged exposure and severe intoxication.[190]

H_2S impairs oxidative metabolism by inhibiting cytochrome oxidase on the mitochondrial inner membrane. The brain and heart are especially vulnerable to H_2S toxicity, because of their high metabolic activity. At low concentrations (less than 100 ppm), H_2S acts as an irritant, causing cough, dyspnea, and tachypnea. High concentrations (greater than 500 ppm) rapidly cause death due to central nervous system depression and apnea. Pulmonary edema at concentrations of 300 to 500 ppm is caused by asphyxial depression of the myocardium plus direct injury to the alveolar epithelium.[189,190] Survivors of significant exposures show inflammation of large and small airways, with wheezing, atelectasis, and impairment of gas exchange.

DIAGNOSIS

The diagnosis is based on a history of exposure plus signs of central nervous system and myocardial depression, conjunctivitis, cough, wheeze, dyspnea, and clinical and radiological evidence of pulmonary edema.

MANAGEMENT

- Remove immediately from exposure.
- Provide supportive care.
- Administer high concentrations of oxygen by mask.
- Provide tracheal intubation and mechanical ventilation with PEEP for pulmonary edema or hypoxic-ischemic encephalopathy.
- Provide myocardial support with inotropic drugs if necessary (see Box 23-18 for specific teaching points).

BOX 23-18 Chemical Warfare Agents Teaching Points

- Remove the patient from exposure.
- Decontaminate the patient.
- Support breathing and oxygenation.
- Consider antidotes: repeated as often as needed.

LIPOID PNEUMONIA AND HYDROCARBON PNEUMONITIS (Table 23-8)

Accidental Ingestion in the Preschool-Age Child

From 1985 through 1989, 129,024 children younger than 6 years in the United States ingested hydrocarbons; of those, 5 died and 168 suffered major effects. This represents 3.3% of all poison exposures in this age group and 4% of all deaths resulting from poisoning.[191] Hydrocarbon ingestion occurs when the child, often a boy between 12 months and 5 years of age, drinks the liquid from a bottle (frequently a soft drink bottle) stored within reach.

Substance Abuse

The intentional inhalation of volatile organic chemicals for recreational use[192] is mainly a phenomenon of the preteen and early teenage years. In the United States in 2001, the lifetime prevalence of inhalant abuse among eighth-graders (the age at which abuse peaks) was 17%: in 1995, the corresponding figure was 22%.[192]

Although pulmonary injury is not a prominent cause of death among solvent abusers, pulmonary edema (most likely cardiogenic) has been found at postmortem in gasoline sniffers.[193] The toxicity of solvent abuse mainly involves the kidneys, central nervous system, bone marrow, heart, and peripheral nerves. In paint sniffers, nonhydrocarbon components of the paint, such as aluminum and silica, may cause more pulmonary damage than the hydrocarbon components.[194]

Inhalation of solvents by bagging (spraying into a plastic bag and inhaling) is more likely than inhalation by huffing (spraying onto a cloth held to the mouth) to lead to asphyxial injury. Toxic or asphyxial myocardial depression causes pulmonary edema. Toxic or asphyxial injury of the central nervous system impairs the respiratory drive. Loss of consciousness and seizures can lead to upper airway obstruction, vomiting, and aspiration pneumonia (see later).[192]

Expiratory wheezing has been found in adolescents examined within hours of inhaling toluene. A group of 37 chronic glue-sniffers had significantly higher residual volumes than a group of controls of similar age, although the FEV_1 and the FEV_1/VC ratio were not different from those of the controls.

Table 23-8
Epidemiology

Toddlers and preschool-age children	Exploratory ingestion of gasoline, kerosene, turpentine, baby oil, furniture polish, etc.
Teenagers and older children	Solvent abuse: gasoline, xylene, toluene, or paint
Teenagers and older children	Inadvertent aspiration of gasoline or kerosene while siphoning from a tank or container
Infants, children with gastroesophageal reflux, debilitated or developmentally delayed children	Administration of liquid paraffin, olive oil, or fish oil (adult-type lipoid pneumonia)
Unusual aspirations	Lip gloss or petroleum jelly on lips, nose, or face

In lung specimens obtained at autopsy from three chronic glue-sniffers who died of traumatic injuries, there were changes suggesting panacinar emphysema, mononuclear infiltration and thickening of some alveolar septa but thinning and rupture of others, smooth muscle hypertrophy in the terminal bronchioles, widespread mucus plugging, and papillomatous hypertrophy of bronchiolar submucosal tissue.[195]

Adult-Type Lipoid Pneumonia

Adult-type lipoid pneumonia is commonly seen in debilitated, chronically ill adults who have taken oil-containing medications such as mineral oil for constipation or oily nosedrops.[196] In infants or children who are debilitated or who have neuromuscular disease or gastroesophageal reflux, viscous oils, including mineral oil and cod liver oil, may be aspirated silently. Forced oral administration of any oily preparation can lead to aspiration of the oil, sometimes causing the child's death.[197] Silent aspiration of oil-based lip gloss, oily nosedrops and petroleum jelly applied to the face, has also been reported in children.[196,198]

Physical Properties of Hydrocarbons (Box 23-19)

Low-viscosity compounds such as gasoline, turpentine, mineral oil (in furniture polish), petroleum ether, lighter fluid, and toluene are far more toxic than more viscous hydrocarbons such as fuel oil, lubricating oil, mineral oil, and petroleum jelly. Highly volatile components evaporate at room temperature, displacing oxygen from alveoli and causing hypoxemia.[199]

DISEASE MECHANISMS

The earliest histological changes are in the pulmonary vessels, leading to hemorrhage and edema; an inflammatory exudate and signs of bronchial injury appear later[200] (Table 23-9).

In the rabbit, intense alveolar hemorrhage and edema are seen within 15 minutes of kerosene instillation into the trachea. These changes appear in a patchy fashion over both lungs. Later, neutrophils are found in the alveolar fluid.[201] Autopsy examination of the lungs of children who die soon after hydrocarbon aspiration also show vascular congestion, alveolar hemorrhage, and edema with later changes of vascular thromboses, interstitial and alveolar inflammatory exudate, and atelectasis and necrosis of the bronchial, bronchiolar, and alveolar walls.[202] In massive ingestion, these changes may

BOX 23-19 Compounds with Low Viscosity and Surface Tension (e.g., Gasoline, Toluene, Turpentine)

Increase the risk of lung injury and death
Reduce effectiveness of laryngeal reflex
Encourage spreading into small airways
More alveolar damage
More damage to lung capillary endothelium
Reduce surfactant effectiveness: more atelectasis and pulmonary edema

Table 23-9
Pathological Changes after Tracheal Instillation of Kerosene

Time	Change
1 hr	Engorgement of large and medium-sized vessels
4 hr	Engorgement of alveolar capillaries
24 hr	Peribronchial inflammation
	Focal areas of alveolar inflammatory exudate and consolidation
72 hr	Early resolution of alveolar exudate
7 days	Resolution of consolidation
	Persistence of some peribronchial inflammation
14 days	Persistence of vascular engorgement
	Resolution of most alveolar and peribronchial inflammation

extend very rapidly over the whole lung within hours of the event, leaving very little air-containing lung.[201] Later, the alveoli become lined with thick hyaline membranes and contain profuse fibrinous clot with erythrocytes, cellular debris, and macrophages containing small oil droplets. The lining of bronchioles is shed into the lumen.

Areas of hyperinflation and emphysematous bullae visible at autopsy can also be seen on chest radiograph.[203] These may be caused by air trapping because of the ball-valve effect of bronchial mucosal edema and sloughed bronchial mucosa. Large pneumatoceles, mainly involving the lower lobes, have been reported to occur uncommonly in children after kerosene ingestion. These pneumatoceles appear after 6 to 13 days in children aged 1 to 5 years who have persistent respiratory symptoms for up to 10 days. They remain visible on radiographs for 1 to 8 months despite the absence of respiratory symptoms. They appear in consolidated areas of the lung, may be single or multiple, and may contain fluid. Pneumothorax, pneumomediastinum, pneumopericardium, subcutaneous emphysema, and pleural effusions have also been reported in children after hydrocarbon ingestion.[204]

Aspiration of more viscous aliphatic hydrocarbons such as mineral oil causes less acute toxicity, with no evidence of endothelial injury. At first, lipid-filled macrophages occupy the alveoli and interalveolar septa as well as the lymphatic vessels and regional lymph nodes. Later, the macrophages disappear, and foreign body granulomas form with fibrosis and giant cells; extracellular oil droplets may be found.[196] Paraffin granulomas may be found in debilitated patients who aspirate mineral oil or oily nosedrops. These form a mass lesion with indistinct borders, often in the posterior axillary segment of the upper lobe, and disappear slowly when oil ingestion ceases.[205,206]

The intensity of lung tissue reaction to animal and vegetable oils is proportional to the amount of free fatty acid present. Generally, this is greater in animal fats (e.g., cod liver oil) than in vegetable oils. Free fatty acids produce a severe injury with tissue necrosis, hemorrhage, vascular thrombosis, neutrophil infiltration, and later, fibrosis, which may obliterate alveoli and cause thickening of the walls of the small muscular arteries.[196,205]

Bacterial clearance from animal lungs is impaired by hydrocarbon ingestion, and secondary infection with aerobic and anaerobic bacteria may follow hydrocarbon inhalation. However, animal studies and clinical experience in children have not found a major role for bacterial infection in this condition.[202] The routine use of prophylactic antibiotics is not recommended in lipoid pneumonia.[202,207,208] In debilitated patients, active infection with atypical mycobacteria occasionally complicates lipid aspiration.[209,210]

PATHOPHYSIOLOGICAL EFFECTS OF HYDROCARBON ASPIRATION

- Alveolar and interstitial hemorrhage
- Leak of fluid and protein from capillaries into alveoli
- Increased intrapulmonary shunt
- Increased respiratory system elastance and work of breathing
- Inhibition of surfactant production causes atelectasis and small airway closure[211]
- Mucosal injury in bronchioles and small bronchi causes gas trapping[200]
- Residual small airways narrowing; gas trapping and inhomogeneous ventilation 8 to 14 years later in asymptomatic children[212]
- Endothelial injury and perivascular inflammation cause thromboses and pulmonary hypertension[213]
- Volatile vapors displace oxygen, reducing alveolar P_{O_2}.

SIGNS AND SYMPTOMS

Respiratory symptoms occur in 25% to 40% of the preschoolers who ingest low-viscosity hydrocarbons (kerosene, mineral oil). Choking, coughing, and gagging are followed by increasing tachypnea with alar flaring and an expiratory grunt within minutes of ingestion. Fever and intercostal retraction may appear within 30 minutes or may be delayed for 1 to 2 days.[202,203] The fever may be high (41° C), and there is usually tachycardia.[203] Auscultatory signs may be absent, even in patients with cyanosis and severe respiratory distress,[202] or there may be crackles, wheezes, and reduced breath sounds in the lung bases, sometimes associated with dullness to percussion.[207] The odor of kerosene or another hydrocarbon may be detectable on the breath or clothing.

Because many hydrocarbons are central nervous system depressants and gastric mucosal irritants, children seen more than 30 minutes after ingestion may be drowsy or semiconscious. Vomiting with inhalation of gastric contents may contribute to further lung injury. The presence of gross pulmonary edema, especially if associated with cardiomegaly and hepatomegaly, implies massive hydrocarbon aspiration and the combination of direct lung toxicity with myocardial depression.[207]

Respiratory signs may disappear within 24 to 48 hours in mild cases, but when complications such as ARDS, secondary bacterial infection, or pneumatoceles ensue, the child may remain symptomatic for 10 days or more.[203,214] In particular, the fever may persist for up to 3 weeks.[203]

RADIOLOGICAL CHANGES

Radiological abnormalities are seen in 75% of infants who ingest hydrocarbons, but only 25% to 50% of these become symptomatic.[215,216] Although radiological changes may appear within 30 minutes of ingestion,[202] chest radiographs taken in the first 2 hours may be deceptively clear or may show only mild hyperinflation of part or all of the lungs.[203] Most patients

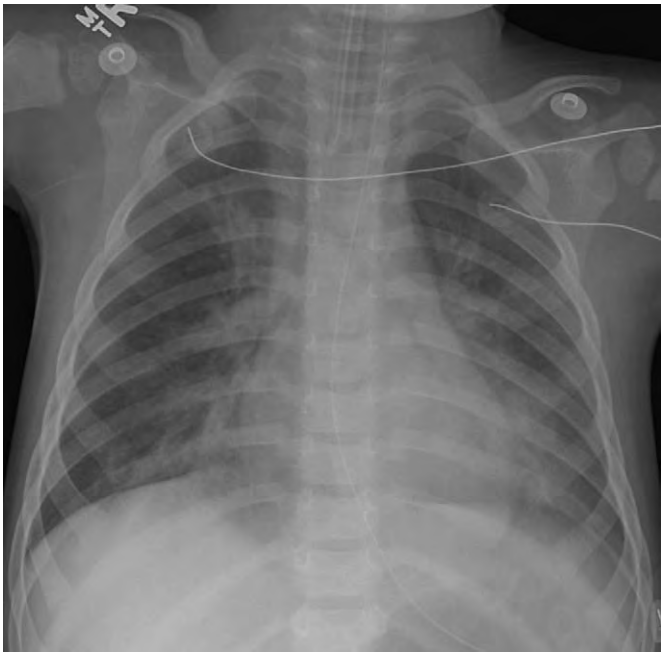


Figure 23-6 Chest radiograph of a 5-year-old, 24 hours after ingestion of kerosene, showing widespread airspace opacities in both lungs with some overinflation.

with hydrocarbon lung injury have radiological signs within 12 hours[202] (Fig. 23-6) Fine, punctate, perihilar densities extend and coalesce, becoming coarse areas of consolidation involving mostly the lower lobes.[201-203] Regions of air trapping may be present in the periphery of the lung, and pneumothorax, pneumomediastinum, or pleural effusion may be seen.

High-resolution CT shows nodular opacities, mainly in the lower lobes, and areas of ground glass opacity, superimposed in some places on thickened septa in a "crazy paving" pattern.[217,218] In most children, the chest radiograph changes disappear within a few days after the respiratory symptoms have resolved. In some cases, radiological signs may persist for months, especially when pneumatoceles or paraffin granulomas are present. Even these eventually disappear completely.[204,206]

INVESTIGATIONS

If there is doubt about the cause of pneumonia from the history, physical examination, and chest radiograph, the presence of fat-laden macrophages in sputum, tracheal aspirate, bronchoalveolar lavage fluid, or an open biopsy specimen from the lung may indicate hydrocarbon inhalation as the cause. This is more likely to be necessary in an older, debilitated child with a swallowing disorder.[219]

MANAGEMENT

Management consists of monitoring for signs of respiratory distress and injury to the heart, brain, liver, and kidneys with supportive treatment as required.

DECONTAMINATION

Induction of vomiting, nasogastric lavage, and mineral or olive oil gavage are contraindicated in any child who has ingested an oil or a hydrocarbon because these procedures are associated with an increased incidence of lipoid pneumonia.[220,221] Even the presence of a cuffed endotracheal tube does not guarantee protection of the lungs from vomited hydrocarbon. The use of activated charcoal is so frequently associated with vomiting that it is not justified in children with hydrocarbon ingestion.

RESPIRATORY MANAGEMENT

Frequent reevaluation of clinical signs, especially in the first 72 hours, and monitoring of respiratory rate, heart rate, and hemoglobin saturation indicate the progress of respiratory failure. Monitoring of arterial blood gases by intra-arterial catheter may be needed in severe cases. The chest radiograph excludes pneumothorax and pneumopericardium in the event of sudden clinical deterioration. Decisions about changes in respiratory care are based on clinical needs rather than on radiographic changes.

Oxygen should be given by mask to any child with respiratory distress, cyanosis, or a low hemoglobin saturation. If the saturation remains below 80% despite the administration of high-flow oxygen by mask and is deteriorating or if the child's respiratory rate is rising rapidly without radiological evidence of pneumothorax, then tracheal intubation and CPAP or mechanical ventilation may be needed. High levels of CPAP, peak airway pressure, and PEEP have a serious risk of pneumothorax, pneumopericardium, or air leak from overinflated areas of the lungs.[212,222] Minimization of this risk requires that airway pressures and tidal volume be no greater than those needed to maintain an arterial pH above 7.1[223] and a PaO_2 above 50 mm Hg. The FIO_2 should be kept below 0.5 if possible. If mechanical ventilation fails to control the respiratory failure, ECMO may be used. Survivors have been reported after the use of ECMO in children with hydrocarbon aspiration.[222]

OTHER MEASURES

Steroids have no place in the treatment of hydrocarbon inhalation; human and animal studies have shown no benefit from their use,[199,208] and the impaired mononuclear cell response in the lung caused by steroids may increase the risk of secondary bacterial pneumonia.[208] The routine use of antibiotics is not justified.[202,208] Rather, clinical monitoring, bacteriological surveillance, and frequent total and differential white blood cell counts should guide antibiotic therapy. Culture of fluid obtained by bronchoscopic or nonbronchoscopic bronchoalveolar lavage via an endotracheal tube may give a more accurate guide to the infecting organism when there is evidence of developing bacterial pneumonia. Wheezing in these children is due to structural damage to the bronchial and bronchiolar walls, and there is no evidence to support the use of bronchodilators.

PROGNOSIS

In the United States in the late 1980s, the mortality rate was 0.01% of children with respiratory symptoms resulting from hydrocarbon ingestion.[191,202] The majority of children deteriorated over the first 24 hours and then improved and became asymptomatic over 3 to 4 days. In more severely affected children, symptoms may persist for 10 days or more,

BOX 23-20 Hydrocarbon Pneumonitis Teaching Points

- The lower the viscosity, the greater is the lung toxicity.
- Most patients with hydrocarbon toxicity develop symptoms within 12 hours.
- Avoid induced vomiting, nasogastric lavage, and milk gavage for hydrocarbon ingestions.
- Avoid corticosteroids and prophylactic antibiotics.

but in other children, the condition may progress to intractable respiratory failure over 2 to 3 days.[222] Some infants have been reported to die after 1 to 2 months of progressive respiratory failure with extensive lung consolidation and recurrent pneumothoraces.[197] Up to 80% of asymptomatic children have residual abnormalities on detailed lung function testing (especially of markers of small airway narrowing) on 8- to 14-year follow-up[212] (see Box 23-20 for specific teaching points).

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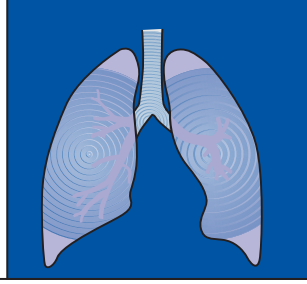

CHAPTER 24

Foreign Body Aspiration

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TEACHING POINTS

- Children younger than 3 years are at higher risk for foreign body aspiration.
- History is the key element in diagnosing an airway foreign body.
- A negative chest radiograph does not exclude the diagnosis of an airway foreign body.
- Education and prevention are importing in avoiding airway foreign body.
- Delayed diagnosis increases complications of airway foreign body.

The propensity of small children to place objects into their mouths is well known. Most objects lodge in the esophagus, but many of these objects are aspirated. Foreign body aspiration attracts a great deal of attention, some of it for the novelty of the aspirated items. However, the danger of foreign body aspiration should never be minimized; in 2003, the National Safety Council reported 4300 deaths from choking in the United States.[1] The majority of these fatalities occur soon after aspiration, with the patient never having been seen by a physician. Two thirds of all deaths related to foreign body ingestion occur in the home, and choking is the fourth most common injury leading to death in the home.

In addition to the danger of the aspiration episode itself, foreign body removal, despite technological advances, remains a technically challenging procedure due to the size of the airways in which the foreign bodies are lodged.

EPIDEMIOLOGY, RISK FACTORS, AND PATHOGENESIS

A child's fascination with placing objects in the mouth begins soon after grasping becomes effective. Other contributing factors include improper preparation of food (e.g., pieces being too large, bones not being removed), an immature swallowing mechanism, hasty eating and drinking, playing while eating, talking with food in the oral cavity, small objects being within grasping distance, and improper supervision of small children playing near infants. Older children commonly force objects into their younger siblings' mouths. There is a male preponderance for airway foreign bodies.[2] Only careful supervision can lessen the chance of aspiration.

Organic material is the most frequent foreign body found in the airway. Nuts, seeds and popcorn are commonly encountered, with peanuts being the most common.[3,4] Nuts should not be given to children younger than age 4 years because this group does not have fully developed oral motor control or the molar teeth to chew them. Children who have diminished perception and sensation are at increased risk of aspiration. The American Academy of Pediatrics recommends that certain foods be kept from children less than 4 years of age (Box 24-1).

Unfortunately, many victims of foreign body aspiration never survive the first few minutes. Most often, these incidents involve aspirated food objects. "Round" foods, such as hot dogs, nuts, and grapes, are most likely to cause asphyxiation.[5] Other dangerous factors include a smooth or slippery surface, compressibility, and failure to break apart easily. Dried beans and peas can cause delayed airway obstruction as they swell with the absorption of moisture.

The U.S. Consumer Product Safety Commission requires age-appropriate labeling on toys and products for older children that contain small parts. Toys for children aged 3 years and older should be kept from young children. Small toy parts are often radiolucent, making diagnosis difficult.

Three distinct clinical phases occur after a foreign body is aspirated. The first is immediately after aspiration. There may be coughing, gagging, choking, stridor, and wheezing. A cyanotic episode may occur. Many caregivers seek medical attention for the patient during this phase. After this initial phase is a quiescent period. This asymptomatic period can last from minutes to months depending on the location of the foreign body, the degree of airway obstruction, and the inflammatory reaction to the material aspirated. During this phase, the foreign body can easily change location, with a subsequent change in signs and symptoms. The third phase is a renewed symptomatic period due to complications relating to the presence of a foreign body. During this phase, airway inflammation or infection results in symptoms such as cough, sputum production, fever, wheezing, and rarely, hemoptysis. Clinical manifestations vary based on the object's location.

Foreign bodies occur least frequently in the larynx. Laryngeal foreign bodies may cause complete obstruction resulting in sudden death unless they are dislodged promptly with intervention such as the Heimlich maneuver where appropriate. Partially obstructive objects may cause stridor, hoarseness, aphonia, croup-like cough, odynophagia, hemoptysis, wheezing, and dyspnea. These symptoms may be secondary to the foreign body itself or may result from a residual laryngeal reaction from a foreign body that has migrated to

BOX 24-1 Foods to Avoid in Children Younger Than 4 Years

Hot dogs
Nuts and seeds
Chunks of meat or cheese
Whole grapes
Hard, gooey, or sticky candy
Popcorn
Chunks of peanut butter
Raw vegetables
Raisins
Chewing gum

From the American Academy of Pediatrics: Parenting corner Q&A: Choking prevention. Available at http://www.aap.org/publiced/BR_Choking.htm.

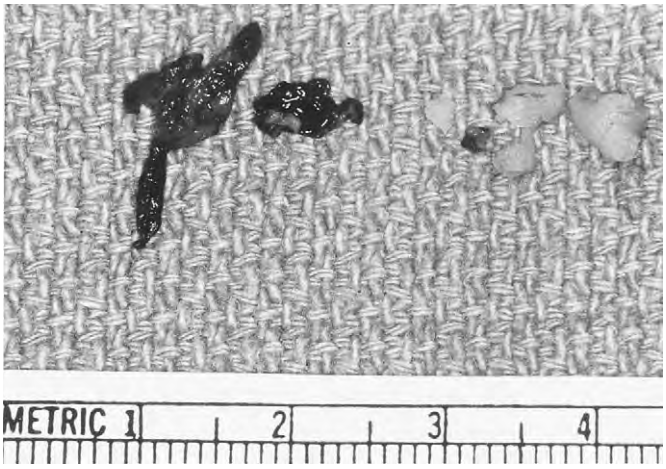


Figure 24-1 Peanut fragments with granulation tissue removed at bronchoscopy.

the trachea. An esophageal foreign body may cause similar symptoms due to inflammation with anterior displacement of the posterior tracheal wall or secretion overflow with resultant laryngeal symptoms.

Tracheal foreign bodies occur rarely. The predominant symptoms are obstruction, stridor, wheeze, and dyspnea. Esclamado and Richardson[6] showed that the incidence of complications in the laryngotracheal foreign body group is at least 4 to 5 times greater than that reported for all aspirated foreign bodies.

Bronchial foreign bodies are the most common, manifesting primarily with symptoms of coughing and wheezing. Hemoptysis and dyspnea may also be present. Foreign bodies in the lower trachea, however, may shift from one bronchus to the other and give rise to a variety of signs and symptoms.

Initially, foreign bodies often cause obstructive emphysema (air trapping); later, atelectasis, pneumonia, and, rarely, lung abscess or empyema occur with bacterial overgrowth. Organic materials are more likely to cause an intense inflammatory reaction with accompanying granulation tissue and purulent mucus[7] (Fig. 24-1). Late manifestations of bronchial foreign body aspiration may be reduced by prior treatment with antibiotics or steroids.

DIAGNOSIS

The initial evaluation of a child with suspected airway foreign body includes three elements: history, physical examination, and radiography. The history is the key element. Children who aspirate foreign objects have a variety of signs and symptoms. The most common include a history of coughing and choking, occurring in up to 91.8% of patients.[8-10] The classic triad of cough, wheeze, and unilaterally reduced breath sounds may be present in half of the patients.[8,9] A history of aspiration may be obtained in the majority of patients with thorough questioning.[2,11] Lack of a clear history or misdiagnosis may delay recognition of a foreign body. Often, a diagnosis of exclusion is made, and patients may see several physicians before the foreign body is identified. Most common misdiagnoses are reactive airway disease, pneumonia, and croup (Box 24-2). Because most aspirated foreign bodies occur in small children, communication after the event is problematic. For example, although the episode may have been witnessed by an older child, that child may not disclose information secondary to fear of repercussion.

BOX 24-2 Differential Diagnosis of Aspirated Foreign Body

Reactive airway disease
Empyema
Pneumonia
Croup
Tracheobronchial tumor
Bronchitis
Tracheomalacia
Psychogenic cough
Bronchomalacia

The physical signs of bronchial foreign bodies vary. Careful auscultation of the chest in a systematic fashion is essential. All lung fields should be assessed for breath sound symmetry (phase, pitch, amplitude, and heterophony) and adventitial breath sounds, particularly wheezing. Asymmetric wheezing is a strong indicator of unilateral bronchial obstruction, although symmetric wheezing may also be present. Depending on the size, shape, and location of the foreign body, breath sounds may vary. Foreign bodies in children have been reported to be located equally in the right bronchus and left bronchus, predominantly in the right bronchus, and even predominantly in the left bronchus.[7,9] This observation may be explained by most children having a fairly symmetric bronchial angle until about 15 years old. Around that age, the aortic knob fully develops, displacing the left main bronchus and creating a more obtuse angle at the carina.[12] Secretions may shift from one location to another, affecting the physical examination. The foreign body may shift position and cause a variation in the aeration distal to the object.

Radiographic studies provide valuable information to the endoscopist. They not only document the presence of a foreign body but also act as an aid in extraction. Studies that are incomplete or are poor in quality may lead to errors or a

delay in diagnosis. Although many foreign bodies are radiolucent, special techniques may help establish a diagnosis.

If a laryngeal or tracheal foreign body is suspected, a lateral neck radiograph may provide useful information. Esclamado and Richardson[6] showed that the neck radiograph is more likely to be abnormal than the chest series with a laryngeal or tracheal foreign body. With high-quality neck radiographs, the caliber of the airway can be clearly seen. When the arms and shoulders are positioned inferiorly and posteriorly, a single lateral radiograph can profile the air column in both the larynx and trachea. However, extreme care must be taken because the patient is at risk for life-threatening airway obstruction.

In cases of suspected foreign body aspiration, a standard chest series should include anteroposterior and lateral end-inspiratory views as well as an end-expiratory radiograph.[13] Radiographs are carefully examined for local atelectasis, local hyperinflation, and visible foreign bodies. Expiratory radiographs delineate postobstructive hyperinflation with air trapping behind the foreign object and subsequent failure of the trapped air to empty on exhalation (Fig. 24-2). This can cause mediastinal shift to the uninvolved side. Unfortunately, expiratory radiographs are often unsuccessful in small children.[9] In these cases, decubitus radiographs or fluoroscopy may provide additional information. Most airway foreign bodies are radiolucent, and some cases present with a bypass valve phenomenon. A normal chest series does not rule out the presence of a foreign body in the airway. The sensitivity of chest radiographs in the evaluation of airway foreign bodies has been reported to be 68% to 76%, with a specificity of 45% to 67%.[14] In various case series, the incidence of a negative chest radiograph in the presence of an airway foreign body has been reported to range from 25.6% to 75%.[2,8] The longer the foreign body has been retained, the more likely is it that there will be findings such as air trapping or consolidation.[9] In the face of a suggestive history, even with negative chest radiographs, bronchoscopy is performed. *History—not radiographs—is the primary determinant of the need for bronchoscopy*.

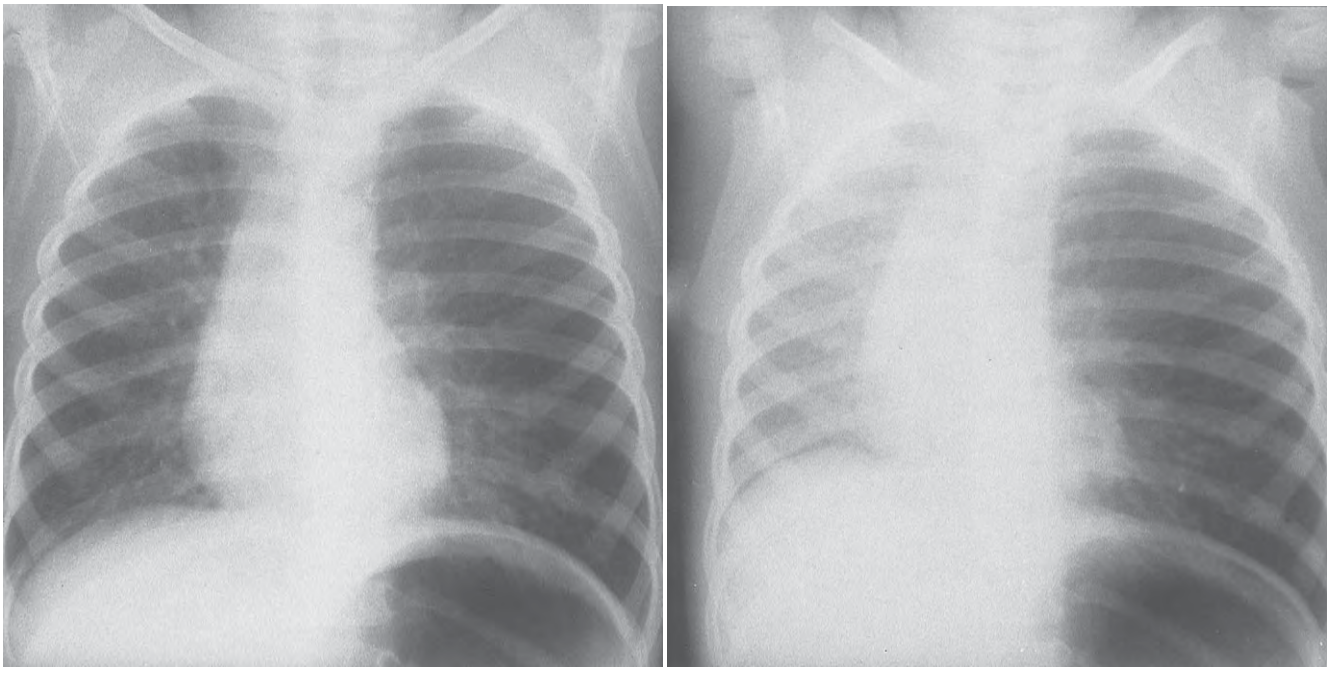
For radiopaque objects lodged far in the lung periphery, simultaneous biplane fluoroscopy is used to visualize the object during extraction. This important technique may serve as a "last chance" to assist removal of a foreign body endoscopically. Thoracotomy is the only alternative if endoscopic efforts fail.

Although computed tomography and magnetic resonance imaging have revolutionized medicine in the last decade, they have little value in the diagnosis and management of foreign body aspiration. Magnetic resonance imaging has been used to diagnose a previously unidentified bronchial foreign body.[15] However, because of the young age of the patients, the time and expense involved, and the need for sedation (or general anesthesia) in a patient with pulmonary compromise, the use of these modalities in foreign body aspiration remains limited.

TREATMENT

Acute Aspiration: Complete Obstruction

In a witnessed foreign body aspiration with acute complete airway obstruction, the Heimlich maneuver is the procedure of choice. Currently, this maneuver is recommended for children older than 1 year of age. For infants younger than 1 year, chest thrusts and back blows in the head down position are recommended.[16] Unlike adults, younger children may not be able to respond to the question traditionally asked of suspected aspiration victims: "Can you speak?" Blind finger



A B

Figure 24-2 Anteroposterior inspiratory (*left*) and expiratory (*right*) chest radiographs. Air trapping in the left lung is caused by a peanut in the left mainstem bronchus.

sweeping in the oropharynx is contraindicated in infants because the foreign body may be pushed down and become lodged in the larynx, converting a partial obstruction into a complete one. This maneuver may also force the foreign body into the esophagus, where it may compress the trachea against the upper sternum.

Questionable Foreign Body Aspiration: Flexible Versus Rigid Bronchoscopy

Because the diagnosis of foreign body aspiration is not always obvious, bronchoscopy may initially serve as a diagnostic procedure. In this setting, either flexible or rigid bronchoscopy is indicated. Selection of a particular technique depends on physician expertise and experience in a particular geographic area.

If a foreign body in a child is confirmed by physical examination or radiographic studies or if the endoscopist has a high index of suspicion that a foreign body is present, rigid bronchoscopy is the preferred technique for removal. The same holds true if a foreign body is noted on flexible endoscopic examination.[17] The flexible bronchoscope is not the instrument of choice for bronchial foreign body removal for several reasons: limited suction, lack of ventilatory capability, limited instrumentation, and lack of airway control. A unique indication for flexible bronchoscopy is a nonradiopaque peripheral foreign body that cannot be seen with a rigid bronchoscope. In this situation, inserting a flexible instrument through a rigid bronchoscope may greatly assist in making a diagnosis.

Rigid Bronchoscopy

In general, a suspected airway foreign body should be removed as soon as possible. Haste should not preclude having the necessary equipment and experienced operating room personnel available. If the *optimal infrastructure* is not available, consideration is given to transferring the patient to another facility.

Airway foreign body removal can be a technically demanding exercise. Removal is facilitated by careful preparation. This includes checking equipment for malfunction before the procedure and having backup equipment available. If possible, a duplicate of the aspirated foreign body is obtained. This facilitates scope and forceps selection by allowing practice attempts to grasp the duplicate (Fig. 24-3).

Two methods of extraction through a rigid bronchoscope are available. The first is forceps removal through a distal lighted bronchoscope. This technique offers a large variety of forceps and tactile feedback. The second method is foreign body extraction with an optical forceps system. This system with fiberoptic lighting and telescopic viewing offers an improved "look" at the aspirated object and serves as an excellent teaching tool. The endoscopist should have experience with both.

Regardless of the technique used, difficulties may be encountered in rigid bronchoscopic foreign body extraction. Objects may fragment or be stripped off the forceps in the larynx. A large laryngeal forceps is made available to deal with this possibility. Occasionally, forceps may be unable to grab a particular foreign body. In these cases, a balloon catheter placed distally or a stone basket used to encircle the object may be helpful.[18,19]

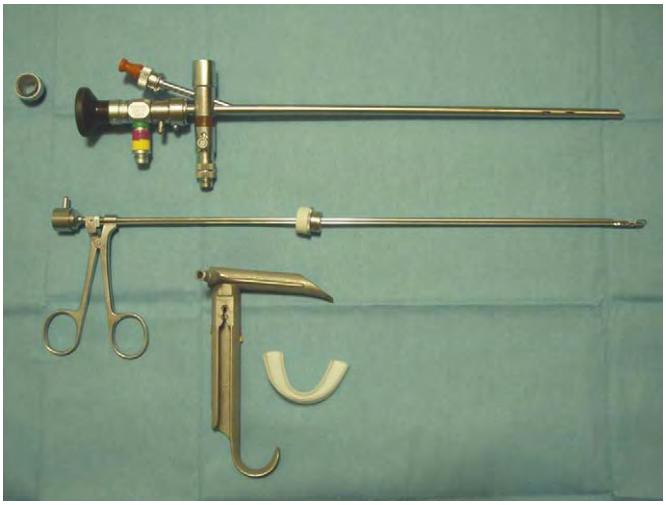


Figure 24-3 Set-up for airway endoscopy and foreign body removal. The instruments depicted include a bronchoscope with a telescope, foreign body grasper, laryngoscope, mouth guard, and glass window.

No more than $1^1/_2$ hours should be spent attempting to remove an aspirated foreign object. Occasionally, edema or bleeding may obscure the endoscopist's view and necessitate stopping a procedure prematurely. In this situation, antibiotics and corticosteroids are administered and the patient brought back to the operating room in 3 to 4 days for another attempt at removal. Rarely, an object may be aspirated that is too large to be removed endoscopically. In this situation, a combined endoscopic and external cervical approach is used.[20] Although this requires a tracheal incision to remove the foreign body, no long-term sequelae should be expected. An endoscopist and two assistants are required to perform this technique successfully.

Most patients who undergo removal of airway foreign bodies have an uneventful postoperative course. For patients who have a long-standing foreign body extracted, productive postoperative coughing may occur as secretions trapped behind the object are released. Hemoptysis from disrupted granulation tissue may also be seen. Antibiotics are not routinely administered after foreign body extraction and postoperative chest radiographs are not routinely ordered. This is obviated by "second-look" bronchoscopy, in which the bronchi are examined immediately after the initial removal to check for remnant material or an additional foreign object.

Alternative Therapies

In the past, methods other than endoscopy have been advocated for the treatment of aspirated foreign bodies. Burrington and Cotton[21] introduced a technique of bronchodilator inhalation followed by postural drainage and percussion. This technique was continued up to 4 days before bronchoscopy. A subsequent report, however, found that this technique had only a 25% success rate compared with an 89% success rate with bronchoscopy.[22] In addition, the authors reported an episode of cardiopulmonary arrest secondary to foreign body migration. Because of the great risk of complications and low success rate, bronchodilation and postural drainage are not recommended.

BOX 24-3 Complications after Airway Foreign Body Removal

- Acute airway obstruction
- Laryngeal lacerations
- Pneumomediastinum
- Bronchial stenosis
- Pneumothorax
- Tracheoesophageal fistula
- Massive hemoptysis
- Distal bronchiectasis
- Laryngeal edema
- Pneumonia
- Abscess
- Parenchyma destruction

Expectant management of aspirated foreign bodies is also not advised. The chance of a complication increases while waiting for an object to be coughed up: The object may migrate, or the inflammatory response becomes more intense. Even in objects thought to be dissolvable, bronchoscopy should be performed. Hard candy, which theoretically should melt away, may cause an intense inflammatory reaction. The hazard of leaving a potential irritant in the airway outweighs the risks of rigid bronchoscopy performed by experienced personnel.

CLINICAL COURSE AND PROGNOSIS

Airway foreign bodies can be removed with a low rate of complications with careful preoperative preparation. Improvements in surgical techniques, instruments, and modern anesthesia have allowed bronchoscopy to be effective in greater than 95% of the patients with a less than 1% complication rate.[12] Although rare, mortality is still a potential complication.[2] A negative bronchoscopic evaluation in 10% to 15% of patients is acceptable to avoid the morbidity of a missed foreign body.[12,23] Potential complications after removal are listed in Box 24-3.

Delay in diagnosis has a marked effect on the rate of complications, probably greater than any other factor.[24] This is not always attributable to caregiver negligence because many patients have been seen previously by a physician. At least 25% of patients who present at least 1 week after aspiration of a foreign body have complications.[2,3] Complications may be as high as 60% in a diagnosis delay greater than 30 days. Bronchiectasis is the most common complication. Lobectomy may be necessary if a chronically retained foreign body causes severe bronchiectasis.[7] Long-term complications have not been associated with inorganic foreign bodies; however, organic foreign bodies have an association with granulation tissue, purulence, and edema.[7] Unfortunately, a low index of suspicion for an airway foreign body can lead to tragedy, as exemplified by two reported cases of death after undiagnosed foreign body aspiration.[25]

Aspiration may be prevented by following guidelines for avoidance of foods or toys that pose a risk for young children. Additionally, children should be monitored during meals and never allowed to run, walk, or lie down with food in their mouths. Clinicians should have a low threshold for bronchoscopy with a suspicious history for foreign body aspiration.

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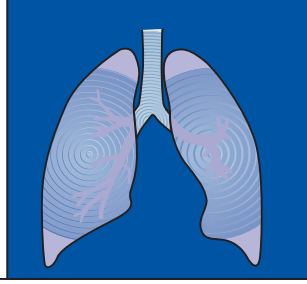


CHAPTER 25

Aspiration Syndromes

John L. Colombo and Heather M. Thomas

TEACHING POINTS

- Aspiration is a common event with a spectrum from normal to subclinical, but disease causing; to massive, leading to acute respiratory failure and death.
- Diagnosis is challenging due to the lack of specific tests able to show cause-effect for aspiration to a clinical syndrome.
- Gastroesophageal reflux is commonly associated with respiratory disease, but aspiration is only one possible mechanism of this association.
- Swallowing is an extremely complex function, and its impairment is consistently reported to be the major cause of recurrent pneumonia in children.
- Both the diagnosis and management of recurrent aspiration and/or gastroesophageal reflux are multifaceted and must be individualized for each patient.

Inhalation of foreign materials into the lungs was noted to be a health hazard by Hippocrates in 400 BC, but it was not until Mendelson's classic description in 1946 that clinicians appeared to recognize the widespread nature and clinical importance of aspiration lung injury.[1] Although much has been learned over the 60 years since Mendelson's description, the diagnosis and treatment, particularly of chronic aspiration, remain a challenge in patients of all ages.

The terms *aspiration pneumonia* and *pneumonitis* are often used as generic descriptions of several clinical syndromes. Clinical findings depend on host factors as well as the quantity and type of material aspirated (Table 25-1). Certainly these processes are not necessarily mutually exclusive, and an individual may suffer from one or more. Aspiration is actually a common event, frequently occurring silently, even in normal individuals, especially during sleep.[2] At the other end of the spectrum is massive aspiration, causing acute respiratory failure. This typically occurs with gastric contents but sometimes from other toxic materials. Gastroesophageal reflux (GER) has increasingly been recognized as having a significant association with many respiratory symptoms and disorders. Other specific types of pulmonary aspiration including foreign bodies, near-drowning, and hydrocarbon aspiration are discussed in other chapters.

It is often not possible to definitively prove that aspiration is the cause of an existing lung disease. Therefore, a large element of clinical judgment is required. The initial step in diagnosis is to recognize both the clinical manifestations of aspiration (see Table 25-1) and conditions that predispose to aspiration (Box 25-1).

ACUTE, LARGE-VOLUME ASPIRATION

Disease Mechanisms

The most common cause of large-volume acute aspiration is aspiration of gastric contents. This can have a broad range of pathological and physiological consequences, depending especially on the pH and volume of the aspirate as well as the amount of particulate material (see Table 25-1). Most information on pathophysiological consequences is necessarily derived from animal studies. Aspiration of large particles can produce acute airway obstruction and severe hypoventilation. Smaller particle or liquid aspirates may induce hypoxemia by a variety of mechanisms, including reflex airway closure, hemorrhagic pneumonitis, destruction and dilution of surfactant with secondary atelectasis, and pulmonary edema from extravasation of intravascular fluids and protein. With acid aspiration, these events are typically more severe and prolonged than with neutral liquids. Mendelson's classic study described an "asthma-like reaction" of obstetric patients who had aspirated large amounts of gastric contents. In subsequent animal studies, he and others showed that large-volume acid aspiration (greater than 1 mL/kg and/or $pH < 2.5$) caused severe hypoxemia. Localized areas of atelectasis may occur within a few minutes after acid aspiration.[3] Other early histological findings include bronchial epithelial degeneration, pulmonary edema and hemorrhage with necrosis of type I alveolar cells followed by acute infiltration of neutrophils and fibrin in alveolar spaces. Over the next 24 to 36 hours a marked increase of neutrophil infiltration results in alveolar consolidation, and mucosal sloughing may be seen in the airways. This correlates with the clinical findings of fever and increased infiltrates on chest radiographs. Hyaline membranes may be seen after 48 hours. Reparative processes, including the regeneration of bronchial epithelium, proliferation of fibroblasts and decreased acute inflammation, begin within 72 hours of an aspiration event. Lungs from animals obtained 2 to 3 weeks after acid aspiration show parenchymal scarring with macrophages, lymphocytes, and hemosiderin, often with bronchiolitis obliterans.[4]

Physiological changes typically occur significantly later, and the inflammatory response is more prolonged with aspiration of small particles than after liquids. Intravascular fluid

Table 25-1
Clinical Findings and Pathophysiologic Events Associated with Aspiration

Syndrome/Clinical Findings	Substances	Major Pathophysiologic Events
Large airway obstruction	Large solids (meat, poultry)	Atelectasis
Atelectasis	Large-bolus liquids or large particles (gastric contents)	Hypoxemia
Asphyxia ("café coronary")		Hypercapnia
Hyperinflation		Bronchitis, bronchiectasis, pneumonia
Pneumothorax		Death
Wheeze, cough		
Apnea or laryngospasm		
Acute chemical injury	Gastric contents (pH<2.5, small particles)	Pulmonary edema
Diffuse infiltrates	Toxic exogenous liquids (hydrocarbons)	Shock
Adult respiratory distress syndrome	Toxic gases	Hypoxemia
Apnea or laryngospasm		Hemorrhagic pneumonia
Tracheobronchitis		Alveolar consolidation with polymorphonuclear neutrophil leukocytes, fibrin
Infectious injury (acute or chronic)	Nasal or oral secretions	Mucosal sloughing
Pneumonia/bronchopneumonia	Gastric contents (hospitalized patients)	Necrotizing pneumonia
Abscess	Exogenous contaminated materials	Alveolar consolidation with polymorphonuclear neutrophil leukocytes, exudate
Empyema or effusion		Bacteria (anaerobic or mixed anaerobic and aerobic), gram-negative bacilli in hospital-acquired abscess
Ventilator-associated pneumonia		
Recurrent chemical injury	Oral, nasal, or gastric contents	
Bronchitis of bronchiolitis		Granulomatous inflammation
Bronchopneumonia or pneumonia		Fibrosis
Atelectasis		Interstitial inflammation
Wheezing, cough		Lipoid pneumonia
Apnea or laryngospasm		Meat or vegetable fibers
Gastroesophageal reflux		Bronchiolitis obliterans

shifts into the lungs occur within minutes after liquid aspiration and usually after 3 to 4 hours with small particles. With aspiration of smaller volumes, of either acid or gastric juices, acute interstitial pneumonia develops followed by chronic airway inflammation, interstitial thickening, granuloma formation, and fibrosis.[5] The critical volume for severe pneumonitis is estimated at 0.8 mL/kg.[6] In animal models, the combination of small particle plus acid aspiration produces greater lung injury, inflammation, and cytokine release, particularly monocyte chemoattractant protein (MCP)-1 and interleukin (IL)-10, than either substance alone.[7]

Although bacterial clearance has been shown to be decreased in animal models, infection does not usually play a primary role in aspiration of gastric contents. However, such aspiration may impair pulmonary defenses, reduce bacterial clearance, and hence predispose to secondary bacterial pneumonia.[8] Infectious complications of aspiration are discussed in the next section.

Clinical Manifestations

Earlier reports of massive aspiration reported mortality as high as 40% to 80%. However, more recent reports involving children and adults indicate mortality rates of 5% or less with no deaths occurring in perioperative aspiration by children in two large series.[9,10] Another large retrospective survey for adults showed no mortality if there was radiographic involvement of three or fewer lobes.[11]

Diagnosis of massive aspiration pneumonia usually involves a witnessed inhalation of vomit or tracheal suctioning of gastric contents, particularly in a patient with artificial airway. In the absence of such events, the diagnosis depends on noting compatible clinical and radiographic findings in a patient at risk for aspiration. Early bronchoscopy has also been reported to be a useful diagnostic adjunct, either in finding gastric contents grossly or microscopically in the tracheobronchial tree or the finding of localized erythema.[12]

Infectious Complications of Aspiration

Although to some the term *aspiration pneumonitis* is synonymous with bacterial pulmonary infection, only about 50% of patients with aspiration of gastric contents develop subsequent pleuropulmonary infections.[13] The risk of infection is increased with conditions listed in Box 25-2. The originating site of bacterial pathogens usually is the oropharynx, but colonizing organisms from the stomach have also been implicated. The bacteriology of aspiration pneumonia is more often determined by the presence or absence of preexisting disease. Detection of superimposed infection can be difficult, and its treatment will depend on the clinical setting.

Disease Mechanisms and Clinical Manifestations

Although most bacterial pneumonias originate from aspiration (usually microscopic) of oral secretions in normal people, this would fall under the category of bacterial pneumonia discussed elsewhere. Early clinical features of large volume aspiration include fever, coughing, wheezing, leukocytosis, and infiltrates seen radiologically. The subsequent development of an infection should be suspected if unexpected deterioration occurs in these findings, particularly after initial

BOX 25-1 Conditions Predisposing to Various Aspiration Syndromes

Anatomical and Mechanical

Nasoenteric tube
Tracheostomy
Endotracheal tube; postextubation
Micrognathia
Macroglossia
Cleft palate
Laryngeal cleft
Tracheoesophageal fistula
Vascular ring
Gastroesophageal reflux
Achalasia (cricopharyngeal)
Gastrointestinal tract obstruction (e.g., esophageal stricture, malrotation)
Collagen vascular disease (scleroderma, dermatomyositis)
Tumors, masses (foreign body, abscess)
Ataxia-telangiectasia

Neuromuscular

Depressed consciousness (e.g., general anesthesia, drug intoxication, head trauma, seizure, central nervous system infection)
Immaturity of swallowing (prematurity)
Cerebral palsy
Hydrocephalus
Increased intracranial pressure
Vocal cord paralysis
Dysautonomia
Muscular dystrophy
Myasthenia gravis
Guillain-Barré syndrome
Werdnig-Hoffman disease

Miscellaneous

Poor oral hygiene/gingivitis
Trauma
Obstructive sleep apnea
Bottle-propping

BOX 25-2 Conditions Predisposing to Infectious Complications of Aspiration

Gingivitis
Decayed teeth
Gastric outlet or intestinal obstruction
Enteral tube feeding
Prolonged hospitalization
Endotracheal intubation
Prone positioning without elevation of head
Use of antacids or acid blockers

improvement. Supporting evidence should be sought with repeat cultures, radiographs, serial white blood cell counts, and inflammatory markers, such as C-reactive protein.

Detection of infectious agents causing aspiration pneumonia depends upon the technique used. Percutaneous transtracheal aspirates have shown a predominance of anaerobic bacteria.[14] Using transtracheal aspiration, Brook and Finegold found anaerobic bacteria in 90% of aspirates. Gram-negative enteric rods were more frequently isolated in children younger than 4 years, and *B. fragilis* was absent in children younger than 2 years. Aerobic and facultative bacteria found included *S. pneumoniae*, group A streptococci, *S. aureus*, *Proteus* spp., *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Escherichia coli*, *Aerobacter* spp., *Haemophilus influenzae*, and others. Investigators in adult patients, using protected specimen brush specimens, have shown mixed results, some indicating high incidence of anaerobic infections[15] and others have found a low incidence.[16] These have primarily studied ventilator-associated pneumonia in adults. Anaerobic organisms predominate in the oropharynx with a ratio between 3 : 1 and 10 : 1. However, *Bacteroides melaninogenicus* and spirochetes are present in fewer numbers in children younger than 13 to 16 years.[17] Organisms obtained from empyema in children, when not excluding those with suspected aspiration, have yielded, in descending order, aerobic bacteria, anaerobic bacteria, followed by mixed aerobic and anaerobic bacteria. Care must be taken to collect and maintain an anaerobic condition to successfully culture for anaerobic organisms.[18]

When aspiration occurs in the hospitalized patient or in a patient receiving broad-spectrum antibiotic therapy, nosocomial and facultative organisms predominate. Most commonly, these include *E. coli*, *Proteus* spp., and *P. aeruginosa*.[19]

Management

Prevention is the mainstay of treatment. Aspiration may be decreased by placing the patient in a semirecumbent position as opposed to supine.[20] Minimizing the amount of subglottic secretions by continuous aspiration decreased the incidence rate of ventilator-associated pneumonia.[21] This is particularly true in the intubated patient receiving enteral feeds. Delivery of continuous feeds to the jejunum as opposed to the stomach may reduce episodes of reflux and aspiration. This fact was supported in a study of 38 critically ill patients randomized to gastric tube feedings or endoscopically placed jejunal tubes. Two patients in the gastric tube–fed group developed nosocomial pneumonia compared with zero in the jejunal tube–fed group.[22] Another study demonstrated a significant reduction in gastroesophageal regurgitation and a trend toward less microaspiration.[23] However, more recent reports have not supported this finding.[24,25] Enteral feeding via the jejunum also decreases gastric distention thereby decreasing respiratory effort. Fasting before procedures requiring anesthesia has long been thought to decrease the incidence of aspiration. Recent evidence suggests that children who are not permitted oral fluids for more than 6 hours preoperatively do not necessarily benefit in terms of intraoperative gastric volume and pH over children permitted clear liquids up to 2 hours before the procedure.[26]

Witnessed aspiration should immediately prompt lateralization of the head and suctioning of the oropharynx. The airway should be secured with an endotracheal tube if the mental status of the patient is compromised or if signs of significant respiratory distress develop. The nasotracheal

intubation route may be superior to the oropharyngeal route in decreasing aspiration in mechanically ventilated children.[27] Supporting ventilation with the use of oxygen, positive expiratory pressure, and/or mechanical ventilation and prevention of further aspiration are critical. Bronchoscopy may be warranted if large particle aspiration is suspected or there is evidence of large airway obstruction. Corticosteroids are controversial in the management of witnessed aspiration and most likely do not add benefit.[28,29]

Patients should be observed closely for the development of aspiration pneumonitis over the next 24 to 48 hours. If the patient has very limited reserve (pulmonary or immunological) or highly infectious aspirate is suspected (see Box 25-2), early empirical antibiotics may be warranted. Otherwise, in the absence of a clinical picture suggestive of pneumonia (fever, leukocytosis, chest radiograph changes, and/or mucopurulent secretions), empirical antibiotic therapy should be withheld to decrease the emergence of resistant organisms. In the presence of signs and symptoms suggestive of a bacterial infection, a culture of the lower respiratory tract, either via bronchoscopy or airway suctioning, should be obtained and appropriate antibiotic therapy should be instituted.[30] Antibiotic choice is based largely on the underlying condition and past medical history of the patient. In the previously healthy individual, in whom anaerobic bacteria are most likely to predominate, initial therapy with penicillin, ampicillin, or clindamycin is recommended. In the treatment of pneumonia in children with underlying chronic lung disease, institutionalized patients, and those having received prior broad-spectrum antibiotic therapy, a second- or third-generation cephalosporin should be considered. In immunocompromised patients, a combination of an aminoglycoside and a synthetic penicillin or cephalosporin such as ceftazidime might be initiated until culture results are available to guide more specific therapy. Culture results should be used to discontinue or narrow antibiotic therapy. Length of antibiotic therapy has not been addressed in a controlled study; however, treatment for 7 to 10 days appears reasonable for patients who respond promptly.

RECURRENT, SMALL-VOLUME ASPIRATION AND GASTROESOPHAGEAL REFLUX (GER)

Introduction

Recurrent, small-volume aspiration, whether it occurs with swallowing or secondary to GER, is commonly encountered in both pediatric and adult medicine. This is often termed "microaspiration" or "silent aspiration." Small-volume aspiration into the lungs is a relatively common event, with normal adults aspirating oropharyngeal secretions during sleep.[2] It is important to remember that aspiration with swallowing and GER, although often found together, may also exist completely independently.

Disease Mechanisms

Often it is difficult to establish a relationship between small-volume aspiration and pulmonary disease. This likely results from a combination of low sensitivity of tests detecting such intermittent aspiration and the low specificity of tests documenting aspiration as the cause of existing disease. It is generally easier to detect GER, and this may be the reason that lung disease is more commonly associated with it. However, direct aspiration with dysfunctional swallowing is a more common cause of recurrent pneumonia than is GER.[31]

Just as aspiration from above can be a normal event, GER also occurs physiologically with an inverse relationship to age in children. However, depending on the criteria used for a diagnosis, 25% to 80% of children with chronic respiratory disease have an *abnormal* degree of GER.[32] Numerous respiratory diseases and symptoms have been associated with GER (Box 25-3). Possible mechanisms to explain this relationship are listed in Box 25-4. Direct aspiration of refluxed material certainly can be expected to cause respiratory symptoms, just as it does by direct aspiration with swallowing. Bronchoalveolar lavage studies have shown airway inflammation and probable gastric contents in children with GER and difficult-to-treat respiratory symptoms.[33] Animal studies have suggested that microaspiration may cause symptoms directly from airway inflammation as well as predisposing to or accentuating airway hyperreactivity.[34,35] The strong association of bottle feeding

BOX 25-3 Disorders Associated With Gastroesophageal Reflux

Asthma
Chronic cough
Pneumonia, bronchitis
Atelectasis
Bronchiectasis
Pulmonary abscess
Pulmonary fibrosis
Bronchiolitis obliterans
Apnea, bradycardia
Acute, life-threatening events
Failure to thrive
Stridor
Laryngitis, hoarseness

BOX 25-4 Mechanisms for the Association of GER and Respiratory Disease

GER Causing Respiratory Disease

Aspiration
Direct effect: tracheitis, bronchitis, pneumonia, atelectasis
Reflex from irritation of the trachea or upper airway, laryngospasm, bronchospasm
Indirect effect: Inflammation or another alteration predisposing to airway hyperreactivity
Esophageal: airway reflex without aspiration

Respiratory Disease Causing GER

Diaphragm flattening and changes in abdominopleural pressure gradient
Effects of medication (e.g., theophylline) causing decreased lower esophageal sphincter pressure

in the crib during early life and later wheezing and asthma indicates a possible human clinical correlation.[36]

Reflex bronchoconstriction from esophageal acidification has been demonstrated in both animals[37] and humans.[38] However, 10 mL of acid infused into the cat esophagus produced less than one third of the increase in total lung resistance evoked by 0.05 mL of acid instilled in the trachea. Both reactions appear to be vagally mediated.[37] In a study of nine asthmatic children, four patients with positive Bernstein test (epigastric pain after esophageal acid infusion but not with saline) developed wheezing when 30 mL of 0.1 N hydrochloride was infused into the distal esophagus during sleep, but five patients with negative Bernstein test studied similarly showed no respiratory effect.[38] Esophageal acidification can also increase nonspecific airway hyperreactivity without necessarily causing a change in baseline pulmonary mechanics.[39]

Both central and obstructive or mixed apnea have been associated with GER.[40,41] However, another study did not find apnea related to GER in premature infants.[42] Other GER-associated respiratory disorders are listed in Box 25-3.

Improvement after antireflux therapy is perhaps the strongest evidence establishing GER as a direct cause of respiratory disease. Generally such treatment has been shown to be more effective in reducing cough than asthma symptom scores or improving pulmonary function.[43-45] However, very few of these studies are prospective, controlled trials.[46,47] See later for more about treatment.

It is also possible that respiratory diseases and/or treatment can provoke GER. More negative intrathoracic pressure and increased abdominal pressure induced by coughing may increase the likelihood of reflux. Hyperinflation and diaphragmatic flattening with secondary stretching of the crura can also predispose to reflux. However, no increased reflux was found during provoked bronchospasm in adults with both asthma and GER.[48] Theophylline and caffeine decrease lower esophageal sphincter pressure, thus predisposing to GER.[49] Positional changes associated with postural drainage and chest physiotherapy have been associated with increased likelihood of GER. Although at least one study has shown increased GER in the sitting position,[50] a small but definitive study has shown improved pulmonary outcomes over 5 years when the head-down position is avoided with CF infant physiotherapy.[51]

Diagnosis

Evaluation begins with a detailed history and physical examination. Other causes of similar findings should be considered (Box 25-5). The patient or caregiver should be asked about the timing of symptoms in relation to feedings and position changes, spitting or vomiting, irritability in an infant, epigastric discomfort in an older child, and nocturnal symptoms of coughing or wheezing. It is important to remember that there may be no symptoms with silent aspiration in a child with depressed cough reflex. For a child with a history of frequent recurrent vomiting, a trial of therapy is usually warranted before any further evaluation is performed. Observation of the child during a feeding is an essential element of the exam when the diagnosis of aspiration is being considered. Particular attention should be given to nasopharyngeal reflux, difficulty with sucking or swallowing, and associated coughing or choking. The palate, tongue, and oropharynx should be inspected for gross abnormalities and stimulated to assess the gag reflex. Drooling or excess accumulation of secretions in the mouth suggest dysphagia or esophageal motility disorder. Auscultation may reveal transient wheezes or crackles after feeding, particularly in the dependent lung segments.

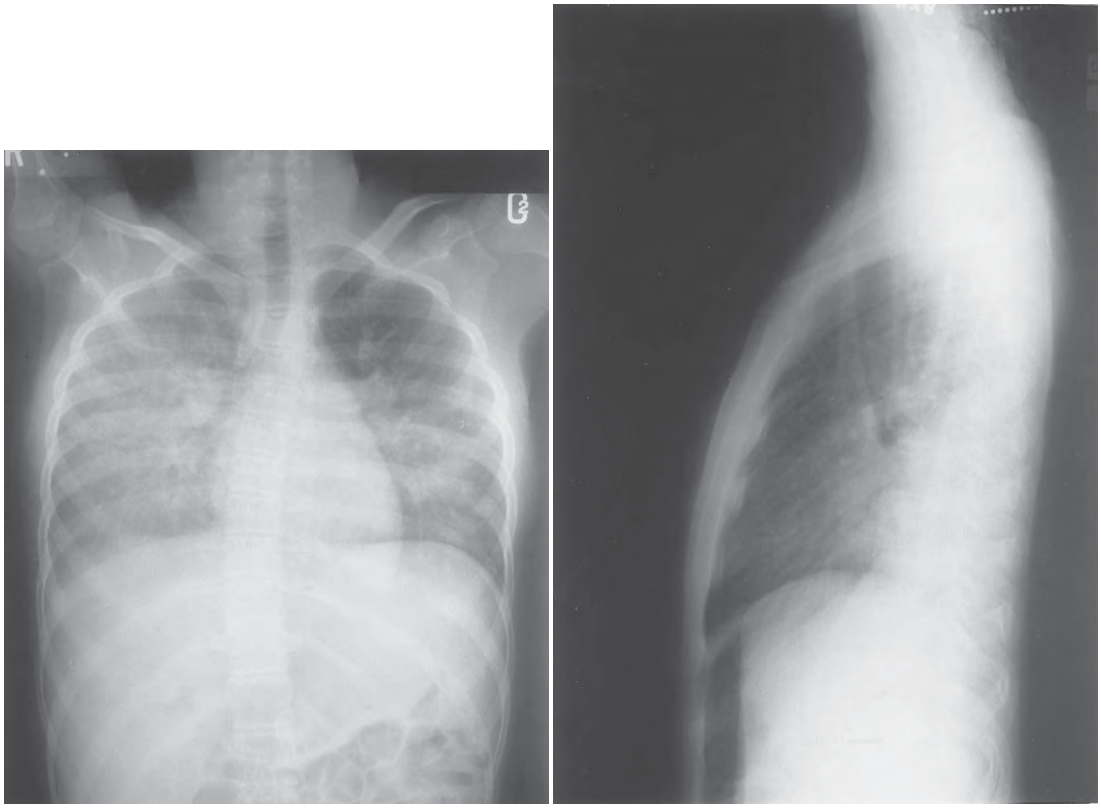
BOX 25-5 Differential Diagnosis of Chronic Recurrent Aspiration

Cystic fibrosis
Interstitial pneumonitis
Asthma
Bronchopulmonary dysplasia
Bronchiectasis
Pulmonary edema
Primary ciliary dyskinesia
Gastroesophageal reflux (without aspiration)
Airway foreign body

A plain chest radiograph is the initial study for a child suspected of having recurrent aspiration. A patient with classic radiographic findings is shown in Figure 25-1. Although segmental or lobar infiltrates localizing to dependent areas may be common, there is a wide variety in radiographic findings. In 22 children with known recurrent aspiration, chest radiograph showed localized infiltrates involving no more than two lobes in 41%, diffuse infiltrates in 27%, and bronchial wall thickening or hyperinflation in 18%. Chest radiograph was normal in 14% of these patients.[52] A computed tomography scan may be helpful in diagnosing lipoid pneumonia (Fig. 25-2), although this would most likely be performed when recurrent aspiration is not highly suspected, and other diagnoses are being explored.

Numerous other tests are available for detecting GER and/aspiration (Table 25-2). A properly performed barium esophagogram may demonstrate reflux into the nasopharynx or direct aspiration into the trachea. It is sometimes difficult to differentiate aspiration through the vocal cords during swallowing from that through a laryngoesophageal cleft. An esophagogram is most useful in detecting anatomic problems, including vascular rings, strictures, hiatal hernias, and tracheoesophageal fistula without atresia (H type). The latter may be difficult to demonstrate. An esophagogram also yields qualitative information on esophageal motility and, when extended, on gastric emptying. A short observation time renders the esophagogram relatively insensitive for detecting aspiration and GER. Because physiological reflux episodes do occur, it can also be nonspecific.[32] However, if repetitive free GER is noted, it is probably unnecessary to do further tests for GER.

A modified barium swallow, using videofluoroscopy imaging, is the most common study for evaluating the swallowing mechanism. Because it uses different textures and quantities of liquid barium or foods laced with barium, it is a sensitive and detailed test for evaluating swallowing, aspiration, and defining food textures and techniques that can be used to reduce aspiration. It has been shown to be much



A B

Figure 25-1 Posteroanterior (**A**) and lateral (**B**) chest radiographs of a 15-year-old patient with mental retardation and recurrent aspiration. The classic findings of dependent area consolidations in the lower lobes and posterior segment right upper lobe are demonstrated.

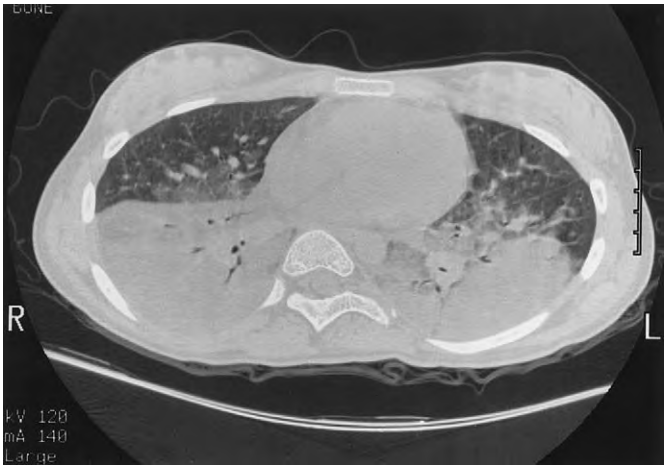


Figure 25-2 Computed tomography scan through the midthorax of the same patient as in Figure 25-1. The density of consolidation measured −35 to −40 Hounsfield units, which is consistent with lipoid pneumonia.

more sensitive than clinical evaluation, particularly for aspiration of solids.[53]

Fiberoptic endoscopic evaluation of swallowing (FEES) is being increasingly used to diagnose dysphagia and aspiration. It is performed with a fiberoptic laryngoscope or bronchoscope passed transnasally with observation of the oral cavity and larynx while the patient is fed small quantities of various textures of liquid or solid foods. Sometimes these are stained with a dye for easier observation. This has been shown to have high correlation with results of modified barium swallow and has the advantage of direct visualization of anatomy by means of fiberoptic laryngoscopy and no radiation. A disadvantage is the invasive nature, which may be less tolerated by some children. However, cooperation with modified barium swallow is also sometimes difficult.[54]

The gastroesophageal scintiscan, also called milk scan, is more physiological and sensitive than the barium esophagogram in detecting GER. Some investigators have found that it can detect aspiration in as many as 25% of children with chronic respiratory symptoms.[55] However, it is generally thought to be less sensitive and specific for a diagnosis of GER than esophageal pH monitoring.[32] Although the scintiscan measures both acid and nonacid reflux, it observes for a much shorter period of time than pH monitoring. It is quite insensitive for the diagnosis of aspiration.[56] Another radioisotope study that has been used for diagnosing aspiration is the "salivagram," which uses a small amount of concentrated marker placed on the tongue or a continuous oral infusion of labeled fluid.[57] This has been proposed to be useful for neurologically impaired children in evaluation for possible laryngotracheal separation.[58]

Monitoring of esophageal pH for 18 to 24 hours is often considered to be the gold standard for detecting significant GER. When performed with high and low esophageal pH probes, both upper and lower esophageal reflux, the duration and frequency of reflux episodes, and nocturnal reflux can be

Table 25-2
Major Diagnostic Tests for Aspiration and Gastroesophageal Reflux (GER)

	Relative Sensitivity
Aspiration	
Modified barium swallow	High
Gastroesophageal scintiscan	Low
Salivagram	Moderate
Bronchial washings for*	High
Lipid-laden macrophage quantitation	
Glucose, lactose	
Pepsin	
Food particles	
Fiberoptic endoscopic evaluation of swallowing (FEES)	High
Dye or other marker studies*	Moderate, low for dye in enteral feeds
GER	
Multichannel intraluminal impedance	High
Esophageal pH monitoring	Moderate-high
Gastroesophageal scintiscan	Moderate
Esophagoscopy, esophageal biopsy	Moderate
Esophageal motility	Low
Barium esophagogram	Low
Empirical trial of therapy	Moderate

*These can also indicate GER in patients with strictly intragastric feedings.

detected. By simultaneously monitoring symptoms or recording polygraph tracings, it sometimes is possible to detect a temporal relationship with esophageal acidification and respiratory abnormalities. The disadvantages include cost (often requiring hospitalization), inability to detect nonacid (e.g., postprandial) reflux, and possible effects of the catheter resting in the nasopharynx and esophagus. It is also important to remember that esophageal pH monitoring may demonstrate a relatively normal amount of GER, which, although not expected to cause esophagitis, may still cause respiratory symptoms or disease.[32]

Impedance monitoring in the pharynx and esophagus is a newer technique for detecting liquid or gas reflux. Unlike pH monitoring, it will detect nonacid reflux. This requires insertion of a probe that measures impedance at various levels along the pharynx and esophagus. There are probes available that monitor impedance and pH simultaneously. Although it has been reported to be more sensitive than pH monitoring, it also misses some episodes of reflux that are detected with pH studies.[59] Esophagoscopy alone is very insensitive for detecting GER; however, when combined with biopsy, it becomes much more useful, with the sensitivity reported as high as 97%.[60]

Tracheobronchial aspirates can be examined for numerous entities to evaluate for aspiration from patients with artificial airway. The most common test is placement of an oral dye and visual examination of tracheal secretions for the presence of staining. Several tests, collectively termed modified Evans blue dye tests, have been used. The sensitivity of these tests greatly depends upon the precise technique used. Impregnating ice chips with Evans blue dye and giving three successive swallows, repeating this on three separate occasions separated by at least 1 hour, followed by suctioning from the tracheostomy, revealed a sensitivity of 82% compared with FEES. For patients receiving mechanical ventilation, the sensitivity was 100%.[61] A more common method is to place four drops of dye on the back of the tongue and follow with tracheal suctioning, observing for stained secretions. The staining of enteral formula to detect aspiration into tracheobronchial secretions has been shown to be insensitive[62] as well as associated with adverse outcomes, including death. For these reasons, this test is not recommended.[63]

Detection of glucose and/or pepsin in tracheal secretions has been studied in mechanically ventilated children. Pepsin appears to be a more specific marker, with glucose concentrations being elevated for reasons other than aspiration.[64]

The finding of lipid in alveolar macrophages has long been associated with lipid aspiration pneumonia.[65] Simply siting lipid-laden macrophages is a nonspecific finding. These cells also occur due to endogenous lipoid pneumonia, particularly with bronchial obstruction, with sepsis, bronchiolitis obliterans, pulmonary hemosiderosis, and in patients receiving intravenous lipid infusions. However, performing semiquantification of these macrophages, and taking into account the reported causes of false positives appears to significantly increase the specificity of this test for children.[66] Lipid-laden macrophages are observed within 6 hours after milk instillation into the rabbit airway. They disappear rapidly, 1 to 2 days after a single milk instillation, and somewhat more slowly after repeated instillations.[67]

Preliminary studies have also proposed examining bronchial washings for several endogenous and exogenous substances including milk antibodies, food fibers, polystyrene microspheres, carbon, and other items. There has been limited experience with these tests in a clinical setting. Further study is required to determine their usefulness.

The diagnosis of recurrent, small-volume aspiration-induced lung injury remains a challenge. Often the best that the clinician can achieve is to demonstrate that aspiration occurs and that existing lung disease is probably caused by aspiration, often by exclusion of other processes.

Management

Chronic aspiration or microaspiration occurs in otherwise normal children as well as children with underlying medical conditions. The extent of therapy should be dictated by the degree of respiratory compromise as well as the underlying condition. The "happy spitter" may require minimal intervention while the neurologically compromised child may require extensive surgical treatment.

Aspiration may occur secondary to material (i.e., saliva, stomach acid) entering the lungs as a result of pharyngeal, laryngeal, or esophageal motor problems. Medical therapy with scopolamine (1.5-mg transdermal patch) or glycopyrrolate (40 to 100 μg/kg/dose three or four times daily) has been shown to be effective in decreasing the amount of saliva.[68] Introducing botulinum toxin A into the salivary glands has been shown to be as effective as scopolamine in decreasing the amount of saliva production.[69] Surgical intervention is an option in children who fail medical management. This includes parotid duct and/or submandibular duct ligation.[70] Children who continue to aspirate and show signs of recurrent pneumonitis may benefit from laryngotracheal separation or isolated tracheostomy. Laryngotracheal separation

(LTS) is a drastic, yet effective, procedure in these children. In one report, 11 children with intractable aspiration pneumonia underwent an LTS procedure and the frequency of suctioning decreased 8-fold, pneumonia was eliminated in 10 patients and all parents rated LTS as excellent or good in terms of its improvement of the quality of life.[71] Because artificial airways can exacerbate aspiration, the benefits should clearly outweigh the risks when isolated tracheostomy is considered for improving airway clearance.

Lifestyle changes form the basis of GER disease (GERD) therapy at all levels of GERD severity. Caregivers should be educated about the importance of small frequent feedings, not jostling the infant after a feeding, preventing air feeding, and holding the infant in a cradled position in order to decrease reflux. Thickening of the formula (1 tablespoon of dry rice cereal per ounce of milk formula) or using a commercially available prethickened formula has benefits for the regurgitating infant, especially the regurgitating infant with poor weight gain.[72,73] Prone positioning during sleep is superior to supine, side, and upright (i.e., sitting in a car seat) positioning in the infant with reflux.[74,75] Risk-to-benefit factors of GERD for sudden infant death syndrome and other issues (e.g., blankets in the bed, second-hand cigarette smoke) should be considered with caregivers before recommending the prone position in the infant with reflux. Consensus from the North American Society for Pediatric Gastroenterology and Nutrition states that prone positioning generally should be avoided due to risks outweighing benefits in children less than 12 months of age.[32] Bottle feeding in the bed or crib before sleep time should be discouraged during the first year of life because the risk of wheezing between the ages of 1 and 5 years increases with this practice.[76] Adolescents and older children with GERD symptoms should avoid caffeine, nicotine, alcohol, and spicy foods that exacerbate symptoms. Weight loss should be encouraged in the overweight child/adolescent.

Pharmacotherapy works mainly by acid suppression or accelerating gastric emptying. Treatment with histamine-2 receptor antagonists such as ranitidine, 2 mg/kg/dose twice daily, reduced by 44% the duration that gastric pH was less than 4, and with three-times-daily dosing, the reduction was 90%.[77] Proton pump inhibitors (PPIs) are generally superior to histamine-2 receptor antagonists.[78,79] Omeprazole and lansoprazole are the PPIs most often used in children. The dosage range for treatment of GERD for omeprazole is 0.3 to 3.5 mg/kg (maximum 80 mg/day), and for lansoprazole, 0.73 to 1.766 mg/kg/day (maximum 30 mg/day).[80] Although the evidence supports the use of cisapride in infants and children with GERD who would benefit from a prokinetic agent, the potential for serious cardiac arrhythmias has limited its use dramatically.[81] Cisapride is not on the market in the United States, nor is it recommended for use in the pediatric population. Most evidence suggests that metoclopramide often contributes more adverse effects than benefits to the treatment of GERD in children.[82,83] If the use of a prokinetic agent is warranted, then erythromycin (1 to 3 mg/kg) in combination with acid suppression could also be considered.[84]

Surgical intervention for GERD is most frequently used for children with neurological impairment. However, underlying lung disease, apparent life-threatening events, and failure to thrive are other common reasons for surgical treatment after failure of medical management in the child with GERD. Nissen fundoplication is the most common procedure performed for the treatment of reflux. The laparoscopic approach has been associated with improved rates of extubation, shorter recovery room stays, shorter durations of chest physiotherapy, fewer intensive care unit admissions, and overall decreased length of stay in neurologically normal and impaired children.[85] In a 2- to 5-year follow-up of a cohort of children who underwent laparascopic fundoplication, 66% of patients reported complete relief and 26% reported considerable improvement of respiratory symptoms.[86] Despite these impressive statistics, the potential complications of this procedure (i.e., gas-bloat syndrome, dumping syndrome, GERD recurrence, dysphagia) must be discussed with families.[87]

Although medical management of the child with GERD is increasing, lifestyle changes should remain an important part of first-line therapy. A search for the underlying cause should always be undertaken. Histamine-2 receptor antagonists remain a reasonable first-line therapy in children with reflux. PPI therapy may be reserved for patients with persistent symptoms, although adult studies have indicated that starting with an empirical PPI trial may be most cost-effective.[88] After failure of medical management, surgical intervention may be appropriate for the child with GERD causing significant respiratory complications. It is important to remember that some children, especially those with profound neurological impairment, may experience recurrent aspiration from the oropharynx in addition to GERD. This is often a reason for "failure" of GERD treatment to reduce pulmonary complications.

PITFALLS AND CONTROVERSIES

- Possibly because of aspiration of oral secretions, tube feeds (even transpyloric) do not necessarily reduce aspiration.
- There is a strong association of gastroesophageal reflux and respiratory disease. Cause-effect relationship remains controversial due to paucity of controlled clinical trials.
- Infectious complications do not occur with approximately 50% of aspiration events. Therefore, antibiotics are not necessarily indicated.
- Adding dye to chronic tube feedings for aspiration detection is insensitive and carries risk of adverse effects.
- Quantity of GER may be "normal" from a gastrointestinal perspective yet cause respiratory disease.
- Thickened feeds reduce vomiting and nonacid GER but do not affect acid GER.
- Most tests for aspiration and GER are helpful when positive but have relatively poor negative predictive value.
- Treatment for GER yields mixed outcomes for respiratory disease, often with improvement in symptoms, but little or no improvement in pulmonary function test results.
- Recent studies in children have not shown increased risk of ventilator-associated pneumonia with use of acid blockers or stress-ulcer prophylaxis.

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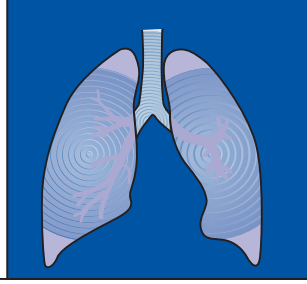

CHAPTER 26 Respiratory Effects of Anesthesia and Sedation

Daniel J. Weiner, Mark Helfaer, and Julian Lewis Allen

TEACHING POINTS

- Safe anesthesia requires careful preoperative assessment, intraoperative monitoring, and knowledge of airway management.
- Important pharmacologic agents include anticholinergics, neuromuscular blockers, sedatives, parenteral analgesics/anesthetics, and inhalational anesthetics.
- There are important effects of anesthesia on lung mechanics, including decreased lung compliance and lung volume, and as a consequence, increased airway resistance.
- Hypoxic vasoconstriction is blunted by general anesthesia, impairing ventilation/perfusion matching.
- Mucociliary clearance can be negatively impacted by anesthesia. Cough, however, can be induced by anesthetics as well as airway instrumentation.

GENERAL CONSIDERATIONS

Preoperative Assessment

Prior to anesthetizing patients for any procedure in general, and bronchoscopy in particular, a preoperative assessment is necessary. The focus of the preoperative assessment is a review of the history with special focus on medications, allergies, and past experiences with anesthetics. Often, history of bronchospasm, "BPD spells," wheezing, and recent upper respiratory infections will guide the choice of anesthetic agents. Cardiovascular disease can present with airway compression and can complicate bronchoscopic evaluation[1] as well as the anesthetic conduct of the case. Aspiration risk must be assessed and minimized. Fasting guidelines should be reviewed and orders should be written in accordance with best practices; a summary of these recommendations is included in Table 26-1. The use of pharmacologic agents to reduce the risk of pulmonary aspiration should be considered cautiously. Agents such as gastrointestinal stimulants, gastric acid secretion blockers, antacids, or antiemetics may reduce the risk of pulmonary aspiration, but the application of this principle has to be applied on a case-by-case basis.[2] The physical examination should focus on the airway, breathing, and circulation as a priority. The airway should be evaluated for any congenital or acquired pathologies that would make control of the airway a challenge, such as loose teeth, excessive secretions, Pierre Robin sequence, and limitation of jaw opening. Bronchodilator therapy or airway distending pressure may be required for children with asthma or airway collapsibility (e.g., tracheomalacia). Cardiovascular concerns include any right-to-left shunts that would add to pulmonary shunting in contributing to desaturations requiring more liberal uses of oxygen. Right-to-left shunting also dictates meticulous attention to the potential for an embolic stroke from, for instance, air in the intravenous line. Issues of pulmonary hypertension should be clarified preoperatively by history, electrocardiogram, and/or echocardiogram. If pulmonary hypertension is present, strategies to minimize decompensation during the procedure include a greater depth of anesthesia, liberal use of oxygen, and minimizing hypercarbia, hypoxia, and acidosis.

Initiation of Sedation and Anesthesia

Whenever anesthetizing a patient, the operator's first focus is on the ability to establish an airway. The patient's ability to protect the airway depends on the depth of sedation/anesthesia (Table 26-2). Preparations must be made to respond to deeper levels of sedation or anesthesia.

Monitoring

Monitoring must be applied to the patient in accordance with anesthesia standards for monitoring (Table 26-3). Pulse

Table 26-1
Fasting Recommendations to Reduce the Risk of Pulmonary Aspiration

Ingested Material	Minimum Fasting Period
Clear liquids (water and juice without pulp)	2 hr
Breast milk	4 hr
Infant formula	6 hr
Non–human milk	6 hr
Light meal (not fatty foods)	6 hr

Reprinted with permission from Practice guidelines for preoperative fasting and the use of pharmacologic agents to reduce the risk of pulmonary aspiration: Application to healthy patients undergoing elective procedures: A report by the American Society of Anesthesiologists Task Force on Preoperative Fasting. Anesthesiology 90(3):896-905, 1999.

Table 26-2
Continuum of Depth of Sedation: Definition of General Anesthesia and Levels of Sedation/Analgesia (Approved by ASA House of Delegates on October 13, 1999, and Amended on October 27, 2004)

	Minimal Sedation (Anxiolysis)	Moderate Sedation/ Analgesia ("Conscious Sedation")	Deep Sedation/ Analgesia	General Anesthesia
Responsiveness	Normal response to verbal stimulation	Purposeful* response to verbal or tactile stimulation	Purposeful* response following repeated or painful stimulation	Unarousable even with painful stimulus
Airway	Unaffected	No intervention required	Intervention may be required	Intervention often required
Spontaneous ventilation	Unaffected	Adequate	May be inadequate	Frequently inadequate
Cardiovascular function	Unaffected	Usually maintained	Usually maintained	May be impaired

Minimal sedation (anxiolysis) is a drug-induced state during which patients respond normally to verbal commands. Although cognitive function and coordination may be impaired, ventilatory and cardiovascular functions are unaffected.
Moderate sedation/analgesia ("conscious sedation") is drug-induced depression of consciousness during which patients respond purposefully* to verbal commands, either alone or accompanied by light tactile stimulation. No interventions are required to maintain a patent airway and spontaneous ventilation is adequate. Cardiovascular function is usually maintained.
Deep sedation/analgesia is a drug-induced depression of consciousness during which patients cannot be easily aroused but respond purposefully* following repeated or painful stimulation. The ability to independently maintain ventilatory function may be impaired. Patients may require assistance in maintaining a patent airway, and spontaneous ventilation may be inadequate. Cardiovascular function is usually maintained.
General anesthesia is a drug-induced loss of consciousness during which patients are not arousable, even by painful stimulation. The ability to independently maintain ventilatory function is often impaired. Patients often require assistance in maintaining a patent airway, and positive pressure ventilation may be required because of depressed spontaneous ventilation or drug-induced depression of neuromuscular function. Cardiovascular function may be impaired.
Because sedation is a continuum, it is not always possible to predict how an individual patient will respond. Hence, practitioners intending to produce a given level of sedation should be able to rescue† patients whose level of sedation becomes deeper than initially intended. Individuals administering moderate sedation/analgesia ("conscious sedation") should be able to rescue† patients who enter a state of deep sedation/analgesia, while those administering deep sedation/analgesia should be able to rescue† patients who enter a state of general anesthesia.
* Reflex withdrawal from a painful stimulus is NOT considered a purposeful response.
† Rescue of a patient from a deeper level of sedation than intended is an intervention by a practitioner proficient in airway management and advanced life support. The qualified practitioner corrects adverse physiologic consequences of the deeper-than-intended level of the sedation (such as hypoventilation, hypoxia, and hypotension) and returns the patient to the originally intended level of sedation.
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oximetry is the mainstay of monitoring to avoid hypoxemia. Carbon dioxide concentrations are often difficult to measure in the absence of a secure airway, but can be measured during bronchoscopy.[3]

When preparing a patient for a procedure, optimal positioning needs to be ensured.[4-6] Adequate padding for pressure points, avoidance of hyperextension of extremities, and eye protection need to be ensured. There is always a possibility of causing a depth of anesthesia greater than intended. In deeper levels of anesthesia, corneal reflexes are blunted, such that accidental injury to the cornea is a possibility requiring either taping the eyes shut or lubricating the eyes with ointment. In addition, the normal airway reflexes are not present. Anesthetics will depress the innervations of the upper airway muscles, making obstruction more likely due to, for example, loss of genioglossus tone. Side lying may minimize some of this loss of airway tone but often makes the bronchos-copy more difficult. Jaw thrust and shoulder rolls in the supine position can overcome these as well. Early on in the preparation, drying agents are often helpful in optimizing views of the airway structures. Anticholinergics are the most commonly used agents, which can also minimize the bradycardias associated with narcotic coadministration.[7]

To establish an airway, the most useful maneuvers are a jaw thrust or placement of an oral airway or a nasal airway to displace the tongue forward.[8] Failing this, the difficult airway algorithm can be used to direct therapies to assure an airway in a step-by-step fashion (Fig. 26-1).

Special Considerations for Airway Procedures

When considering bronchoscopy, decisions of the merits of flexible versus rigid bronchoscopy should be addressed. Retrieval of airway foreign bodies is best addressed by rigid bronchoscopy.[9] The latter most regularly requires neuromuscular blockade, because patient movement when the rigid bronchoscope is in the airway can cause injury. Flexible bronchoscopy is superior for evaluation of more distal airways,

Table 26-3
Standards for Basic Anesthetic Monitoring (Approved by the American Society of Anesthesiologists House of Delegates on October 21, 1986, and Amended on October 25, 2005)

Measure	Monitor
Concentration of inspired oxygen	Oxygen analyzer and low oxygen alarm
Oxygenation	Pulse oximetry
Ventilation	Clinical: chest rise and auscultation. When possible, and always when an endotracheal tube is in place: expired carbon dioxide concentration.
Circulation	EKG, heart rate, and blood pressure at least every 5 mins
Temperature	Thermometer (especially with small infants or neonates)

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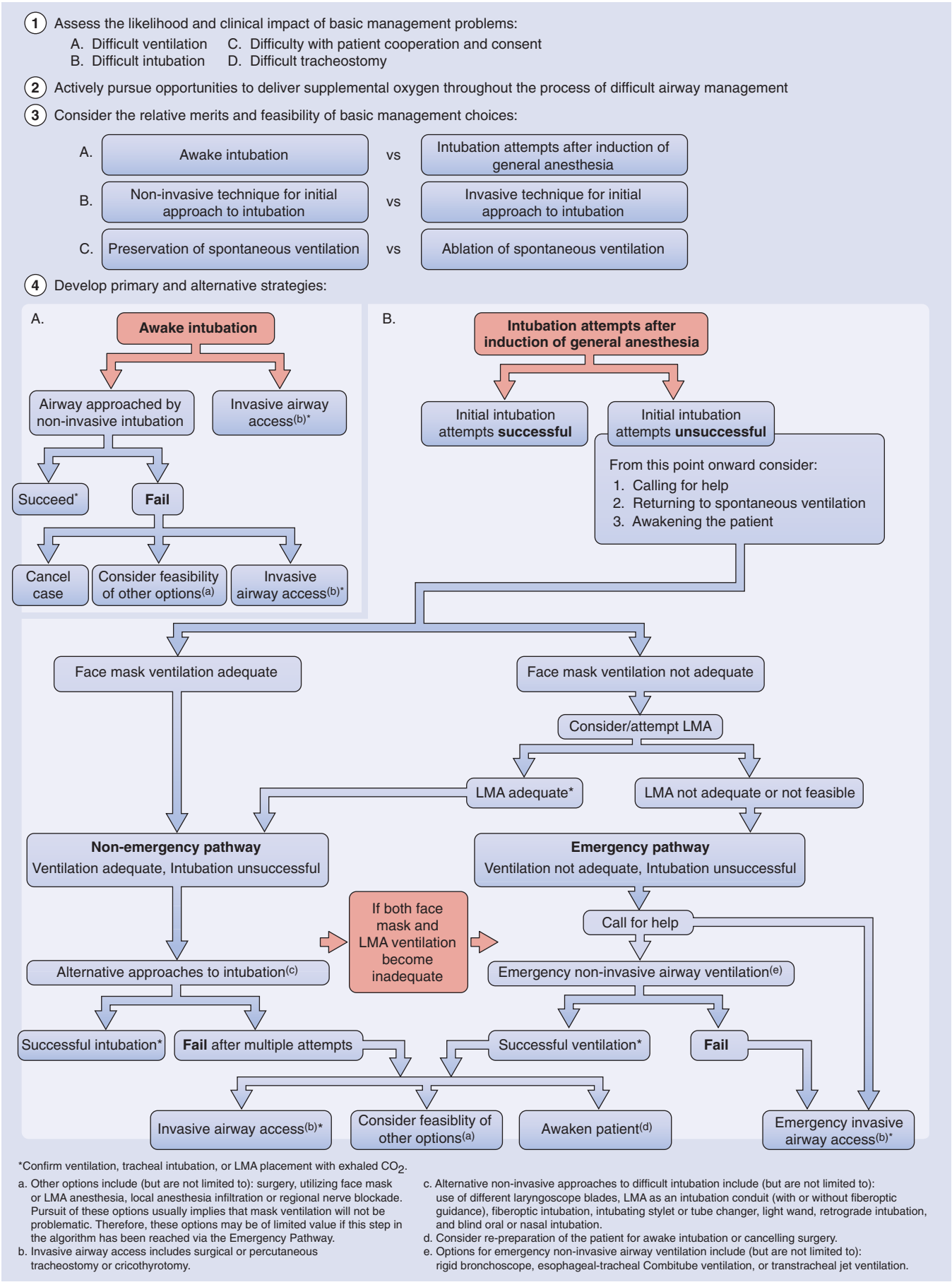


*Confirm ventilation, tracheal intubation, or LMA placement with exhaled CO_2.

a. Other options include (but are not limited to): surgery, utilizing face mask or LMA anesthesia, local anesthesia infiltration or regional nerve blockade. Pursuit of these options usually implies that mask ventilation will not be problematic. Therefore, these options may be of limited value if this step in the algorithm has been reached via the Emergency Pathway.

b. Invasive airway access includes surgical or percutaneous tracheostomy or cricothyrotomy.

c. Alternative non-invasive approaches to difficult intubation include (but are not limited to): use of different laryngoscope blades, LMA as an intubation conduit (with or without fiberoptic guidance), fiberoptic intubation, intubating stylet or tube changer, light wand, retrograde intubation, and blind oral or nasal intubation.

d. Consider re-preparation of the patient for awake intubation or cancelling surgery.

e. Options for emergency non-invasive airway ventilation include (but are not limited to): rigid bronchoscope, esophageal-tracheal Combitube ventilation, or transtracheal jet ventilation.

Figure 26-1 Difficult airway algorithm. A loss of protective airway reflexes and control of breathing necessitates that the practitioner must be in a position to take over these normal physiologic functions, have a step-wise plan if initial efforts are not successful, and outline both procedures and necessary equipment. (Reprinted with permission from 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 98:1269-1277, 2003. Erratum in: Anesthesiology 101:565, 2004.)

and for obtaining bronchoalveolar lavage for cultures or cytology.

Flexible bronchoscopy is most commonly performed through the nose, but alternative approaches such as through the mouth with or without a laryngeal mask airway can be considered.[10,11] If assessment of glottic or supraglottic function (e.g., of vocal cords) or of dynamic airway collapsibility is required, light sedation is often required. The anesthetic may need to be deepened once supraglottic function is assessed and progression below the vocal cords is required. A greater depth of anesthesia can be accomplished systemically with potent inhaled anesthetics or intravenous anesthetics such as ketamine, propofol, or narcotics. Greater depths of anesthetics will affect airway tone, pulmonary blood flow, and functional residual capacity. The effects of lidocaine are often underestimated; lidocaine can affect upper airway tone and lead to upper airway collapse, mimicking obstructive apnea. Likewise, inhalational anesthetics can cause asynchronous breathing patterns.[12]

Patients with bronchomalacia or laryngomalacia[13] often require more tone to maintain airway patency. In these cases, agents causing muscle relaxation can worsen airway obstruction. Neuromuscular blockade affects only striated, and not smooth, muscle paralysis, so these agents may have a variable effect on the pathology of malacia.

CLASSES OF INHALED AND INTRAVENOUS ANESTHETIC/SEDATING AGENTS

Adjuvant Agents

ANTICHOLINERGIC AGENTS

Anticholinergic agents will block the vagotonic effects such as bradycardia with manipulation of the airway.[7] In addition, these agents will minimize secretions, allowing better views during bronchoscopy. Atropine is the mainstay of this group of agents. An absolute minimum dose (0.15 mg) is usually suggested despite the size and weight of the patient. Smaller doses present problems with measurement, the possibility of inadequate muscarinic blockade, as well as increased risk of tachycardia. Glycopyrrolate as an antimuscarinic agent has the advantage that, as a quaternary ammonium salt, it does not cross the blood-brain barrier and causes less tachycardia. There is very little effect on dead space ventilation with vagal blockade. There are effects of bronchodilation especially in the case of a viral illness causing bronchoconstriction. Blocking the muscarinic 3 receptor may limit bronchospasm, which may optimize ventilation/perfusion ($\dot{V}/\dot{Q}$) matching[14] (Table 26-4).

NEUROMUSCULAR BLOCKADE

Neuromuscular blockade is often used for rigid bronchoscopies, but for flexible bronchoscopy where functional assessment of vocal cord function is desired, paralysis is counterproductive. Recently, there is increasing use of short-acting nondepolarizing agents such as vecuronium or rocuronium. Respiratory mechanics, as expected, are profoundly affected by neuromuscular blockade.[15] Succinylcholine is an agent with fewer indications due to complications, which, although rare, can be life threatening.

LIDOCAINE

Directly anesthetizing the airway provides a systemic anesthetic drug-sparing effect, and for endotracheal intubation this is most commonly provided with intravenous lidocaine. Alternatively, lidocaine can be nebulized[16] and inhaled, allowing anesthesia of the upper airway, glottis, and trachea. In addition, local instillation at the time of the bronchoscopy allows for local anesthesia as well. Caution should be exercised if exceeding 5 mg/kg lidocaine by any of these routes of administration, for systemic absorption is excellent in the airway.[17] Seizures are the most concerning side effect and can be mitigated by other agents such as benzodiazepines. Topical lidocaine, by either nebulization or direct instillation, will affect upper airway muscle tone and can worsen malacia.[18]

Sedative Agents

BENZODIAZEPINES

Anxiolysis is a primary goal of anesthesia. This can be achieved pharmacologically with benzodiazepines. Alternatively, there are psychological adjuvants to minimize anxiety in patients prior to procedures.[19,20] As a goal of anesthetizing children, amnesia is of great importance. Antegrade amnesia is often induced by benzodiazepines. Benzodiazepines can be administered early in the procedure or as a premedication. Midazolam has the advantage that it can be administered by the oral, intramuscular, rectal, intranasal, or intravenous routes. It is short acting and water soluble outside of the body, and it becomes lipid soluble when injected into a nonacidic medium such as the blood. Other benzodiazepines such as diazepam last longer than midazolam and can be administered via the oral or intravenous route. Lorazapam can be given via the intramuscular route, unlike diazepam. Benzodiazepines as a single agent do not substantially affect respiratory function, but when combined with other agents, they can profoundly affect the drive to breathe, including blunted carbon dioxide response as well as hypoxic drive to breathe. Benzodiazepine overdose can be treated with flumazenil, although seizures are a serious side effect. Waiting for spontaneous reversal with time is the most conservative approach to cases of overdosing. Retrograde amnesia cannot be reliably achieved, although scopolamine has been advocated for this. The potent penetration into the brain makes it a less attractive agent as an antisialagogue and cardiac vagolytic. The neurologic effects persist for many hours after the procedure, making the postoperative care challenging.

Chloral hydrate is an agent with a long history of use in children, although there is a paucity of literature supporting its use. It can be administered enterally or rectally. There are very few studies evaluating the utility of choral hydrate for pediatric bronchoscopies, but there are studies evaluating chloral hydrate for other procedural sedations (such as for infant pulmonary function testing). In general, as a single agent, the usefulness is somewhat limited.[21-25]

Dexmedatomidine is a new agent that is a specific α_2-adrenergic agonist and has provided useful sedation in adults. The usefulness in children is being evaluated.[26]

NARCOTICS

Narcotics are the most potent antitussive agents and therefore are quite helpful in airway procedures. In addition, ade-

Table 26-4
Anesthetic, Sedating, and Adjuvant Agents

Class	Agent	Purpose	Route of Administration	Reversal Agent	Cautions	Effect on Pulmonary Vasculature	Effect on Bronchial Tone	Effect on CO_2 Response	Effect on O_2 Response
Anticholinergics	Glycopyrrolate Atropine	Dries secretions Maintains heart rate	IV, IM, PO	Physostigmine	No CNS effects Possible CNS effects		Some bronchodilation	Minimal	Minimal
Narcotics	Fentanyl	Anesthetizes airway	IV, IM, PO, intranasal	Naloxone		Excellent anesthetic for pulmonary hypertension	Minimal	↓ Ventilatory drive	↓ O_2 response
	Morphine Remifentanil		IV, IM, PO, inhaled IV						
	Meperidine		IV, IM, PO		Seizures				
Inhaled anesthetics	Nitrous oxide	Anesthetizes whole body	Inhaled			Minimal		↓ Ventilatory drive	↓ O_2 response
	Halothane				Hypotension Calcium	Vasodilators	Dose-dependent bronchodilation	Increased apneic threshold	Paralyzes HPV
	Sevoflurane				Flush machine; first case Monday AM	Minimal dilation	Dose-dependent bronchodilation		
	Isoflurane						Dose-dependent bronchodilation		
	Desflurane				↑ Bronchospasm, laryngospasm		Dose-dependent bronchodilation		
Other agents	Chloral hydrate		Rectal, enteral			Variable	Variable	Variable	
	Propofol	Anesthetizes whole body	IV		Sulfites in generic, infectious, egg allergy; shake before using	\			
	Ketamine	Anesthetizes airway, preserving cardiovascular function	IV, IM		Sensitizes airway, causes secretions			\	

quate analgesia by a narcotic will facilitate procedures such as bronchoscopy. As a sole agent, it takes very high doses to blunt the responses to airway manipulation, but narcotics are a mainstay of anesthesia for bronchoscopic evaluation. Short-acting agents are optimally used for brief evaluations and prompt recovery.[27] Narcotics will universally decrease apneic threshold, and therefore preparations should be anticipated to control the airway. Many different narcotics, summarized in Table 26-4, can be used.

Anesthetic Agents

PARENTERAL AGENTS

Ketamine is an intravenous agent[28] used for many procedures in children. It is touted to be a safe agent, but when given to very sick patients, the direct negative inotropic effects can cause cardiovascular collapse. Likewise, like all potent intravenous agents, the effects are dose dependent, and large doses of ketamine will cause apnea and can ablate the cough reflex. Emergent delirium is a serious side effect that is seemingly unpredictable. Attempts at preventing this with other agents such as benzodiazepines have met with mixed results without consistent success. Ketamine may also increase airway secretion production and should be combined with an anticholinergic agent.

Propofol, administered intravenously, is becoming increasingly popular for many procedures in adults and children.[27] The amnestic effects are dose dependent and variable, so often a benzodiazepine is coadministered to ensure amnesia. Lidocaine is frequently coadministered to minimize the stinging sensation engendered by direct intravenous administration. Additionally, propofol can produce myotonic activity during administration that can mimic seizures. Continuous propofol infusions in the pediatric intensive care unit are contraindicated due to cases of unexplained metabolic acidosis and death in children. However, short-term use for procedural sedation is a safe practice. The infectious risks of propofol administration must be considered carefully; the solution is a rich medium for growth of bacteria, and there have been cases of serious infectious consequences of propofol prepared in a nonsterile manner. The generic preparation contains sulfites, which can cause allergic responses in sensitized individuals.

Etomidate, also administered intravenously, is sometimes used despite a paucity of pediatric data. Although touted as preserving cardiopulmonary function, potential complications include the drug's proemetic effects as well as effects on steroidogenesis.

INHALATIONAL AGENTS

Inhaled anesthetics are often the ideal agents to use during an airway procedure. Halothane is less commonly used and is being supplanted by newer, safer agents that are far better tolerated, such as sevoflurane.[29] These agents can be used as total anesthetics, providing all the necessary components of hypnosis, sedation, analgesia, bronchodilation, and airway anesthesia.[30] Assurance must be focused on adequate depth of anesthesia. Unfortunately, depth of anesthesia is difficult to assess. Bispectral (BIS) monitoring is sometimes utilized to evaluate the depth of hypnosis in adults, but it has not been consistently validated in children.[31] Manipulation of the airway in an inadequately anesthetized patient (i.e., stage 2 anesthesia) can result in severe laryngospasm, bronchospasm, and decompensation. The inhaled agents also have the advantage of preserving spontaneous ventilation (albeit with a blunted carbon dioxide response to breathing), thus allowing for assessment of vocal cord function. Some agents such as sevoflurane are much better tolerated than are other agents such as desflurane. First cases in the operating room on Monday morning should be preceded by adequate flushing of the machine to avoid toxic byproducts. The improved tolerance to sevoflurane includes lower risks of laryngospasm and bronchospasm during the procedure and on emergence from the procedure (see Table 26-4).

MECHANICS (LUNG, CHEST WALL, AND FUNCTIONAL RESIDUAL CAPACITY)

Total respiratory system compliance (C_{rs}) decreases during anesthesia, although the mechanisms by which this occur are somewhat controversial. One hypothesis is that anesthetics (or mechanical ventilation during anesthesia) might directly alter pulmonary surfactant, although evidence for this is quite limited.[32] Alternatively, C_{rs} might be reduced as a consequence of lowered lung volume (see later) due to airway closure or atelectasis. Although not an effect of anesthesia per se, CO_2 insufflation for laparoscopic procedures is a well-defined cause of decreased lung compliance.[33]

Airway resistance also decreases with inhaled anesthestics; the decrease is thought to be due to direct inhibition of autonomic mediators (e.g., acetylcholine) on airway smooth muscle (ASM) tone.[34] Ketamine may induce bronchodilation via release of cathecholamines and their effects on β_2-adrenergic receptors on ASM or via other mechanisms.[35,36] Airway resistance can also increase as a result of histamine release due to neuromuscular blockade, although this is not always clinically apparent. In one study, rapacuronium decreased forced expiratory flows in children anesthetized with remifentanil and propofol, although total respiratory system resistance increased nonsignificantly.[15] Changes in forced expiratory flow and mechanics with mivacurium were comparatively much smaller. Upper airway resistance increases due to loss of pharyngeal muscle tone, and this is usually managed with use of distending pressure, an artificial airway, or both. A variety of techniques have been used to measure mechanics, including single-breath occlusion techniques[37] and low-frequency forced oscillation.[38]

Anesthetics and muscle relaxation can affect both the chest wall (including the diaphragm) and the lung, such that the elastic recoil of the respiratory system increases, favoring a decrease in lung volume (Fig. 26-2). This mechanism has been well demonstrated in an animal model.[39,40] It is therefore not surprising that resting lung volume (functional residual capacity [FRC]) decreases 15% to 20% during anesthesia with spontaneous breathing. This reduction occurs early during anesthesia, and the degree of reduction is not significantly affected by the use of paralytics. These effects might be particularly important in infants, whose chest wall is highly compliant compared with their lungs (or compared with the chest walls of older children), further reducing elastic recoil pressure and FRC. Indeed, infants actively maintain their lung volume above that which would be passively determined

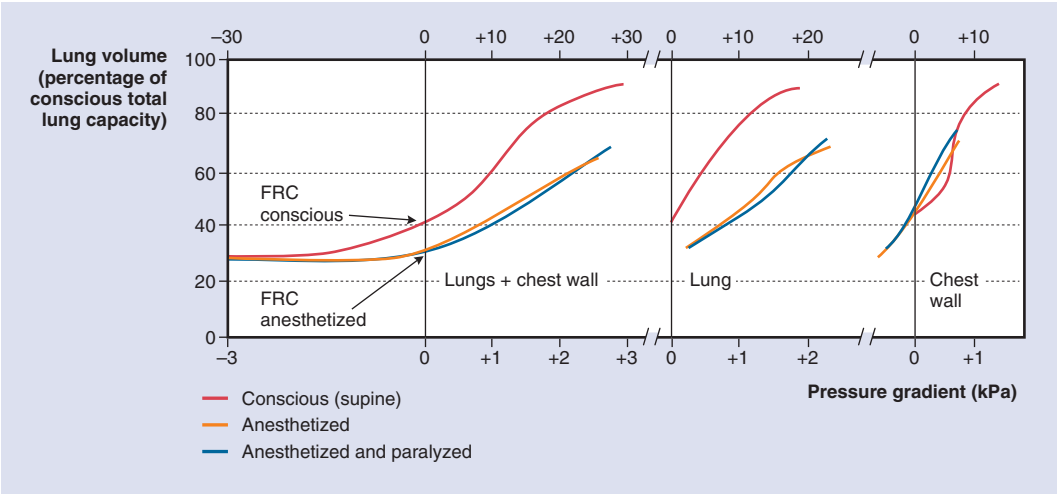


Figure 26-2 Pressure and volume relationships in healthy adults before and after anesthesia (with and without paralysis). The respiratory system (lungs + chest wall) becomes significantly less compliant during anesthesia, without significant differences related to use of paralysis. The majority of these mechanical changes appear to be due to changes in lung, rather than chest wall, compliance. Note that FRC (denoted by the arrows) decreases significantly with anesthesia. (Redrawn with permission from Nunn JF: Nunn's Applied Respiratory Physiology, 4th ed. Stoneham, Mass, Butterworth-Heinemann, 1993.)

by elastic recoil with strategies such as postinspiratory activity of the diaphragm and glottic braking[41,42]; the effectiveness of these strategies are likely attenuated during anesthesia.

These effects can reduce the lung volume to near residual volume, and potentially below the closing capacity, resulting in airway closure and atelectasis. This lowered lung volume reduces lung compliance and increases airway resistance, offsetting the beneficial effects of anesthetics on airway smooth muscle tone. Significant atelectasis increases $\dot{V}/\dot{Q}$ mismatch and intrapulmonary shunt (see later).

VENTILATION AND BRONCHOMOTOR TONE

The reductions in lung and respiratory system compliance and in FRC cause functional reductions in ventilation in patients undergoing anesthesia. Diminished neural drive also reduces minute ventilation and alters the pattern of inspiratory muscle activation between the diaphragm and intercostal muscles. Anesthesia preferentially depresses the intercostal muscles over the diaphragm, leading to an altered pattern of chest wall motion (Fig. 26-3). These changes may or may not be compensated for by the administering anesthetist, who can control the rate and depth of respiration, the PEEP, and the fractional inspired concentration of oxygen.

The presence of an endotracheal tube can promote bronchospasm in some susceptible patients. This complication is more likely in the setting of asthma, but viral upper respiratory tract infections can also predispose to airway hyperreactivity in otherwise healthy children. Although in the past, a recent (in the past 2 to 4 weeks) or current URI usually was viewed as cause for cancellation of anesthesia (usually for 4 to 6 weeks), these guidelines have been somewhat relaxed.[43-45]

Increased airways resistance can also result from upper airway obstruction due to anesthesia-induced loss of upper airway muscle tone, because muscles of the upper airway are the most susceptible respiratory muscles to the depressant

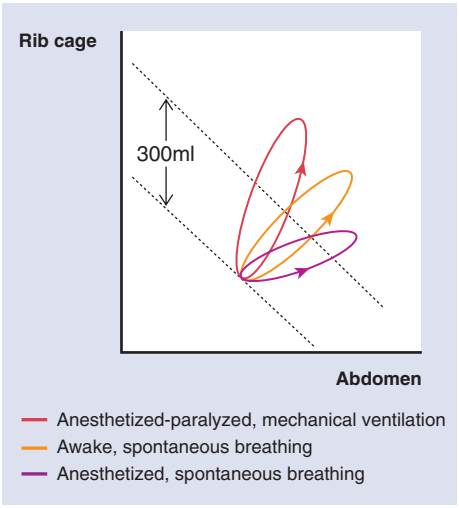


Figure 26-3 Rib cage and abdominal excursions (measured by inductance plethysmography) and their relative contribution to tidal volume change in awake, anesthetized, and paralyzed subjects. Note that the rib cage contribution to ventilation decreases during anesthestized spontaneous breathing, and is increased by mechanical ventilation. (Redrawn with permission from Handbook of Physiology: Section 3. The Respiratory System, Section Editor: Alfred P. Fishman: Volume III: Mechanics of Breathing, edited by Peter T. Macklem and Jere Mead, Part 2. Bethesda, MD, The American Physiological Society, 1986.)

effects of anesthesia. In the absence of an endotracheal tube, use of a laryngeal mask or face mask with an oral airway ameliorates this complication in both infants[46] and young children.[47] Finally, because airway caliber is lung volume dependent, the reduction of FRC due to anesthesia can increase airways resistance. However, most anesthetic gases have bronchodilating effects, and this can counteract the reduction in FRC, leading to little net change in the airways resistance in the spontaneously breathing patient (Fig. 26-4, points B-D). Administration of PEEP can counteract this

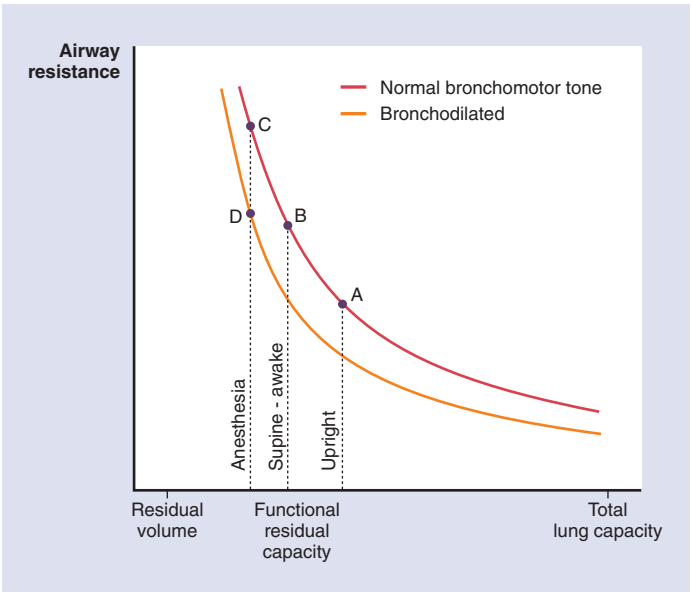


Figure 26-4 Airway resistance as a function of lung volume. Airway resistance rapidly increases as lung volume decreases below functional residual capacity and with reduction of FRC during anesthesia (points B-C). Bronchodilation with inhaled anesthetics offsets the change in resistance due to lowered lung volume (points C-D). (Redrawn with permission from Nunn JF: Nunn's Applied Respiratory Physiology, 4th ed. Stoneham, Mass, Butterworth-Heinemann, 1993.)

increase of lower airways resistance resulting from reduction of FRC, as well as the increase of upper airways resistance resulting from loss of upper airway motor tone. Such PEEP may be intentionally administered, or result from either advertently or inadvertently choosing a respiratory rate and ventilation strategy in which the expiratory time is short relative to the expiratory time constant of the respiratory system.

During anesthesia, ventilation to the dependent regions is markedly diminished, probably due to atelectasis engendered by the low FRC state (Fig. 26-5). Use of computed tomography has clearly demonstrated atelectasis in dependent lung regions.[48] In addition, anesthesia alters the vertical distribution of ventilation along the normal lung, with less prominent differences of ventilation between lower and upper regions seen than in the awake state (Fig. 26-6). Application of PEEP restores much of the normal ventilation gradient by recruiting atelectatic areas and perhaps by overdistending apical lung regions, making them less compliant.[49]

PULMONARY BLOOD FLOW AND PULMONARY VASCULAR RESISTANCE

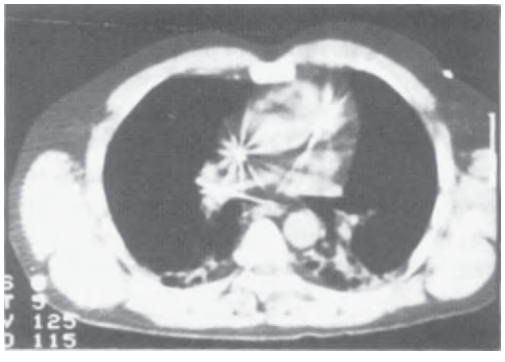
In contrast to the distribution of ventilation, lung perfusion increases from the upper to the more dependent regions of the lung, except at the bottom-most region, in which pulmonary blood flow is also diminished (see Fig. 26-6). The vertical distribution of blood flow is similar to that in the awake state and is related to the hydrostatic gradient.

Hypoxic pulmonary vasoconstriction is diminished by up to 50%, but not abolished, by several inhalational anesthetics; this may not be the case with intravenous anesthetics such as barbiturates. Loss of hypoxic pulmonary vasoconstriction, while somewhat of a protection against rises in pulmonary artery pressure engendered by alveolar hypoxia, leads to regions of low $\dot{V}/\dot{Q}$.

VENTILATION/PERFUSION MATCHING

The multiple inert gas elimination technique has clarified the mechanisms of gas exchange abnormalities that occur during anesthesia. The redistribution of ventilation (and to a lesser extent perfusion) during anesthesia also leads to alterations in $\dot{V}/\dot{Q}$ matching (Fig. 26-7). Greater relative ventilation to the apices leads to increased regional dead space ventilation ($\dot{V}/\dot{Q} > 1$) in a tidal volume–dependent fashion (Fig. 26-8).

Figure 26-5 Three-dimensional reconstruction of chest computed tomography scans of a patient under anesthesia. Note bilateral dependent atelectasis that is less prominent toward the lung apices. (Reprinted with permission from Hedenstierna G: Respiratory Measurement [Principles and Practice Series]. Ames, IA, Blackwell BMJ Books, 1998.)



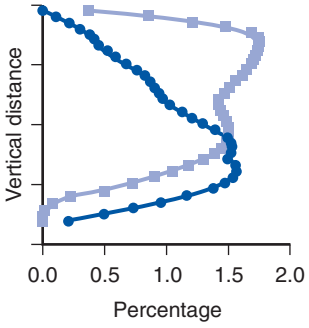


Figure 26-6 Anatomic and physiologic assessment of ventilation/perfusion. The CT scan (*left*) demonstrates dependent atelectasis in this anesthetized patient. Ventilation and perfusion are assessed (at *right*) using SPECT and radioactively labeled albumin. Perfusion (*dark circles*) is highest in the lower regions, while ventilation (*light squares*) is highest in the upper regions and absent in the atelectatic areas at the bottom. (Reprinted with permission from Hedenstierna G: Respiratory Measurement [Principles and Practice Series]. Ames, IA, Blackwell BMJ Books, 1998.)

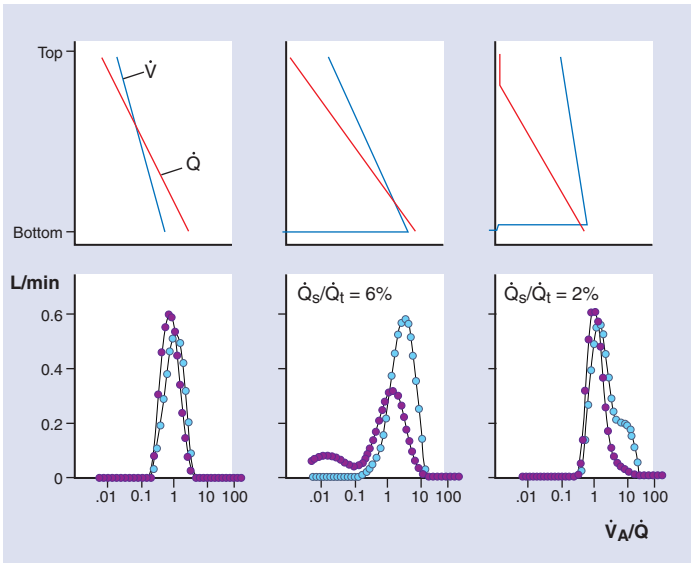


Figure 26-7 Ventilation (*blue circles*)/perfusion (*purple circles*) relationships during anesthesia. $\bar{V}/\dot{Q}$ distributions (as assessed by multiple inert gas technique) are depicted at the *bottom*, and relationships of ventilation and perfusion to lung zones are depicted at the *top*. Note the unimodal distributions of ventilation and perfusion, centered around $\bar{V}/\dot{Q} = 1$ in the awake patient (*left*) and that ventilation and perfusion both increase toward the bases. In the anesthetized patient (*center*), there are increased lung units with very low $\bar{V}/\dot{Q}$ (shunt), which results in oxyhemoglobin desaturation and decreased perfusion to some lung units with preserved ventilation (higher $\bar{V}/\dot{Q}$), which results in hypercarbia. Application of 10 cm H_2O PEEP (*right*) tends to restore normal $\bar{V}/\dot{Q}$ distribution and decrease shunt, although some areas with high $\bar{V}/\dot{Q}$ are receiving increased ventilation. (Reprinted with permission from Hedenstierna G: Respiratory Measurement [Principles and Practice Series]. Ames, IA, Blackwell BMJ Books, 1998.)

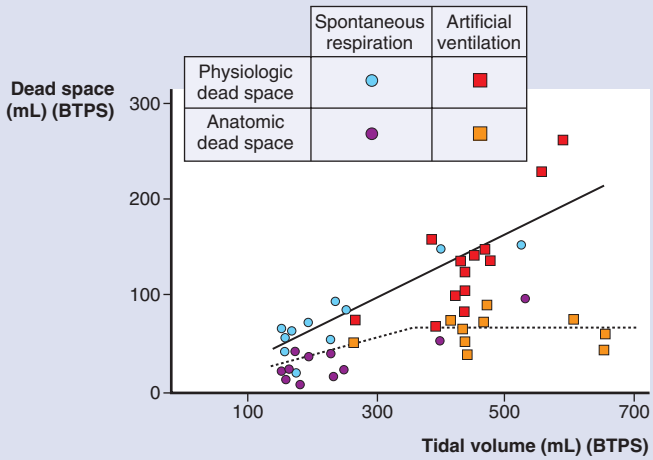


Figure 26-8 Anatomic and physiologic dead space during spontaneous and mechanical ventilation (during anesthesia). Physiologic dead space (anatomic dead space plus alveolar dead space) increases linearly with tidal volume, during both spontaneous and mechanical ventilation, maintaining a constant $\bar{V}_d/\bar{V}_t$. Anatomic dead space remains relatively constant over a range of normal adult tidal volumes but decreases at low tidal volumes (<350 mL). Thus, the increase in physiologic dead space during anesthesia is largely due to increased alveolar dead space. (Redrawn with permission from Nunn JF: Nunn's Applied Respiratory Physiology, ed 4. Stoneham, Mass, Butterworth-Heinemann, 1993.)

Loss of hypoxic pulmonary vasoconstriction results in low $\dot{V}/\dot{Q}$ regions ($\dot{V}/\dot{Q} < 1$), while atelectasis can cause frank shunting ($\dot{V}/\dot{Q} = 0$). Low and zero $\dot{V}/\dot{Q}$ regions widen the A – a gradient for oxygen, while dead space regions increase the dead space to tidal volume ratio, resulting in alveolar hypoventilation and hypercarbia. Application of PEEP can reduce low $\dot{V}/\dot{Q}$ and shunt, thereby reducing the A – a gradient for oxygen.[50,51] Supplemental oxygen increases alveolar P_{O_2} as well. PEEP, however, can increase dead space ventilation (see Figure 26-7, *right*) and must be used judiciously, in order to prevent hypercarbia. The latter can also be diminished by increasing the ventilatory rate.

The addition of pressure support ventilation to end-expiratory pressure further enhances gas exchange in anesthetized children, decreasing end-tidal P_{CO_2}, respiratory rate, work of breathing, and pressure-time product.[52]

Sedation can also cause $\dot{V}/\dot{Q}$ mismatch. Conscious or deep sedation has been associated with oxygen desaturation to less than 90% in 1.7% of children undergoing flexible fiberoptic bronchoscopy. This complication is associated with age less than 2 years, laryngotracheal abnormalities, and deep (compared with conscious) sedation.[53]

CONTROL OF VENTILATION

There are five main determinants that control breathing: carbon dioxide concentrations in the blood and brain, oxygen concentrations, acid-base status in brain, degree of stretch sensed in the lungs, and conscious control (such as anxiety). All anesthetic agents affect each of these, to varying degrees.

One afferent limb of this response is in the central chemoreceptors in the floor of the fourth ventricle. These cells respond to the acidity of the cerebrospinal fluid. The acidity is most affected by carbon dioxide, which diffuses freely from the arterial blood to the cerebrospinal fluid. Other causes of acidity such as ketoacidosis can stimulate this response as well. Another afferent limb is in the carotid and aortic bodies' peripheral chemoreceptors, which respond to the oxygen and, to a lesser extent, carbon dioxide concentrations in arterial blood. The carotid body is located at the division of the common carotid artery into the external and internal carotid arteries. The aortic body is found on the aortic arch and may exert its predominant effects on circulation rather than ventilation. The afferent limb from the carotid body is carried along the glossopharyngeal nerve, and the afferent limb from the aortic body is along the vagus nerve. Virtually all anesthetics affect these physiologic responses. Irritant receptors in the wall of the bronchi cause coughing, breath-holding, and sneezing. These receptors can be anesthetized by local and/or systemic administration of lidocaine. In the elastic tissues of the lung and the chest wall are receptors that respond to stretch. In the absence of adequate stretch such as diminished tidal volumes, these receptors stimulate hyperventilation. These stretch receptors are very difficult to anesthetize, so in the face of restrictive lung disease, hyperventilation is only minimally affected by anesthetic agents. There are also stretch receptors in the blood vessels of the lung, which, when distended, such as in heart failure, stimulate breathing. Narcotics administered by inhalation or systemically can diminish this cause of dyspnea.

Anxiety can lead to hyperventilation, which can disturb the acid-base status of the body as well as the normal control of breathing. The most effective way to pharmacologically treat this is with benzodiazepines.

The efferent limb from the respiratory center passes down the spinal cord to the diaphragm, intercostal muscles, and accessory muscles of inspiration in the neck. The diaphragm is supplied by the phrenic nerve (spinal nerves C3-5) The intercostal muscles are segmentally innervated by intercostal nerves (T1-12) The accessory muscles in the neck are supplied from the cervical plexus.

The effects of the anesthetics on respiratory control are summarized in Table 26-4. The effects of the anesthetics are often synergistic rather than additive, so that a small amount of a potent inhalational anesthetic as well as a narcotic will have a profound effect on carbon dioxide responsivity as well as apneic threshold. Decrease in the apneic threshold results in the initiation of breathing at a higher level of arterial carbon dioxide than is usual (around 40 mm Hg). The ventilatory responses to CO_2 (slope and apneic threshold) both decrease in a dose-dependent manner. It is a common misconception that some agents such as ketamine do not affect carbon dioxide responsivity, apneic threshold, or cardiovascular stability. Although this is true to some degree, ketamine can affect these factors in a dose-dependent manner. Because the doses required to affect these physiologic changes are higher than those with other agents, ketamine is viewed as a safer agent. This agent, as well as propofol and etomodate, must be treated with the same degree of respect as any of the anesthetic agents, for deeper levels of anesthesia can be achieved quickly with escalating doses of any anesthetic. Many anesthetics have an effect on muscle strength independent of the neural control of breathing. Benzodiazepines relax muscles and diminish respiratory muscle strength at the level of the spinal cord.

MUCOCILIARY CLEARANCE

Normal mucociliary clearance is important for local defense of the airways against infection and obstruction by secretions. Mucociliary clearance can be affected by either alteration of ciliary motion or alteration of airway secretions. Inhalation of dry gases (such as could occur during mechanical ventilation in the operating room) can diminish ciliary function but can be reversed with the addition of humidification to the inspired gas. Studies of respiratory secretions obtained from endotracheal tubes during elective surgery demonstrated no abnormalities in mechanical properties (e.g., viscoelasticity, rigidity), suggesting that mucociliary transport is altered via other mechanisms.[54] A cuffed endotracheal tube can cause direct trauma to airway mucosa and its ciliated epithelium, mechanically impairing ciliary clearance. In animal models, several inhaled anesthetics (including halothane and enflurane), as well as some intravenous agents (i.e., thiopental), have been shown to diminish ciliary activity.[55,56] This may be due to decreasing beat frequency or synchronous motion of the cilia. These effects may be prolonged, and should be considered especially important for patients with impaired cough clearance (e.g., neuromuscular weakness) or underlying diseases (cystic fibrosis, ciliary dyskinesia), which could further impair clearance of secretions.

COUGH

The incidence of significant symptomatic cough during general anesthesia is 4% to 6%.[57,58] Coughing can happen at any time during anesthesia and can significantly interfere with operative procedures. However, the most vulnerable periods are during intubation/induction and emergence. Irritation of laryngeal and tracheal receptors is more likely to cause cough than is irritation of bronchial receptors during anesthesia.[59] The depth of anesthesia also plays a role; light anesthesia exaggerates the cough reflex and prolongs it, while the deepest levels of anesthesia suppress the cough reflex (see Table 26-2). Various anesthetic agents have differing potentials for inducing cough; for example, isoflurane is more potent than halothane in precipitating the cough reflex.[60,61]

Various agents have been used to suppress anesthetic-induced cough. Intravenous lidocaine suppresses cough during intubation.[62,63] It was most effective when given at a dose of 2 mg/kg 1 to 5 minutes before intubation.[64] Lidocaine can also be given via endotracheal tube or instilled through the instrument channel of the bronchoscope to effectively suppress cough during anesthesia.[65] Albuterol and atrovent are not as effective.[45]

HEMATOLOGIC/OXYGEN DELIVERY EFFECTS

Some topical/local anesthetics (e.g., lidocaine, prilocaine,[66] benzocaine,[67,68] cetacaine) can oxidize the iron molecule in heme ($Fe^{2+} \rightarrow Fe^{3+}$), producing methemoglobin and reducing oxygen affinity. Congenital enzyme deficiencies (cytochrome b5 deficiency) or hemoglobin variants (e.g., hemoglobin M) can accentuate this potential toxicity. The presence of high concentrations of MetHb can produce erroneous readings with noninvasive pulse oximetry, with SpO_2 values trending toward 85% regardless of the PaO_2 and SaO_2. However, this is not simply an interesting artifact of measurement, as actual oxygen content [CaO_2 (mL/dL) = 1.34 mL of O_2/dL × Hb g/dL × SaO_2%] and delivery (delivery = content × ca rdiac output) will be reduced. Treatment of symptomatic methemoglobinemia involves use of methylene blue to reduce the heme in methemoglobin and avoidance of inciting agents.

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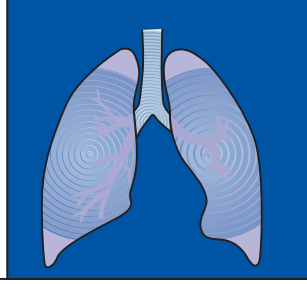

CHAPTER 27 Therapy-Induced Pulmonary Disease

Jonathan Steinfeld and Daniel V. Schidlow

TEACHING POINTS

- Therapy-induced pulmonary disease is often a diagnosis of exclusion.
- One therapy may cause several different pathologic patterns.
- Acute and chronic pathology may be present at the same time.
- The entire respiratory system is susceptible to injury.
- Prognosis is extremely variable.

More than 350 pharmacologic agents can cause pulmonary disease.[1] With few exceptions, most reports of therapy-induced pulmonary disease concern adult patients. The incidence of such disease in the pediatric population is very difficult to estimate. Usually the diagnosis is one of exclusion, as there are no specific laboratory tests to corroborate a causative effect for many of these agents. Adding to this uncertainty, the signs and symptoms of therapy-induced pulmonary disease are often similar to the pulmonary complications of an underlying disease. Furthermore, the onset of lung disease may occur long after the administration of the medication has been started or discontinued. Physicians must be aware of the agents that commonly lead to pulmonary disease and constantly be alert for symptoms that can be due to new therapies, which have not been previously described.

This chapter highlights some of the more common therapies that damage the lungs, but it is not comprehensive. Literature and Internet searches are recommended for more complete information. The Website www.pneumotax.com is an excellent resource that may be searched by either medication name or pattern of injury.

PATHOGENESIS

The two main routes for therapies to affect the respiratory system are through either inhalation or systemic circulation. A third, less common route, radiation therapy, directly damages cells.

The vast majority of deleterious inhaled agents are industrial and nontherapeutic. Patients may inhale smoke or other particulate matter that can damage epithelial cells directly or induce bronchospasm.

Medications given systemically, either orally or intravenously, reach the lungs through the bronchial blood supply. Although not harmful in their native states, medications are biotransformed—or activated—in the lungs. This biotransformation has two phases.[2] In phase I, the medication undergoes an oxidative reaction through enzyme systems such as cytochrome P450–dependent mono-oxygenases, flavin-containing mono-oxygenases, or prostaglandin synthase. This metabolite is then conjugated in phase II. Conjugation typically increases excretion by binding a lipid soluble particle to a water-soluble carrier. Damage can occur if the metabolite from phase I is not cleared by phase II or if the phase II metabolite is so toxic that any accumulation leads to cellular injury.

The bioactivated metabolites of certain medications damage cells through oxidative stress. Harmful medications create reactive electrophilic metabolites, which lead to cellular dysfunction or mutations when they bind to essential macromolecules. Other medications produce activated oxygen species, such as superoxide anion, hydrogen peroxide, and hydroxyl radicals. These oxygen free radicals overwhelm native antioxidant defense systems, creating oxidative stress.

PATHOLOGY

The entire respiratory system is susceptible to therapy-induced injury. The airways, alveoli, interstitium, vasculature, and the pleural spaces can all experience damage by medications. It is helpful to classify the different types of histologic damage; however, because the lungs' response to injury is limited, there is significant overlap from even one harmful agent. In fact, acute and chronic injury may be seen in the same biopsy. See Box 27-1 for histologic patterns that have been associated with therapy-induced pulmonary disease.[3] Other manifestations, such as bronchospasm and cough, do not have histologic findings.

CLINICAL MANIFESTATIONS

Despite the lungs' relatively limited pathologic responses, therapy-induced lung disease has many clinical manifestations. Dividing these manifestations anatomically helps to make some sense of this wide spectrum. Therapeutic damage can be classified anatomically: the airways, alveoli, interstitium, vasculature, and pleural spaces. These are not discrete categories, as very frequently there is overlap in damage to several anatomic regions from the same agent.

BOX 27-1 Histologic Patterns Associated with Therapy-Induced Pulmonary Disease

Pulmonary edema
Alveolar hemorrhage
Alveolar proteinosis-like reaction
Diffuse alveolar damage
Organizing pneumonia
Usual interstitial pneumonia–like pattern
Diffuse cellular interstitial infiltrates ± granulomas
Nonspecific interstitial pneumonia
Acute or chronic eosinophilic pneumonia
Small-vessel angiitis
Pulmonary arterial hypertension
Pulmonary veno-occlusive disease

From Flieder DB, Travis WD: Pathologic characteristics of drug-induced lung disease. Clin Chest Med 25:37-45, 2004.

BOX 27-2 Therapies Associated with Airways Disease

Bronchospasm
- Amphotericin B
- Aspirin
- β-Blockers
- Erythromycin
- Methotrexate
- Nitrofurantoin
- NSAIDs

Cough
- ACE inhibitors
- Fentanyl
- Methotrexate
- Nebulized hypertonic saline
- Nebulized medications
- Nitrofurantoin
- Propofol

Bronchiolitis obliterans organizing pneumonia (BOOP) or bronchiolitis obliterans (BO)
- Amiodarone
- Amphotericin B
- Bleomycin
- Carbamazepine
- Interferon α
- Minocycline
- Nitrofurantoin

AIRWAYS

Damage to the airways can lead to bronchospasm, cough, bronchiolitis obliterans organizing pneumonia (BOOP), or bronchiolitis obliterans (BO).[4] Box 27-2 lists therapies that commonly affect the airways.

Bronchospasm can present as cough, wheezing, or simply chest tightness. Children who are able to do pulmonary function testing may show a decreased FEV_1/FVC ratio or FEF_{25-75}. Bronchospasm can be caused by a large list of medications and exposures but is most commonly caused by aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs), or β-blockers.

While aspirin should be avoided in all pediatric patients, there are still many over-the-counter preparations that contain aspirin that parents may be unaware of. Aspirin-induced asthma has been recognized since 1922 and has been estimated to be present in up to 4% of children.[5,6] NSAIDs are a commonly used class of medications that lead to bronchospasm through the same mechanism as aspirin. Both aspirin and NSAIDs inhibit cyclooxygenase, which leads to decreased prostaglandin synthesis and subsequently increases activation of the leukotriene pathways. Leukotrienes are proinflammatory agents that increase mucus secretion, vascular permeability, airway edema, and eosinophil recruitment.[7]

β-Blockers are also rarely used in pediatrics but can lead to exacerbations in children with asthma. Although the exact mechanism is unknown, it follows that because β-agonists relieve bronchospasm in asthmatics, the delivery of a β-blocker will create bronchospasm. β-agonists do not relieve the bronchospasm because the receptors are already blocked; therefore, inhaled anticholinergics are the treatment of choice.

Cough can be caused by airway irritation, stimulation of cough receptors, or an unknown pathophysiology. Nebulized medications, such as hypertonic saline and antibiotics, irritate larger airways—which leads to coughing. This cough is typically self-limited and temporally related to the medication responsible. Reaction to fentanyl is a good example of cough secondary to a pulmonary chemoreflex, as 50% of patients will cough due to stimulation of the J receptors.[4] Angiotensin-converting enzyme inhibitors are notorious for having cough as a side effect, the exact mechanism of which is unknown.

BOOP can be caused by antimicrobials, chemotherapy, cardiac medications, and anti-inflammatories. Currently, more than 20 different medications have been linked to causing BOOP.[8] Drugs that are strongly associated with BOOP include minocycline, nitrofurantoin, bleomycin, amiodarone, carbamazepine, penicillamine, gold therapy, and illicit drug use. Unfortunately, it is often difficult to determine whether BOOP is secondary to the primary disease or the therapy used to treat that disease.

BOOP causes lower airway obstruction because of an intraluminal organized mass. The lumina of the small airways and alveolar spaces are filled with a polypoid endobronchial connective tissue mass.[4] Bronchiolitis obliterans differs from BOOP in that it spares the alveoli. The small bronchi and bronchioles are "obliterated" by fibrous tissue. Patients with either condition may present with such nonspecific symptoms as cough or shortness of breath. Pulmonary function testing shows an obstructive defect with air trapping. Luckily, many of the reported cases of therapy-induced BOOP have improved after cessation of the drug, although some have required glucocorticoids.[8]

Alveoli

Alveolar spaces can be the initial area of therapy-induced lung disease or, more commonly, the end result of interstitial damage. Alveolar damage includes exogenous lipoid pneumonia, radiation pneumonitis, eosinophilic pneumonia, pulmo-

BOX 27-3 Therapies Associated with Alveolar Disease

Amiodarone
Bleomycin
Eosinophilic pneumonia
Gold salts
Lipoid pneumonia
Methotrexate
Nitrofurantoin
Phenytoin
Radiation pneumonitis

BOX 27-4 Therapies Associated with Interstitial Pneumonitis

Amiodarone
Anti-metabolites
Bleomycin
Methotrexate
Nitrofurantoin

From Camus P, Fanten A, Bonniaud P, et al: Interstitial lung disease induced by drugs and radiation. Respiration 71:301-326, 2004.

nary edema, and acute respiratory distress (ARDS). Box 27-3 lists therapies that commonly lead to alveolar disease.

Exogenous lipoid pneumonia can be a consequence of a variety of therapies. From mineral oil for constipation to oily nasal drops for nasal congestion, culture-specific therapies may place children at high risk of aspiration.[9] The severity of the pneumonia is dependent on the amount as well as the type of oil aspirated. Animal oil produces an intense inflammatory response, while mineral oil has more of a foreign body–like reaction. Lipid-laden macrophages can be found on bronchoalveolar lavage with Oil-Red-0 or Sudan black stain.

Acute radiation pneumonitis occurs in 5% to 10% of patients who receive radiation therapy to the chest.[10] Lung cancer secondary to metastases is the disease most frequently associated with pneumonitis, but radiation for the treatment of breast cancer, Hodgkin's disease, and non-Hodgkin's lymphoma may damage normal lungs. Pneumocytes, endothelial cells, and the interstitium are the first site of injury. Next, surfactant leaks into the alveolar spaces and interstitial edema develops. In the later stages, the chronic inflammatory response develops into pulmonary fibrosis. Patients may present with dyspnea out of proportion to the area irradiated 4 to 6 weeks after therapy.

Eosinophilic pneumonia, also known as hypersensitivity pneumonitis, occurs when eosinophils migrate and preferentially accumulate in the lung tissue. Eosinophils fight microorganisms by releasing cytotoxic chemicals from their granules. If an eosinophil in the lungs degranulates in response to a drug, then these chemicals will also harm the surrounding lung tissue. Patients may have a cough, dyspnea, or no symptoms at all. Therapy-induced eosinophilic pneumonia may also present with systemic reactions, like a fever or rash. Chest radiographs demonstrate patchy segmental or subsegmental infiltrates that are often migratory. Peripheral blood eosinophils are usually elevated. The ideal test is either bronchoscopy or lung biopsy. However, because the symptoms typically resolve with the removal of the offending agent, invasive studies may not be necessary. In contrast to therapy-induced eosinophilic pneumonia, idiopathic chronic eosinophilic pneumonia typically does not have systemic symptoms and patients improve quickly with corticosteroids.[11]

Therapy-induced pulmonary edema and ARDS are typically caused by idiosyncratic reactions to medications. The pathophysiology behind these reactions is poorly understood, but capillary leak, hypervolemia, and anaphylaxis have all been suggested as possible mechanisms.[12] Pulmonary edema can be caused by a wide variety of therapies. Fewer therapies cause ARDS; these are commonly antineoplastics, immune suppressants, amiodarone, nitrofurantoin, and talc. Symptoms are vague and chest radiographs are nonspecific—except for the notable absence of the cardiomegaly that typically accompanies pulmonary edema.

Interstitium

Therapy-induced interstitial lung disease (ILD) presents in a wide variety of histologic patterns. Damage can manifest as cellular and fibrotic nonspecific interstitial pneumonia, pulmonary infiltrates and eosinophilia, organizing pneumonia, lymphocytic interstitial pneumonia, desquamative interstitial pneumonia, pulmonary granulomatosis–like reaction, and a usual interstitial pneumonia–like pattern.[3] The list of medications that can lead to ILD is extensive and medications frequently cause more than one pattern of histopathologic damage[13] (Box 27-4). The histology is so nonspecific that the mechanism of injury is often unknown.

Bleomycin is an antineoplastic agent used to treat lymphomas and testicular carcinomas whose mechanism of action is to reduce oxygen to free radicals, and it is notorious for its toxic pulmonary effects. Bleomycin has been extensively studied in animals—although rarely in humans.[14] While chemotherapy with bleomycin can induce BO with organizing pneumonia or eosinophilic hypersensitivity, the most common pulmonary manifestation is interstitial pneumonitis leading to pulmonary fibrosis. Depending on the criteria used for diagnosis, bleomycin-induced pneumonitis (BIP) may occur in anywhere from none to 46% of patients.[14] The lungs are particularly susceptible to drug accumulation because pulmonary epithelial cells have lower levels of bleomycin hydrolase.[15] Damage occurs due to a decrease in alveolar type I cells. Alveolar type II cells are vulnerable to bleomycin only during periods of proliferation or differentiation into type I cells. The subsequent loss of type I cells creates interstitial inflammation. Fibroblastic repair and collagen synthesis lead to the deposition of fibrin and collagen in the septal walls.[16]

Vasculature

Damage to the pulmonary vasculature leads to several different types of lung injury. The most common histopathologic pattern is pulmonary capillaritis—which has been reported after diphenylhydantoin, propylthiouracil, and all-*trans* retinoic acid. Neutrophils infiltrate the interstitial spaces leading

BOX 27-5 Therapies Associated with Vasculitis

Amiodarone
Heparin
Leukotriene antagonists
Nitrofurantoin
Penicillamine
Propylthiouracil
Streptokinase
Surfactant

to edema and neutrophilic fragmentation. The inflammatory response to the damaged neutrophils also destroys the capillary walls, allowing red blood cells and more neutrophils to freely enter the alveolar spaces.[17] While this histologic pattern is similar to the alveolar hemorrhage seen in systemic lupus erythematosus (SLE), it is rare in drug-induced lupus.[18]

Several chemotherapeutic agents have been reported to cause pulmonary veno-occlusive disease through either an immune response or a hypersensitivity reaction. The pulmonary vasculature is occluded by fibrin, creating pulmonary hypertension, signs of left atrial hypertension, and alveolar hemorrhage.[17] Alveolar hemorrhage is also present during the diffuse alveolar damage (DAD) that occurs after chemotherapy and crack cocaine use.

Alveolar hemorrhage may occur without any signs of vasculitis. Anticoagulation therapy leads to alveolar hemorrhage, which is characterized by red blood cells packing into alveolar spaces without any other inflammation or damage.[17] See Box 27-5 for therapies that commonly lead to vasculitis.

Pleural Spaces

Close to 30 different therapies have been reported to cause pleural disease (Box 27-6). Presentations include asymptomatic pleural effusions, pleural fluid eosinophilia, or acute pleuritis. Pleural effusions have been reported with the use of two European β-blockers (practolol and oxyprenolol), methotrexate, and sclerosing agents such as sodium morrhuate and absolute alcohol.[19] Pleural effusions secondary to amiodarone toxicity are rare and almost always associated with parenchymal infiltrates.[20] Pleural effusions with greater than 10% nucleated cells are defined as pleural fluid eosinophilia. Of the eight drugs associated with this eosinophilia, isotretinoin, dantrolene, nitrofurantoin, and valproic acid are frequently used in pediatric patients.

More than 80 medications have been implicated in drug-induced lupus (DIL). Pleural effusions and pleuritis are very common in DIL, with a prevalence ranging from 15% to 60%.[21] Pleural effusions are exudative and usually have normal pH and glucose levels. DIL pleuritis rapidly improves after the discontinuation of therapy and only rarely do prolonged symptoms require treatment with NSAIDs or corticosteroids.[19]

BOX 27-6 Therapies Associated with Pleural Disease

Amiodarone
Dantrolene
Isotretinoin
Methotrexate
Nitrofurantoin
Sclerosing agents
Therapy-induced lupus
  Chlorpromazine
  Hydralazine
  Isoniazide
  Penicillamine
  Quinidine
Valproic acid

DIAGNOSIS

With the ever-expanding list of medications that can damage the lungs, it is difficult to determine exactly which drug is the culprit. Some medications cause damage immediately, while others may not show clinical signs for years. Often, patients are on multiple medications, and it is not immediately clear which is the offending agent. In addition, there are many disorders, especially rheumatologic diseases, where both the disease and the therapy can lead to pulmonary pathology. To further cloud the issue, some over-the-counter medications can create clinical pictures that mimic primary diseases. The anorectics, for example, are well known to induce pulmonary hypertension. However, because few patients will admit to taking appetite suppressants, they may be misdiagnosed with primary pulmonary hypertension.[22] In an effort to help clinicians, Irey[23] created a list of questions to help guide the evaluation of suspected therapy-induced pulmonary disease (Box 27-7).

BOX 27-7 Evaluation of Suspected Therapy-Induced Pulmonary Disease

Correct identification of the drug in question
  Was the patient taking the drug?
  What dose?
  What duration?
Exclusion of other primary or secondary lung diseases
Temporal eligibility: appropriate latent period (exposure to toxicity)
Remission of symptoms with removal of challenge
Recurrence with rechallenge
Singularity of drug
  Are there multiple medications?
Characteristic pattern of reaction to specific drug
  Previous descriptions
  Quantification of drug levels that confirm abnormal levels
Degree of certainty of drug reaction
  Causative
  Probable
  Possible

From Irey NS: Teaching monograph: Tissue reactions to drugs. Am J Pathol 82:613-647, 1976.

Pulmonary function testing should be attempted in all children capable of proper technique. Lower airways obstruction is an indication of airways disease such as BO. A restrictive defect may be seen in interstitial disease and sometimes with pleural disease. Patients with pneumonitis and interstitial disease will have an increased diffusion capacity for carbon monoxide (DLCO). However, patients with alveolar hemorrhage will have a decreased DLCO due to the red blood cells' affinity for carbon monoxide.

A chest radiograph is a quick, helpful, noninvasive study that guides further diagnostic testing. Findings can include hyperinflation, pleural effusion, nonspecific "ground glass" opacification, an interstitial pattern, or a normal study. High-resolution computed tomography (HRCT) further identifies interstitial disease, pleural thickening, and pneumonia. Combining findings from HRCT with the patient's clinical presentation often provides sufficient information to avoid further diagnostic procedures.[24]

Flexible bronchoscopy and bronchoalveolar lavage (BAL) is more invasive than radiographic studies but is typically well tolerated. Findings such as increased numbers of eosinophils, lymphocytes, and dysplastic type II cells support a diagnosis of eosinophilic pneumonia, hypersensitivity pneumonitis, or chemotherapy lung.[21] Another major role of the BAL is to obtain cultures for viral, bacterial, and fungal pathogens to exclude an infectious etiology. Other helpful findings are cytologic atypia, lymphocytic alveolitis, or an increased eosinophil count. The BAL should also be examined for hemosiderin-laden or lipid-laden macrophages, which can be seen in pulmonary hemorrhage and mineral oil aspiration respectively. In some rare cases—such as in gold therapy—the medication itself is present in alveolar macrophages.[25] The presence of the drug indicates that the patient is taking the medication; however, it does not determine whether or not drug levels are toxic.[3]

Flexible bronchoscopy with a transbronchial biopsy is a minimally invasive procedure, but it is often not very helpful. Specimens are small and obtained blindly, so patchy areas of disease may be missed. If the diagnosis is still in question, then a large sample of lung tissue from an open lung biopsy is more useful. An open, or thoracoscopic, lung biopsy is considered the gold standard for diagnosis because the histologic pattern of the disease process can be clearly identified and tissue can be sent for culture. Physicians, and patients, often prefer not to perform an open lung biopsy due to the high amount of pain and discomfort for a purely diagnostic procedure.

TREATMENT AND PROGNOSIS

The wide variety of therapies that damage the lungs makes it impossible to recommend one therapy for all pathologies. The standard of care has been to remove the harmful agent and minimize the inflammatory reaction that it has created. In some cases, the decision is straightforward. For example, patients who experience pleural fluid eosinophilia secondary to nitrofurantoin can be switched to a different antibiotic. On the other hand, radiation therapy, and subsequent pneumonitis, may be unavoidable for certain types of cancer. When possible, steps should be taken to avoid pulmonary injury—such as minimizing the use of supplemental oxygen for patients receiving bleomycin. After the offending agent has been withdrawn, some pulmonary disease manifestations resolve rapidly while others require treatments such as corticosteroids or NSAIDs for complete resolution.

Prognosis is dependent on which pathologic manifestations have occurred and what therapy is responsible. Some patients may have no residual damage, and others may not live through the initial presentation.

SPECIAL CONSIDERATIONS IN PEDIATRICS

Different diseases, medications, and presentations must be taken into account for children with therapy-induced lung disease. For example, premature infants are often treated with exogenous surfactant, which can lead to pulmonary hemorrhage. In addition, children with encopresis and constipation are often treated with mineral oil despite the fact that they are at risk for aspiration, and subsequent lipoid pneumonia, due to poor swallowing coordination.[9,26]

Conversely, advanced age often places patients at higher risk for pulmonary pathology. Elderly patients are at much greater risk of methotrexate lung disease; patients from 50 to 59 years of age have twice the risk, while patients older than 60 years of age have six times the risk.[27] For bleomycin, patients older than 70 years of age are more susceptible to BIP.[14] One study even found a higher incidence of fatal BIP for each decade over 30 years of age.[28]

Nonspecific presenting symptoms are especially difficult in pediatrics. Very young patients cannot give an accurate history—or even a complete list of symptoms. Wheezing and decreased exercise tolerance can easily be mistaken for new onset asthma. Fortunately, most pediatric patients do not have the long list of medications that adult patients typically have, and if therapy-induced pulmonary disease is suspected the cause may be determined after investigation.

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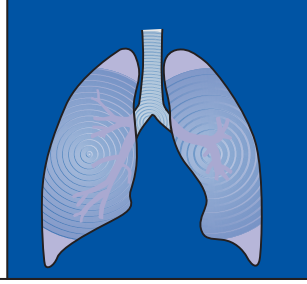


CHAPTER 28 Respiratory Disorders of the Newborn

J. Jane Pillow and Alan H. Jobe

TEACHING POINTS

- Respiratory illness is a major cause of neonatal morbidity and mortality.
- Most neonatal respiratory illness initially manifests with tachypnea, grunting, and cyanosis in the hours after birth.
- Neonatal respiratory distress syndrome, the most common respiratory disease in the newborn period, is due to structural and functional immaturity of the respiratory system and is characterized by surfactant deficiency.
- Exclusion of congenital pneumonia, congenital heart disease, congenital malformations, or significant air leak phenomena such as pneumothorax, are important considerations during initial management of neonatal respiratory distress syndrome.

RESPIRATORY DISTRESS SYNDROME

Respiratory distress syndrome (RDS) is the most common cause of respiratory failure in the preterm infant. Although many disorders can manifest with "respiratory distress" in the neonate, the term RDS is used to characterize the immature lung disease in a preterm infant resulting from insufficient surfactant. RDS is a major cause of morbidity and mortality in premature infants born before week 30 of gestation. The introduction of surfactant treatment has changed the clinical course of this disease and has decreased the morbidity and mortality rates.

Epidemiology, Risk Factors, and Pathogenesis

The incidence of RDS decreases as gestational age increases (Box 28-1). In preterm infants, less than 32 weeks' gestation, the incidence of RDS was reported as 71%.[1] The higher incidence and severity of RDS in male compared to female premature infants is explained by increased circulating androgens in males, which delay lung maturation with decreased surfactant production by type II pneumocytes.[2] Black preterm infants develop RDS less frequently than white infants of similar gestational age, and the condition is less severe.[3] The incidence of RDS is increased with maternal diabetes because high fetal insulin levels decrease lung surfactant and structural maturation.[4,5] Birth by cesarean section prior to onset of labor also increases the incidence of RDS.[6,7] Perinatal asphyxia is associated with increased RDS, probably because of the cardiovascular shock and associated persistent pulmonary hypertension.[8] In contrast, prolonged rupture of membranes[9] and other causes of chronic fetal stress, such as maternal drug abuse and chronic congenital infections, tend to decrease the incidence of RDS.[10] Antenatal administration of corticosteroids[11,12] to the mother also decreases the incidence of RDS. Recent studies suggest that maternal hypertension increases rather than decreases the incidence of hyaline membrane disease (HMD).[13]

The six stages of lung development were reviewed in Chapter 3. A preterm infant can be born during canalicular, saccular, or early alveolar stages of lung development. The gas exchange surface may range, therefore, from primitive airspaces with undifferentiated pneumocytes and no juxtaposition of airway epithelium and capillaries, to a lung that is similar to the relatively mature structural, mechanical, and biochemical functioning lung of the term neonate.

Surfactant

Surfactant appears in the fetal lung at 23 to 24 weeks' gestation, when osmophilic inclusions can be first detected in the type II pneumocytes. However, adequate amounts of surfactant are not secreted until about 35 weeks' gestation normally, when the incidence of RDS markedly decreases. Surfactant reduces surface tension in the alveolar spaces, facilitating lung expansion and preventing alveolar collapse during expiration in the human neonate. Spontaneous or mechanical ventilation of the surfactant-deficient lung causes epithelial injury and pulmonary edema which is prevented with exogenous surfactant treatment.[14,15] Surfactant is composed mainly of phospholipids but also contains proteins. Phosphatidylcholine is the most abundant phospholipid in surfactant, representing 80% of the total mass of lipid components. The major phosphatidylcholine species are essential for the surface tension–lowering properties. The other phospholipids in surfactant are phosphatidylglycerol, phosphatidylinositol, phosphatidylserine, phosphatidylethanolamine, and sphingomyelin. Phospholipids may also impart semipermeability to membrane aquaporins and consequently play a role in fluid clearance.[16] The surfactant proteins A, B, and C constitute 10% of pulmonary surfactant. They contribute to the proper function of surfactant by facilitating the formation of phospholipid films at the air-fluid interface of the alveolus by participating in the recycling of surfactant and functioning as host defense proteins.[17]

After synthesis in the type II pneumocyte, the lipid and protein components form into membrane-limited

BOX 28-1 Risk Factors for Respiratory Distress Syndrome

Increased incidence	Decreased incidence
Low gestation	Prolonged rupture of membranes
Male sex	Chronic congenital infections
White race	Maternal substance abuse
Maternal diabetes	Antenatal corticosteroid exposure
Cesarean section pre-onset of labor	
Perinatal asphyxia	
Maternal hypertension	

organelles—the lamellar bodies, which are intracellular storage pools of surfactant. Secretion of surfactant by exocytosis is promoted by mechanical stretch of the lung and physiologic and pharmacologic agents such as beta-adrenergics and purinergic agonists.[18] Within the alveolar space, lamellar bodies transform into the highly surface active form of tubular myelin (Fig. 28-1).[17,19] Surfactant proteins A and B are critical to the structure and function of tubular myelin.[18] In the newborn lung, surfactant components are efficiently recycled from the airspace to the type II cell for re-secretion.

In the very immature infant, in addition to surfactant deficiency, an excessively compliant chest wall and weakness of the respiratory muscles can contribute to alveolar collapse. This collapse alters the ventilation-perfusion relationship, producing a pulmonary shunt with progressive arterial hypoxemia that can lead to metabolic acidosis. Both hypoxemia and acidosis cause vasoconstriction of the pulmonary vessels and reduce pulmonary blood flow. Pulmonary vascular hypertension may produce right-to-left shunting through both the foramen ovale and the ductus arteriosus, worsening the hypoxemia.

The pulmonary blood flow, which is initially decreased, may subsequently increase because of a reduction in pulmonary vascular resistance and persistence of an open ductus arteriosus. Excessive pulmonary blood flow results in accumulation of fluid and proteins in the interstitial and alveolar spaces. The presence of proteins in the alveolar space promotes surfactant inactivation.[20]

The presence of both intrapulmonary and extrapulmonary shunting explains the characteristic hypoxemia in infants with RDS. Atelectasis (with impaired ventilation in some areas) and an increase in dead space caused by poor perfusion of other portions of the lung can elevate the partial pressure of arterial carbon dioxide ($PaCO_2$) in the more severe cases. The premature infant with RDS responds to the loss in lung volume and increase in $PaCO_2$ by increasing the respiratory rate. Hypoxemia, if severe, leads to progressive acidosis, which might contribute to further pulmonary vasoconstriction. If present, perinatal asphyxia and arterial hypotension worsen the metabolic acidosis (Fig. 28-2).

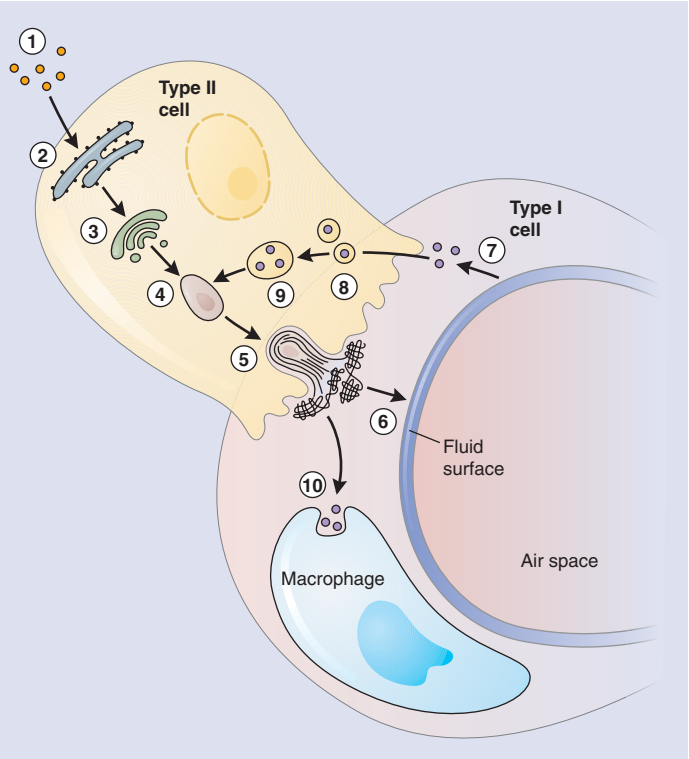


Figure 28-1 Surfactant system. Surfactant is synthesized in the type II pneumocyte from precursors (1) in the endoplasmic reticulum (2) via the Golgi apparatus (3), acquiring the form of lamellar bodies (4). Lamellar bodies are secreted into the alveoli by exocytosis, where they transform into tubular myelin (5) and form a fluid lining of the alveolar airspace (6). Surfactant is then recycled as small vesicles (7) into the type II cell for later re-secretion by using endosomes (8) and multivesicular bodies (9). Some surfactant is also taken up by alveolar macrophages (10). (From Hawgood S, Clements JA: Pulmonary surfactant and its apoproteins. J Clin Invest 86:1-6, 1990.)

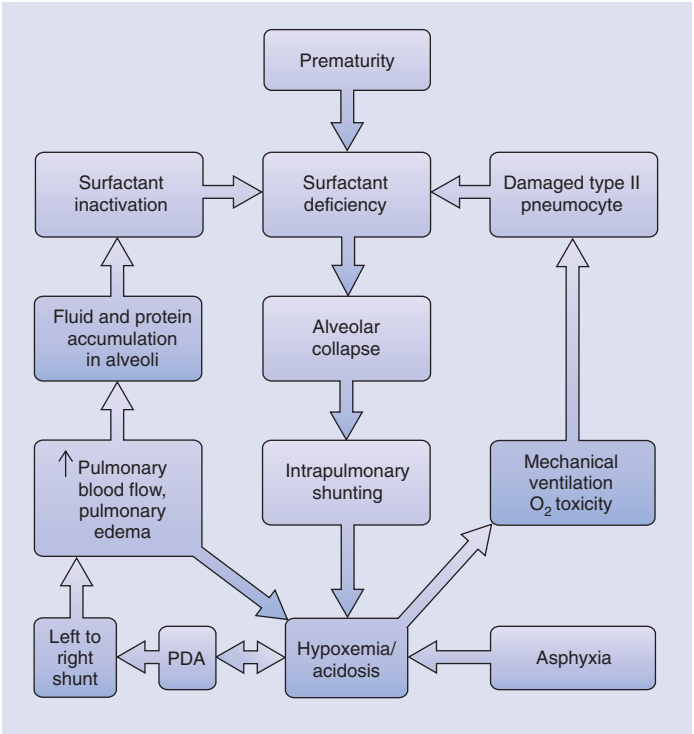


Figure 28-2 Pathophysiology of respiratory distress syndrome. PDA, patent ductus arteriosus.

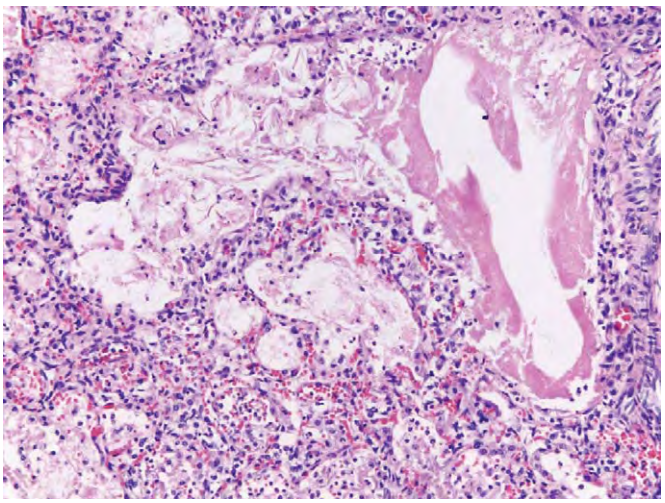


Figure 28-3 Microscopic findings at autopsy in an infant with respiratory distress syndrome (RDS), showing the presence of diffuse alveolar collapse with hyaline membranes lining the few remaining dilated airspaces. Early pneumonic change is also evident.

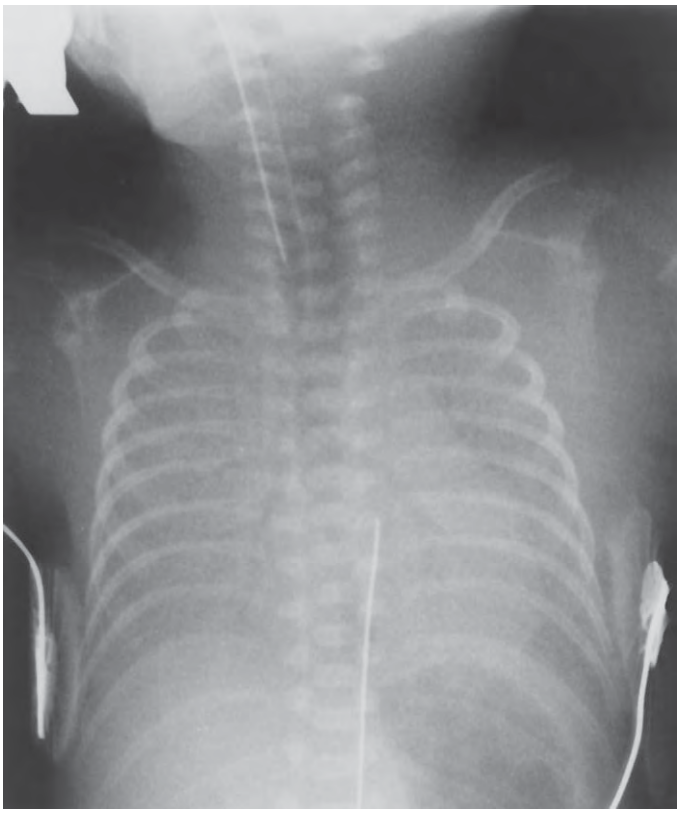
At autopsy, the lungs appear solid and congested with diffuse atelectasis. Microscopically, hyaline membranes line most of the remaining airspaces (Fig. 28-3). The hyaline membranes are a coagulum of plasma proteins leaked from damaged epithelium. Hyaline membrane disease and associated epithelial necrosis is less severe in autopsy specimens of infants that were treated with exogenous surfactant.[21]

Clinical Features and Diagnosis

The clinical signs of RDS usually appear in the first minutes or hours of life in the affected premature infant (Table 28-1). The signs are characterized by a progressive increase in the respiratory rate as well as subcostal and sternal retractions, grunting, cyanosis, and a bilateral decrease in breath sounds. The chest radiograph shows increased density of both lung fields with reticulogranular (ground glass) appearance, air bronchograms, and elevation of the diaphragm. A marked radiographic improvement can be observed after treatment with exogenous surfactant (Fig. 28-4). The oxygen (O_2) requirement varies depending on the severity of the disease course. Characteristically, arterial blood gas analysis reveals hypoxemia and hypercarbia and, occasionally, a mild metabolic acidosis.

Other causes of respiratory distress in the newborn should be considered in the differential diagnosis. These include pneumonia, congenital heart disease and other congenital anomalies, anemia, polycythemia, and hypothermia.

Without treatment with exogenous surfactant, the severity of the respiratory failure usually increases during the first 2 or 3 days of life. In the absence of complications, the respiratory status subsequently improves, and in infants older than 32 to 33 weeks' gestation, lung function usually normalizes by 1 week of life. In smaller infants, especially those <26 to 28 weeks' gestational age, the clinical course is generally prolonged and is frequently complicated by volutrauma and/or barotrauma from mechanical ventilation, patent ductus arteriosus (PDA), nosocomial infections, and intraventricular hemorrhage. The use of exogenous surfactant has dramati-



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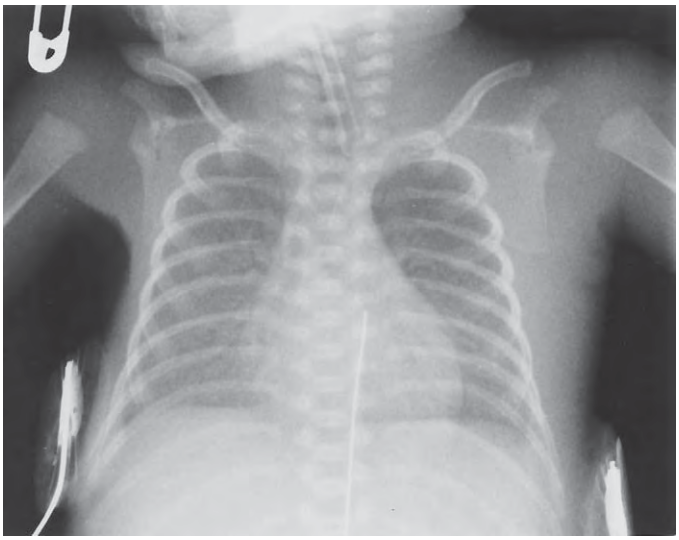

B

Figure 28-4 Chest radiographs of an infant with respiratory distress syndrome. A, Shortly after birth, a diffuse ground-glass appearance resulting from atelectasis with air bronchograms can be observed. **B,** Radiographic improvement with better aeration is evident after treatment with exogenous surfactant.

Table 28-1
Neonatal Respiratory Distress: Differential Diagnosis

	Predisposing Factors	Gestational Age	Distress Severity	Onset of Symptoms	Hypoxemia	Hypercapnia	Response to O_2	Response to IPPV	Breath Sounds	Signs of Infection	Chest Radiograph	Course*
RDS	Prematurity	Preterm	+++ to ++++	First hours	++ to ++++	+ to +++	++	Improved	Decreased Crackles	Negative	Hazy, granular air bronchogram	2-5 d
TTN	Cesarean section, maternal overhydration	Full term Near term	++	First hours	+	+	+++	Not indicated	Crackles	Negative	Hazy, vascular markings; Cardiomegaly	↑1-3 d
Pneumonia	Maternal infection	Preterm Full term	++ to ++++	First day or later	++ to ++++	+ to ++	++	Variable, possible improvement	Decreased Crackles	Positive	Patchy or granular Pleural effusion	3-7 d
MAS	Fetal distress	Full term Postterm	++ to +++	From birth	+ to ++++	+ to +++	++	Variable, possible improvement	Crackles, Bronchial sounds	Negative	Patchy hyperinflation	3-7 d
PPHN	Asphyxia: MAS Sepsis Hypoplastic lungs	Full term	++ to +++	First day	++++	+	+ to ++++	Improved with hyperventilation Worsens with excessive pressure	Variable	Negative or positive	Variable (depends on underlying condition)	1-5 d
Pulmonary gas leak	Positive-pressure ventilation	Preterm Full term	+ to ++++	Variable	+ to ++++	+ to ++++	++	Variable	Decreased Asymmetric	Negative	Lung collapse Mediastinal shift	Until drained
CHD ↑PBF	Unknown	Full term Preterm	+ to +++	Variable: 2-3 days	+	+ to ++	++	Variable, possible improvement	Normal or crackles	Negative	Hazy, vascular markings Cardiomegaly	↑Until corrected
↓PBF	Unknown	Full term Preterm	– +	First day	++ to ++++	– to +		None Worsening with excessive pressure	Normal	Negative	Dark, vascular markings	↓Until corrected

*Uncomplicated course.
CHD, congenital heart disease; IPPV, intermittent positive pressure ventilation; MAS, meconium aspiration syndrome; O_2, oxygen; PBF, pulmonary blood flow; PPHN, persistent pulmonary hypertension of the newborn; RDS, respiratory distress syndrome; TTN, transient tachypnea of the newborn.

cally changed the natural course of the disease by rapidly decreasing the oxygen requirements (supplemental oxygen is not required) and reducing the incidence of gas leaks (see section on surfactant replacement therapy).

Treatment

In addition to the administration of exogenous surfactant, the general management of infants with RDS includes careful stabilization, proper monitoring of cardiopulmonary function, adequate respiratory support, and thermal, metabolic, and nutritional support.

Prevention

Because RDS occurs primarily in the preterm infant, prevention of prematurity is the most effective way to avoid this disease, although this is seldom possible. The widespread use of antenatal glucocorticoids to accelerate fetal lung maturation has reduced the incidence and severity of RDS in recent years.[22,23] A reduction in functional residual capacity (FRC) and a marked decrease in lung compliance are characteristics of RDS.[24] Some alveoli are collapsed because of surfactant deficiency, whereas others are filled with fetal lung or edema fluid, thereby explaining the decrease in FRC. In response to this, the premature infant with RDS frequently develops a grunting respiration that prolongs expiration and protects against further loss in FRC. Lung compliance is markedly reduced to values that are well below 0.5 mL/cm H_2O/kg of body weight,[25] less than half the normal value. Giving continuous positive airway pressure (CPAP) or positive end expiratory pressure (PEEP) can minimize this loss in FRC.

ANTENATAL PREDICTION OF LUNG MATURATION

In 1973, Gluck and Kulovich[10] described the relation of lecithin and sphingomyelin in the amniotic fluid as indicators of fetal lung maturity. This test is possible because the fetal lung secretes fluid and surfactant into and changes the composition of the amniotic fluid. The incidence of RDS is only 0.5% when the lecithin-sphingomyelin ratio is 2 or more, but it is close to 100% when the ratio is lower than 1. Phosphatidylglycerol, which appears in the amniotic fluid at about 36 weeks' gestation, is a further indicator of lung maturity.[26] Newer tests of lung maturity that include lamellar body counts are now available for lung maturity testing.[27,28]

INDUCTION OF FETAL LUNG MATURATION

Many hormones positively or negatively influence lung maturation in experimental systems. Agents that can accelerate lung maturation are corticosteroids, thyroid hormones, epidermal growth factor, and cyclic adenosine monophosphate. These substances may act by stimulating the synthesis of surfactant.[29] Only corticosteroids have been shown to decrease the incidence and severity of RDS consistently in randomized controlled trials.[11,12,30,31] At least two distinct mechanisms promoting lung maturation have been identified: (1) a relatively rapid change (within 15 hours) in lung structure that is associated with improved compliance, increased lung volume, and decreased capillary protein leak; and (2) a slower, increased synthesis and secretion of surfactant by type II cells.[32] The delay between corticosteroid administration and upregulation of surfactant production and secretion limits the effectiveness of corticosteroids administered less than 24 hours before delivery. Although initial trials suggested that the combined antenatal use of corticosteroids with thyrotropin-releasing hormone (TRH) could further reduce the incidence or severity of RDS,[33] subsequent publications did not confirm the beneficial effect of antenatal TRH.[34-36]

RESUSCITATION IN THE DELIVERY ROOM

A skilled neonatal resuscitation team present at the delivery can help to facilitate neonatal adaptation and avoid injury of preterm infants at risk of RDS. Hypothermia should be avoided by keeping the infants in a neutral thermal environment in which O_2 consumption is reduced to a minimum. All infants with RDS should be admitted to a neonatal intensive care setting, where continuous monitoring of heart rate, respiratory rate, blood pressure, arterial blood gases, and metabolic parameters is possible.

OXYGENATION AND VENTILATION

Traditional teaching suggested maintaining a partial pressure of arterial oxygen (Pa_{O_2}) between 50 and 80 mm Hg; differences in the oxygenation-dissociation curve of fetal hemoglobin suggest that Pa_{O_2} at the lower end of this range are more appropriate to avoid oxygen toxicity. A Pa_{O_2} of 41 mm Hg (5.5 kPa) is enough to saturate 90% of fetal hemoglobin at a physiologic pH.[37] Prolonged hyperoxia should be avoided because it is a risk factor for the development of retinopathy of prematurity[38] and bronchopulmonary dysplasia (BPD).[39] Current practice uses oxygen saturation pulse oximetry to continuously monitor oxygen saturations to target saturation levels of 88% to 94% to minimize hyperoxia and to limit the number of blood gas samples needed for patient management. Transcutaneous CO_2 monitors also provide continuous information that is noninvasive and can help detect complications such as pneumothorax or to guide management during intubations or surfactant therapy.

MECHANICAL VENTILATORY SUPPORT

Larger infants with RDS (especially those >1500 g) and with mild to moderate hypoxemia and minimal hypercarbia may need only supplemental oxygen. Infants with RDS with respiratory failure have persistent hypoxemia (Pa_{O_2} < 50 mm Hg), are not responsive to the administration of supplemental oxygen, and usually have respiratory acidosis. In these infants, especially those with no or minimal hypercarbia, the use of CPAP is an effective form of treatment.[40] CPAP increases the FRC and stabilizes the airspaces, preventing their collapse during expiration. CPAP effectively reduces oxygen requirements and the need for mechanical ventilation in larger infants (≥1200 g).[41,42] Although the idea of using CPAP soon after birth, including in the delivery suite, in premature infants at risk for RDS has been effective in clinical series,[43-45] there are currently insufficient data from controlled randomized trials[46,47] to support a clinical benefit for this treatment over routine intubation and treatment with surfactant.[48]

In infants for whom CPAP does not work, particularly very small premature infants or those with hypoventilation and hypercarbia, positive-pressure ventilation is required after endotracheal intubation. A myriad of ventilatory strategies have been used over the last decade reflecting the increas-

ing technical refinement of commercial ventilation and monitoring equipment suitable for use in the very small infant. Whereas pressure-limited, time-cycled ventilators were the previous mainstay of mechanical ventilation for preterm newborn infants, there is increasing evidence that volume-targeted ventilatory modalities provide significant clinical benefit, although this has not yet been demonstrated for the outcomes of BPD or death.[49] Infants extubated to CPAP immediately after exogenous surfactant administration are more likely to remain extubated at the end of the first week of life compared to infants who are initially maintained on mechanical ventilation.[50]

The respiratory failure and hypoxemia in infants with RDS are due mainly to an intrapulmonary shunt caused by perfusion of poorly ventilated airspaces (see Fig. 28-2). Increments in the mean airway pressure are required to achieve alveolar recruitment and to obtain adequate oxygenation. Mean airway pressure is a function of the inspiratory and expiratory time, peak inspiratory pressure, PEEP, and bias flow. The use of short inspiratory times (0.25 to 0.50 second) and high respiratory rates appear to reduce both the incidence of pulmonary gas leak and the mortality rate,[51-55] and are sufficient to achieve adequate gas exchange. The use of PEEP is an effective way of maintaining the FRC, and pressures of 4 to 6 cm H_2O are usually required during the acute phase of RDS. When hypercarbia is present, an increase in the peak inspiratory pressure or a decrease in the PEEP improves the tidal volume and minute ventilation. In addition, the respiratory rate can be increased, but excessive rates must be avoided to prevent gas trapping, especially in infants with increased airway resistance.

Weaning from intermittent positive-pressure ventilation can be a long and difficult process, particularly in infants with very low birth weights. Methylxanthines such as theophylline and caffeine act as respiratory stimulants and can facilitate weaning.[56] The use of nasal CPAP immediately after extubation, particularly in the very small preterm infant, improves the success rate of weaning.[57]

High-frequency ventilation is another therapeutic alternative that has been evaluated in neonates with severe RDS. Despite the theoretical benefit of reduced volutrauma, systematic review of controlled randomized trials using a high-volume strategy have demonstrated only a small reduction in the outcome of BPD or the combined outcome of BPD or death at 36 weeks' PMA. There is no evidence of significant adverse effects of high-frequency ventilation in the preterm infant. Only a few studies have reported long-term outcome to date.[58]

Asynchrony between the ventilator and patient ventilation is a major clinical problem associated with the use of intermittent mandatory ventilation causing impaired gas exchange, increased energy consumption, reduced venous return, and wide fluctuations in blood pressure potentially promoting intraventricular hemorrhages.[59] Assist control ventilation (also known as synchronized intermittent positive pressure ventilation) results in faster weaning than is achieved with synchronized intermittent mandatory ventilation. No advantage of synchronized ventilation over conventional ventilation on the incidence of BPD or death has been shown for the very small premature infant.[60] The promotion of spontaneous breathing in the ventilated preterm infant may be critical to avoidance of ventilator-induced diaphragmatic dysfunction.[61]

SURFACTANT REPLACEMENT THERAPY

Systematic reviews of multiple clinical trials show that the intratracheal administration of exogenous surfactant decreased mortality by up to 40%, and the risk of pneumothorax by between 30% and 65%.[62-64] Surfactant treatments have had no consistent effects on outcomes of chronic lung disease (CLD), patent ductus arteriosus, or intraventricular hemorrhage. The presence of surfactant proteins in the surfactant preparations may aid surfactant adsorption and resist surfactant inactivation. New surfactant preparations are being developed that contain phospholipids with recombinant or analog peptides of the hydrophobic surfactant proteins SP-B and SP-C. Initial clinical studies suggest these new surfactants are similar in terms of efficacy and safety to animal-derived surfactants.[65] The new synthetic surfactants avoid the batch-to-batch variability of natural surfactant protein levels and the hypothetical risk of transmission of unconventional infectious agents from animal-derived products.

For infants judged to be at high risk of developing RDS (less than 28 weeks' gestation or <1 kg),[43,44] very early (delivery room) treatment rather than treatment after the development of RDS can reduce the development of pneumothorax and pulmonary interstitial emphysema as well as decrease mortality.[66] Although the administration of surfactant before the signs of RDS are established might promote more homogeneous distribution throughout the lung, treatment of established RDS avoids unnecessary surfactant treatment and the associated costs for many infants who would never develop RDS. The benefits of very early treatment will be less apparent if infants are treated as soon as RDS is diagnosed, generally at <1 to 2 hours of age.

After its administration, exogenous surfactant rapidly improves arterial oxygenation and the alveolar-arterial oxygen difference, reducing the requirements of ventilatory support (Fig. 28-5). Interpretation of studies investigating changes in the lung mechanics occurring in response to surfactant administration are complicated by differences in management techniques, patient characteristics, surfactant preparations used, and ventilation strategies. A combination of mechanisms appears responsible for improving gas exchange following administration of surfactant, including recruitment of alveolar space, distention of already aerated alveoli, and stabilization of gas exchange units. The increase in lung volume results in improved compliance.[67]

ACID-BASE BALANCE

Metabolic acidosis should be prevented because it increases pulmonary vascular resistance and may impair cardiovascular function. Severe metabolic acidosis in the course of RDS is most commonly a manifestation of perinatal asphyxia, sepsis, intraventricular hemorrhage, or circulatory failure. It is, therefore, essential to promptly investigate and correct the cause.

BLOOD PRESSURE AND FLUID MANAGEMENT

Pulmonary edema can contribute to the pathophysiology of RDS. Infants with RDS tend to have a low urine output during the first 48 hours, followed by a diuretic phase with

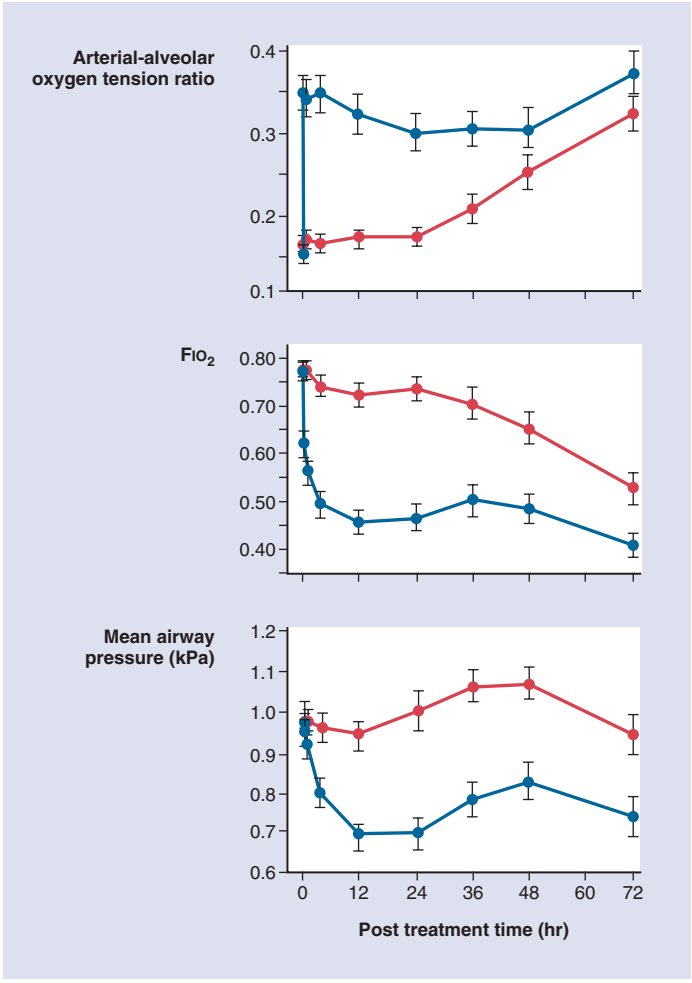

Figure 28-5 Mean values for the arterial-alveolar oxygen tension ratio, fraction of inspired oxygen (FIO_2), and mean airway pressure before and after treatment with exogenous surfactant (*blue circles*) or air placebo (*red circles*) in infants with RDS. (From Horbar JD, Soll RF, Sutherland JM, et al: A multicenter randomized, placebo-controlled trial of surfactant therapy for respiratory distress syndrome. N Engl J Med 320:959-965, 1989.)

weight loss. Fluid overload should be avoided. Fluid intake is usually started at 60 to 80 mL/kg/day and then increased gradually over the next few days, although great individual variations exist. Higher fluid intake may be necessary, especially in the infant with a very low birth weight and high insensible water losses. Fluid intake must be adjusted according to changes in weight, urine output, and serum electrolyte levels. The use of phototherapy, low ambient humidity, and radiant warmers increases fluid requirements. Excessive administration of fluids during the first days may contribute to the development of PDA[68] and BPD.[69] Because spontaneous diuresis has been described before improvement in respiratory status, the use of diuretics during the course of RDS is seldom necessary. Systematic review of diuretic administration in RDS suggests no long-term benefit and the transient improvement in pulmonary function did not outweigh an increased risk for patent ductus arteriosus and for hemodynamic instability.[39]

Careful assessment of systemic blood flow is essential to avoid reduced perfusion of critical organs. It is important to recognize that arterial blood pressure is an unreliable indicator of low systemic blood flow: babies can have low blood flow without hypotension and infants with hypotension may have normal systemic flow.[70] Perinatal asphyxia, sepsis, and hypovolemia are the most common conditions that can produce hypotension and, if suspected, should be treated accordingly. It is important to avoid the excessive use of fluids in an attempt to correct hypotension. Pressor use, such as dopamine, may increase peripheral resistance and further compromise systemic flow despite an apparent increase in arterial blood pressure.[70]

NUTRITION

Adequate nutritional support is essential for these infants; it is achieved during the first days of life by the use of parenteral nutrition. Oral feedings are started as soon as the infant is clinically stable and can begin when the infant is receiving ventilatory support.

ANTIBIOTICS

Neonatal pneumonia, particularly that caused by group B streptococci, should always be considered in the differential diagnosis of RDS, particularly in larger infants with respiratory failure. Conditions that are associated with an increased incidence of infection in the premature infant include: prolonged rupture of membranes, maternal fever during labor, fetal tachycardia, leukocytosis or leukopenia, hypotension, and acidosis. Before findings from blood cultures become available, especially when some of these risk factors are present, the use of penicillin or ampicillin and an aminoglycoside is recommended.

Complications

PATENT DUCTUS ARTERIOSUS

With the survival of smaller infants and the use of exogenous surfactant, early PDA as a complication of RDS has become an increasing problem in the management of the very low birth weight infant during the first days of life. The incidence of PDA in the premature infant with RDS may be as high as 90%,[71] and in two thirds of infants less than 30 weeks of gestational age, the PDA does not close by 5 days of age.[72] Several factors contribute to the slower and less predictable closure of the ductus arteriosus in preterm infants including the following: persistent elevation of the pulmonary vascular resistance due to lung disease, impaired sensitivity of the ductus arteriosus tissue to oxygen, increased circulating prostaglandin E_2, and increased sensitivity of ductal tissue to prostaglandin E_2 and nitric oxide. Sepsis has also been associated with an increased risk of PDA.[73]

A PDA is associated with a left-to-right shunt and increased pulmonary blood flow and pulmonary artery pressure.[74,75] In some studies, increased pulmonary blood flow was associated with reduced lung compliance that improved after PDA ligation,[76,77] although this was an inconsistent finding and not easily reproduced in animal models. Increased pulmonary blood flow can lead to left ventricular failure, hemorrhagic pulmonary edema, and adversely alter oxygenation and lung fluid balance.[78] Leakage of plasma proteins into the alveolar space may inhibit surfactant function.[20] Shear and stretch stress injury resulting from exposure of the lung vasculature

to systemic blood pressure may injure the endothelium, cause profound changes in the pulmonary vascular bed structure and function at the cellular level, and alter regulation of vascular tone and growth.[79]

Physical examination of the infant with symptomatic PDA generally reveals crackles and an active precordium, bounding pulses with a wide pulse pressure, poor peripheral perfusion, and in most but not all cases, a systolic heart murmur best heard below the left clavicle. Radiographically, evidence of pulmonary edema is observed, often in association with cardiomegaly (Fig. 28-6). The presence of a PDA should be confirmed by Doppler echocardiography, and if a clinically significant duct is identified, proper treatment should be promptly initiated. This consists of fluid restriction, adequate respiratory support, and pharmacologic treatment using prostaglandin inhibitors. The systematic review of prophylactic indomethacin treatment for PDA showed an association with a lower incidence of PDA, less subsequent medical treatment of the PDA, and less subsequent PDA ligation, but there were no differences in the incidences of CLD or other morbidities (e.g., necrotizing erterocolitis, feeding intolerance, or retinopathy of prematurity).[80,81] Early targeted treatment of asymptomatic PDA also reduces the incidence of symptomatic PDA on day 3 and may avoid unnecessary treatment of some infants who might never have developed a PDA.[80] Ibuprofen is another prostaglandin inhibitor that has similar efficacy to indomethacin for PDA closure, but is potentially less nephrotoxic (lower serum creatinine values, higher urine output), and has less adverse decrease in organ blood flow and vasoconstrictive adverse effects.[82] If closure of the symptomatic PDA cannot be achieved with medical treatment, surgical ligation should be considered because there may be an increased mortality associated with failed medical closure of the symptomatic PDA. The need for surgical ligation should be weighed against the possible side effects of the surgical procedure, including transport of the infant to an appropriate care facility. The benefit of surgical ligation over nonclosure of the symptomatic persistent PDA has not been subjected to a rigorous, well-designed randomized controlled trial.

HEMORRHAGIC PULMONARY EDEMA

Most cases of pulmonary hemorrhage in the newborn are secondary to severe hemorrhagic pulmonary edema as a complication of RDS and PDA. The incidence of pulmonary hemorrhage in premature infants with RDS is approximately 1%, although at autopsy around 55% will have alveolar hemorrhage.[83] The hemorrhagic fluid in the airspaces most likely represents capillary rupture and interstitial fluid.[84] Histologically, pulmonary hemorrhage can manifest as either interstitial or alveolar hemorrhage[85] (Fig. 28-7).

The associated predisposing factors include perinatal asphyxia, hypothermia, hypoglycemia, congestive heart failure, coagulopathy, pneumonia, severe sepsis, and excessive fluid administration.[86] Pulmonary hemorrhage has also been related to the use of exogenous surfactant,[87] related to increased left-to-right shunt through the ductus arteriosus.[71]

Pulmonary hemorrhage complicating RDS is usually observed in the first 5 to 7 days of life. When it is massive, pulmonary hemorrhage may be catastrophic and rapidly fatal with a sudden deterioration of the respiratory status that is generally associated with bradycardia, metabolic acidosis, and shock. Hemorrhagic fluid is seen coming from the nose and the mouth or through the endotracheal tube. The chest radiograph commonly shows a diffuse opacification of both lung fields.

The immediate management of pulmonary hemorrhage consists mainly of providing adequate ventilatory support. Increasing PEEP reduces the left-to-right ductal flow[77] and may prevent alveolar and small airway closure and severe pulmonary edema. Fluid restriction is indicated when the hemorrhage is due to left ventricular failure. If the cause of pulmonary edema and hemorrhage is a PDA, the PDA should be treated promptly, as should any other underlying cause. Although pulmonary hemorrhage is potentially a complication of surfactant therapy, surfactant treatment posthemorrhage may improve outcome by counteracting the inhibition of natural surfactant by hemoglobin and red blood cell lipids.[88]

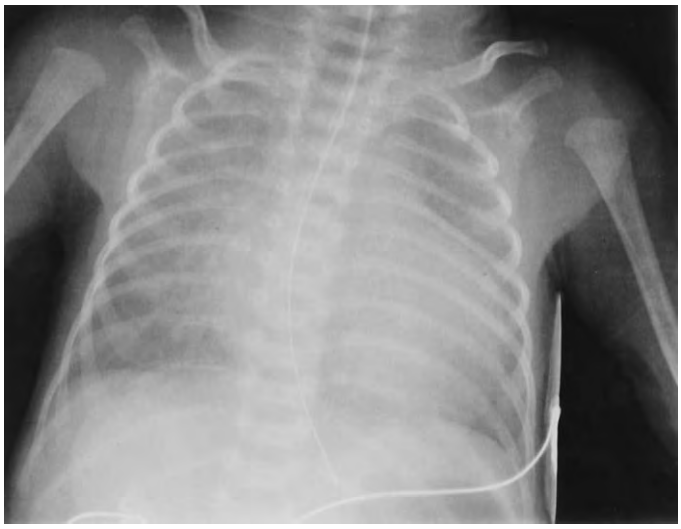

Figure 28-6 Chest radiograph showing cardiomegaly and pulmonary edema in an infant with patent ductus arteriosus (PDA).

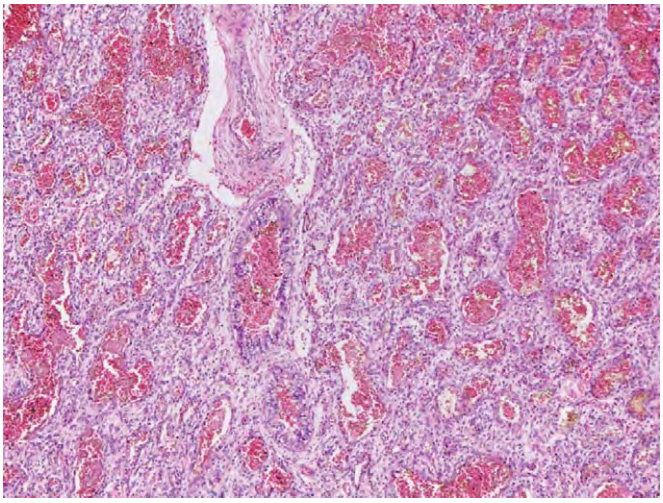

Figure 28-7 Microscopic findings in an infant with pulmonary hemorrhage complicating respiratory distress syndrome. Abundant red blood cells are seen in the pulmonary interstitium and inside the airspaces. Some hyaline membrane formation is also evident.

TRANSIENT TACHYPNEA OF THE NEWBORN

Also known as wet lung syndrome or RDS type II, transient tachypnea of the newborn (TTN) was first described by Avery and colleagues in 1966.[89] The original description was based on a group of predominantly full-term newborns who presented with tachypnea soon after birth and had similar radiographic findings with a benign clinical course. This transient respiratory symptomatology was attributed to a delayed resorption of alveolar fluid, which reduced lung compliance and caused a mild impairment in gas exchange.

Epidemiology, Risk Factors, and Pathogenesis

Transient tachypnea of the newborn affects 1% to 2% of all newborns,[90] primarily full-term infants. Several perinatal risk factors, including elective cesarean section,[91] excessive administration of fluids to the mother during labor,[92] male gender, and macrosomia, have been linked to the development of TTN.[90] Meta-analysis of clinical trials does not currently support a role for delayed clamping of the umbilical cord in TTN.[93]

The removal of fetal lung liquid from the lung at birth is an essential step for newborn adaptation to extrauterine life. The clearance of such liquid has been attributed at least in part to the mechanical compression of the chest at birth.[94] More importantly, there is an antenatal reduction in fetal lung liquid[95] that results from a shift of fluid from the lung lumen into the interstitium.[96] The initiation and process of labor is an important factor in this antenatal redistribution and absorption of lung liquid,[97] explaining, in part, the higher incidence of TTN observed after elective cesarean section.[98,99]

The secretion of fetal lung liquid is decreased or stops during labor. Fetal epinephrine levels increase and activate β-adrenoreceptors, which increase Na^+ transport and fluid resorption. The absorption of fetal lung fluid can be blocked by the administration of amiloride—an Na^+ channel antagonist.[100] Other hormones, including thyroxine and glucocorticoids, also upregulate Na^+ channel-mediated fluid absorption. Additionally, arginine vasopressin, somatostatin, dopamine, and serotonin rise during labor in a similar fashion to epinephrine and are candidates as regulatory hormones for lung fluid resorption. Male sex[101] and maternal history of asthma are associ-ated with the development of TTN.[102] Genetic predisposition to β-adrenergic hyporesponsiveness is proposed as a mechanism to the association between TTN and maternal asthma.[103]

With aeration of the lungs at birth, the fetal lung fluid absorbed across the pulmonary epithelium initially accumulates in the interstitial fluid of ventilated regions of the lung, particularly around the perivascular spaces. Lung fluid is slowly resorbed from the interstitium over a 2 to 6 hour period via vascular and lymphatic systems. The lymphatic system accounts for around 11% of fluid resorption of animals in labor,[96] and up to 50% of fluid resorption for animals not in labor. Any condition that increases hydrostatic pressure in the pulmonary vasculature can interfere with the appropriate resorption of fluid into the pulmonary circulation. Increased hydrostatic pressure can explain the higher incidence of TTN observed after excessive administration of fluids to the mother. Mild left ventricular dysfunction has also been described in infants with TTN.[104] An excessive amount of liquid in the lung may explain lower neonatal thoracic gas volumes after cesarean section compared to vaginal delivery. Infants born via cesarean section take up to 48 hours to establish their full lung volume.[105]

Clinical Features and Diagnosis

Transient tachypnea of the newborn usually manifests in the first few hours of life (see Table 28-1) with tachypnea. The respiratory rate commonly fluctuates between 80 and 120 breaths/minute. Retractions, nasal flaring, grunting, and cyanosis can also be present. Classically, TTN affects full-term infants, particularly those who are large for gestational age, although it can affect larger premature infants. Most such infants have a perinatal history with risk factors for the development of TTN, such as elective cesarean section or excessive administration of fluids to the mother. In addition to respiratory distress, these newborns may have a barrel chest and coarse breath sounds. The results of arterial blood gas analysis may be normal, although they frequently show a mild to moderate degree of hypoxemia. These patients usually require less than 40% oxygen to maintain adequate arterial oxygenation. Occasionally, hypoxemia is accompanied by mild hypercarbia, but both conditions tend to be transient and disappear within the first 24 to 48 hours.

The chest radiograph is characteristic. There are prominent, usually ill-defined central markings which suggest vascular engorgement, branching out from the hila.[89] The interlobar fissures may appear prominent, and small pleural effusions can be seen. The cardiac silhouette is usually enlarged (Fig. 28-8). All these findings are transient and disappear in 48 to 72 hours.

Probably the most challenging step in establishing the diagnosis is ruling out other pathologic conditions with similar clinical presentations. Because TTN occurs predominantly in full-term newborns, it is very important to rule out pneumo-

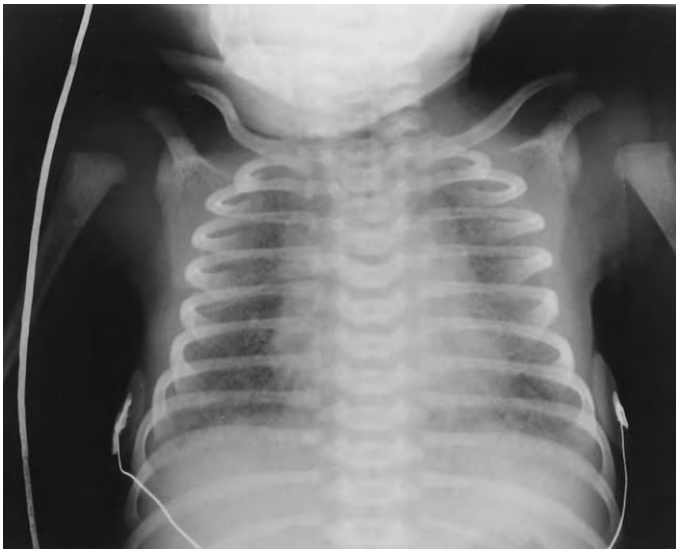

Figure 28-8 Radiographic findings in an infant with transient tachypnea of the newborn (TTN). Increased bilateral markings with prominent interlobar fissures and small pleural effusions can be observed. The heart appears slightly enlarged.

nia, especially that caused by group B streptococci. In infants with pneumonia, the perinatal history may be consistent with that of infection, such as maternal fever or prolonged rupture of membranes. Such infants also frequently have other clinical signs of infection, such as arterial hypotension, temperature instability, leukocytosis, and leukopenia. Other important differential diagnoses to be considered are meconium aspiration syndrome (MAS), RDS (particularly in the large premature infant), congenital heart disease and other congenital anomalies, and pulmonary gas leaks. The clinical course of infants with TTN is benign. The tachypnea and the radiographic abnormalities usually resolve in 24 to 72 hours.

Treatment, Clinical Course, and Prognosis

Because of the benign course of TTN, treatment consists mostly of proper stabilization, adequate monitoring, and careful evaluation to rule out other, more serious conditions. Oxygen should be provided as necessary to maintain normal oxygenation, and generally, mechanical ventilation is not required. Fluid restriction is indicated until the symptoms resolve; oral feedings can be started as soon as the infant is able to tolerate them. Diuretics do not affect the clinical course of the disease.[106,107] The use of antibiotics is indicated in cases in which the diagnosis of neonatal pneumonia is suspected and until the cultures and the clinical evaluation of the infant permit the clinician to rule out this diagnosis.

NEONATAL PNEUMONIA

Because of its grave prognosis, neonatal pneumonia should always be considered in the differential diagnosis in newborns with respiratory distress. The lung is one of the most frequent organs involved in early onset neonatal sepsis. Pneumonia in the newborn period can be acquired during intrauterine life, at the time of delivery, or after birth. Although the most common etiology is bacterial infection, it can be caused by different microorganisms, including viruses and fungi.

Epidemiology, Risk Factors, and Pathogenesis

Infection as a primary cause of death accounts for up to 50% of neonatal autopsies. More than 80% of infants that die from infection in the first 48 hours of life are associated with a pneumonia.[108] In infants who survive, the incidence is difficult to establish because of the frequent inability to make a definitive diagnosis. In a study comparing clinician- and pathologist-stated causes of death, the diagnosis most frequently omitted by clinicians was pneumonia (26.5% of cases).[109] The radiographic incidence of pneumonia was 4% among term infants born to mothers with documented amnionitis.[110] In a prospective study of 19,596 newborns, the incidence of early onset pneumonia was 1.79 per 1000 live births.[111] A higher incidence has been described in black infants[112] and in infants born to low-income families.[113] The agents and mechanisms of pulmonary infection differ depending on the type of neonatal pneumonia.

TRANSPLACENTALLY ACQUIRED PNEUMONIA

Transplacentally acquired pneumonia is a relatively rare event and includes those pneumonias caused by rubella virus, cytomegalovirus, *Treponema pallidum*, and occasionally *Listeria monocytogenes*. Many of these infants are stillborn or die in the first days of life. A hematogenous spread to the fetus from a mother with sepsis or bacteremia is the mechanism of infection in transplacentally acquired pneumonia. A classic example is pneumonia alba, a severe consolidated pneumonia caused by congenital syphilis.

PNEUMONIA ACQUIRED FROM COLONIZATION OF THE AMNIOTIC FLUID

Classically, the responsible microorganism infects the infant via an ascending route from the vaginal canal, usually producing chorioamnionitis, especially after a prolonged rupture of membranes during labor. The infection may also be acquired without evidence of chorioamnionitis during the passage through the birth canal.

In this type of infection, group B streptococci are responsible for the majority of cases of neonatal pneumonia and sepsis in the United States and Europe,[111,114,115] whereas *Escherichia coli* is the main responsible organism in developing countries.[109] The rate of maternal vaginal colonization with group B streptococci at the time of delivery is approximately 20%, and early onset group B streptococcal disease affects 1.8 per 1000 live newborns.[116] Mothers of affected infants usually have complications such as preterm delivery, prolonged labor, prolonged rupture of membranes, and intrapartum fever. In early onset disease, the infants have symptoms at or shortly after delivery, which suggests that most of these infections begin in utero.[116]

Other microorganisms included in this group are *Klebsiella* species, *Haemophilus influenzae*, *Enterobacter* species, *Listeria monocytogenes*, *Chlamydia trachomatis*, *Ureaplasma urealyticum*, *Candida* species, and herpes simplex virus. When neonatal pneumonia is associated with chorioamnionitis in the mother, aspiration of infected amniotic fluid is probably the main mechanism of infection. This is suggested by the presence of amniotic debris and maternal leukocytes in the histologic examination of the lungs.[117] However, chorioamnionitis per se is not always associated with pneumonia, and other factors, such as fetal asphyxia, seem to play an important role. If present, asphyxia can trigger gasping respiratory movements in the fetus that can cause the aspiration of contaminated amniotic fluid.

Any obstetric factors that predispose to chorioamnionitis can also favor the development of neonatal infection. In the case of group B streptococci, the rate of symptomatic early onset disease with pneumonia is considerably increased if there is premature onset of labor,[118] prolonged rupture of membranes, prolonged labor, or maternal postpartum bacteremia.[119]

When the infant acquires the infection during passage through the vaginal canal, the aspiration of infected materials is the route of infection. In these infants the histologic presentation is similar to that in older children and adults (i.e., bronchopneumonia with evidence of bronchitis and bronchiolitis, pleuritis, alveolar hemorrhage, and occasionally pulmonary necrosis with the presence of bacteria). In group B streptococcal pneumonia, hyaline membranes, similar to those observed in RDS, can be found in sections of the lungs.[120] The cytopathic effects of herpes simplex virus can be observed in the lungs of infants with pneumonia caused by herpes infection.

PNEUMONIA ACQUIRED AFTER BIRTH

In infants who remain hospitalized after birth, particularly if the lungs require mechanical ventilation, infection may be transmitted from contaminated personnel or equipment. *Staphylococcus aureus;* coagulase-negative staphylococci; *Pseudomonas*, *Proteus*, *Serratia*, *Enterobacter*, and *Candida* organisms; and respiratory syncytial virus are among the most frequent pathogens that cause nosocomial pneumonia in these high-risk infants. If the patient has been discharged home, viral pneumonias such as those produced by respiratory syncytial virus or adenovirus may occur during the first month of life. C. *trachomatis*, although acquired at birth, usually manifests later, producing afebrile pneumonia during the first 3 months of life.[121]

In nosocomial pneumonia, several mechanisms of infection can be implicated, including contact with contaminated personnel, inhalation of infected aerosols in the nursery, use of contaminated respiratory equipment, and hematogenous dissemination from bacteremia or a distant source. The histologic presentation varies depending on the etiologic agent. *S. aureus* and *Klebsiella pneumoniae* may produce extensive tissue damage with microabscesses, empyema, and pneumatoceles.[122] *E. coli*, a necrotizing agent, may also produce pneumatoceles.[123] In pneumonia caused by C*andida* species, yeasts and pseudohyphae can be observed on postmortem examination of lung tissue. Cytomegalovirus may also cause neonatal pneumonia. Cytomegalic inclusion bodies are evident on microscopy of lung tissue (Fig. 28-9).

Clinical Presentation and Diagnosis

Transplacentally acquired pneumonia is usually symptomatic shortly after birth (see Table 28-1). There may be a history of antenatal complications such as intrauterine growth restriction or fetal distress during labor. Respiration is likely to be depressed at birth, so these infants require resuscitation and, frequently, mechanical ventilation. Besides the classic signs of respiratory distress with retractions, grunting, tachypnea, and cyanosis, these infants commonly have other signs of congenital infection, such as low birth weight, hepatosplenomegaly, petechiae, and neurologic abnormalities. Total immunoglobulin M blood levels are usually elevated, and serologic tests for specific etiologic agents should be performed when congenital infection is suspected.

When pneumonia has been acquired from contaminated amniotic fluid or in the birth canal, the infant may not be affected in the first hours after birth, so a high index of suspicion should be maintained in every newborn with risk factors for neonatal infection. Neonatal pneumonia can manifest with overt or subtle clinical signs. Classic signs are those related to the respiratory system, such as respiratory distress, cyanosis, and crackles found during the physical examination. Perhaps more important are nonspecific signs, the most common being apnea, lethargy, hypotension, tachycardia or bradycardia, poor peripheral perfusion, and temperature instability. These clinical manifestations usually appear during the first 24 hours of life but sometimes are present at birth. In premature infants who have respiratory distress and a chest radiograph suggestive of RDS, pneumonia cannot be excluded. For this reason, appropriate cultures should be performed and antibiotic therapy started in any patient who is suspected of having RDS and who has perinatal risk factors and clinical or laboratory signs suggestive of infection.

The chest radiograph in infants with pneumonia may be quite variable but most commonly shows bilateral diffuse densities or may have a granular appearance, like that of RDS, especially in the case of group B streptococcal pneumonia (Fig. 28-10). Radiographic changes may be present at birth or rapidly progress in severity during the first hours of life, sometimes to a complete opacification of both lungs.

The white blood cell count can reveal leukopenia or leukocytosis, frequently with a leftward shift in the differential count. A positive urine latex agglutination assay for group B streptococci can point the clinician to the diagnosis, but there

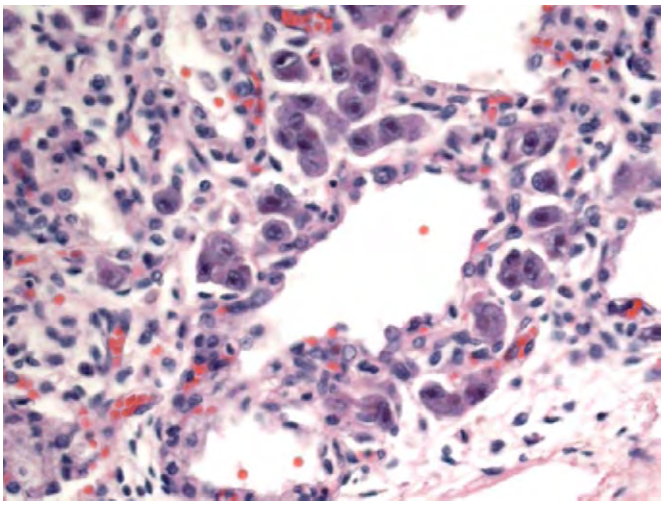

Figure 28-9 Neonatal pneumonia caused by *Cytomegalovirus* organisms. Cytomegalic inclusion bodies are evident.

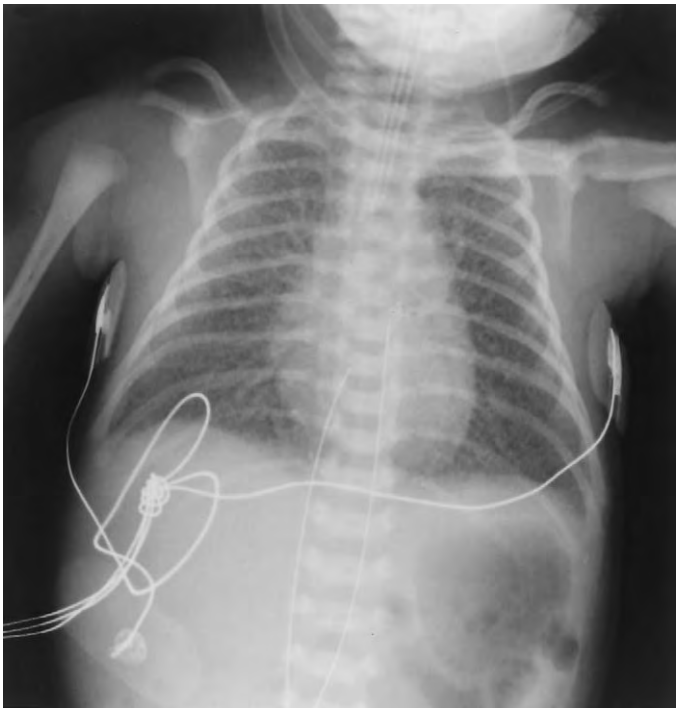

Figure 28-10 Chest radiograph of an infant with group B streptococcal pneumonia. Note the bilateral diffuse densities that are similar to those observed in infants with respiratory distress syndrome (RDS).

is a high incidence of false-positive and false-negative results. Blood should always be drawn for culture, and when the results are positive, they confirm the diagnosis, but negative results do not rule out the possibility of pneumonia. In one review of early onset neonatal pneumonia, the findings from blood cultures showed the presence of organisms in only 46% of 35 cases.[111]

The presence of white blood cells and bacteria in Gram stain of early tracheal aspirates suggests pneumonia, and the bacteria grown in these aspirates correlates well with those found in simultaneously performed blood cultures.[124,125] However, in the case of nosocomial pneumonia, findings from tracheal aspirates may not be helpful in making the diagnosis. In neonates whose lungs are chronically ventilated, positive findings from tracheal aspirates occurred with equal frequency among infants suspected of having pneumonia and in the control group.[126] If a pleural effusion is present, bacteriologic studies of pleural fluid can also be diagnostic.

Any infant developing a nosocomial infection should be suspected of having pneumonia. This is particularly true for low birth weight infants who deteriorate while requiring mechanical ventilation. Increased requirements of oxygen and ventilatory support, any signs of systemic infection, a change in the characteristics of the tracheal secretions, the colonization of tracheal secretions with an unusual microorganism, and a worsening of the chest radiograph are the most common signs of nosocomial pneumonia. A high index of suspicion should be maintained in these infants because some of the most frequent nosocomial infections, such as those caused by C*andida* organisms or coagulase-negative staphylococci, usually have a subacute presentation with vague symptoms.[127,128] If nosocomial pneumonia is suspected, a complete blood count and appropriate cultures from blood, trachea, urine and, if possible, cerebrospinal fluid should be obtained before treatment is initiated.

Treatment

The goal of treatment should be to achieve adequate antibiotic coverage while providing good supportive care. Proper stabilization of the infant, adequate oxygenation and ventilation, hemodynamic status, temperature control, and fluid management are essential for the recovery of the patient. Careful respiratory management best prevents complications such as pulmonary hypertension, gas leaks, and CLD.

The choice of antibiotics frequently has to be made before cultures are available and is based mainly on the age of the infant and the presence of risk factors for a certain etiologic agent. During the first 5 to 7 days of life, the use of ampicillin and an aminoglycoside provides adequate coverage for group B streptococci, *L. monocytogenes*, and the most frequent, gram-negative bacteria. If late onset pneumonia is suspected and the etiology is unknown, coverage for *Staphylococcus* organisms is necessary, as is the use of aminoglycosides or broad-spectrum cephalosporins for gram-negative bacteria. If C*andida* pneumonia is strongly suspected, the use of amphotericin is indicated. Herpes simplex pneumonia should be considered, especially in the infant who becomes ill 5 to 7 days after birth and has risk factors or other manifestations of herpetic infection. Acyclovir is the treatment of choice for this infection. After the initial treatment, the antibiotics can be changed according to the results of the cultures or the clinical course of the disease. Antibiotics are usually continued for 10 to 14 days. The use of granulocyte transfusions or intravenous immunoglobulin for the treatment of neonatal infections is still controversial.

Complications

Pulmonary hypertension can complicate the course of neonatal pneumonia.[129] In group B streptococcal infection, exposure of type III antigen to blood components within the vascular space can promote the adherence of neutrophils to the endothelial cells.[130] These neutrophils can liberate inflammatory mediators, vasoactive substances such as thromboxane, and leukotrienes, that constrict the pulmonary blood vessels.[131-133]

Septic shock is another frequent complication and is often the cause of death in these infants. Pulmonary interstitial emphysema (PIE) and other types of gas leaks can develop at any time of the clinical course, particularly when mechanical ventilation is required. Pulmonary hemorrhage secondary to vascular damage and pulmonary hypertension can also complicate the evolution of neonatal pneumonia.[84] Neonatal pneumonia caused by *U. urealyticum* has been related to the development of CLD in the premature infant.[134-136]

Clinical Course and Prognosis

The overall mortality rate for early onset neonatal pneumonia has been estimated to be around 29% but is much lower in late-onset pneumonia.[111] Infants who die of early onset pneumonia are more likely to be premature and have a rapid clinical deterioration and a radiographic picture resembling severe RDS.[111] In infants who survive, the severe lung injury related to the inflammatory process plus the damage produced by prolonged mechanical ventilation and oxygen toxicity places them at high risk for developing CLD.

MECONIUM ASPIRATION SYNDROME

Meconium aspiration syndrome (MAS) is a consequence of aspiration of meconium occurring before, during, or immediately after delivery and is one of the most common causes of respiratory failure in infants born at term or after term. The presence of meconium in the amniotic fluid is extremely uncommon in preterm deliveries.[137] The almost exclusive occurrence of asphyxia due to meconium aspiration in the term and post-term infant is probably a developmental phenomenon related to levels of motilin, a substance that stimulates peristalsis. Although the incidence of meconium-stained amniotic fluid has remained stable at approximately 12% of all deliveries, meconium is present below the vocal cords in less than one half of such infants, when the airway is visualized immediately after birth.[138-140] Over the last 2 decades, the incidence of MAS per se has decreased from 5% to 1.5% of infants born at greater than 37 weeks' gestation with meconium-stained liquor,[141] due to reduction in the incidence of post-term deliveries. The risk and the severity are considerably increased when the meconium is thick or particulate.[138,142,143] Some infants born through meconium-stained fluid develop respiratory illness even when no meconium is visualized below the vocal cords at birth, indicating aspiration occurred in utero.

Epidemiology, Risk Factors, and Pathogenesis

Although there is net movement of fluid out of the lung during normal fetal breathing activity, meconium can be aspirated into the distal airways before birth because it is occasionally found in the lungs of stillborn infants.[144,145] The passage of meconium into the amniotic fluid is frequently associated with some degree of fetal distress, but it may also occur in normal or breech deliveries without evidence of asphyxia.[140,143,146,147] In cases of asphyxia, it results from increased intestinal motility produced by the hypoxic stress. The hypoxia and acidosis induce deep fetal respiratory efforts that increase the likelihood of aspiration of meconium-contaminated fluid into the lower airways. Meconium may also be aspirated in the perinatal period (Fig. 28-11).

A number of different damaging effects of meconium on the airways and lung tissue contribute to respiratory disease caused by meconium aspiration.[148] When thick particulate meconium is aspirated into the small airways, the airways become partially obstructed, resulting in gas trapping and overinflation distal to the obstruction. Alveolar gas distal to the completely obstructed small airways is reabsorbed, and the alveoli collapse, increasing the intrapulmonary shunting and arterial hypoxemia. High oxygen concentrations increase the likelihood of collapse distal to obstructed airways. Chemical pneumonitis arising from the interaction of the meconium with the respiratory tissue develops between 24 to 48 hours after meconium inhalation and is accompanied by a marked inflammatory reaction and development of capillary leakage, reducing the diffusing capacity and contributing to hypoxemia.[149] The presence of meconium in the lung results in an increase in pulmonary artery pressure[150] which can be further exacerbated by the presence of hypoxia and acidemia. The inflammatory response to intrapulmonary meconium may exaggerate any vasoconstriction, while chronic hypoxia may result in remodeling of the pulmonary vasculature. The presence of the organic matter in the lung predisposes the infant to pulmonary infection despite the initial sterile nature of the inhaled material. Meconium inhibits surfactant function, further promoting the development of atelectasis.

Clinical Presentation and Diagnosis

Infants who aspirate meconium are born mostly at or after term (see Table 28-1) and frequently have a history of fetal distress, low Apgar scores, and meconium-stained amniotic fluid.[137,142] Their skin, nails, and umbilical cords are also meconium stained. They have signs of respiratory distress shortly after birth, with tachypnea, intercostal retractions, and cyanosis, if not given supplemental oxygen. The chest appears overdistended and is frequently barrel shaped with a protruding sternum. The breath sounds are usually obscured by coarse bronchial sounds, and prolonged expiration indicates small airway obstruction. The chest radiograph shows patchy areas of increased density in both lungs, alternating with hyperlucent areas (Fig. 28-12). The diaphragm is occasionally depressed.[151,152]

Arterial blood gas analysis during the first hour of life may show metabolic acidosis reflecting perinatal asphyxia. The arterial oxygen tension is always lower than normal unless the infant is given supplemental oxygen. The severity of the hypoxemia depends on the degree of the pulmonary damage, and the hypoxemia is aggravated by pulmonary hypertension, which may result in right-to-left shunting through the foramen ovale and ductus arteriosus. The $PaCO_2$ is commonly elevated and in the more severe situations may require the use of mechanical ventilation to correct the alveolar hypoventilation and respiratory acidosis.[153]

Infants with severe MAS have frequent, potentially life-threatening complications including air leak syndromes, persistent pulmonary hypertension of the newborn (PPHN), and

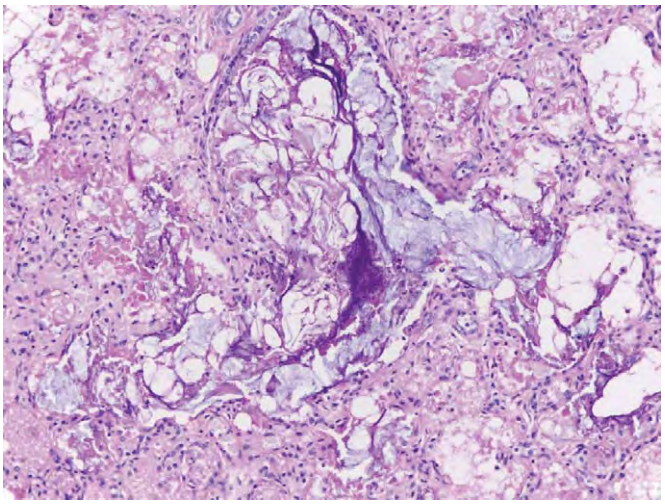

Figure 28-11 Microscopic picture of lung tissue from an infant who died from meconium aspiration syndrome (MAS): An alcian blue/PAS diastase stain has been used. The lungs show patchy aeration. The pulmonary vasculature appears thick walled. Occasional groups of aspirated squamous cells are seen. Mucin stain (*blue*) shows mucus consistent with meconium. There are some areas of congestion and focal areas of hemorrhage. PAS, periodic acid–Schiff.

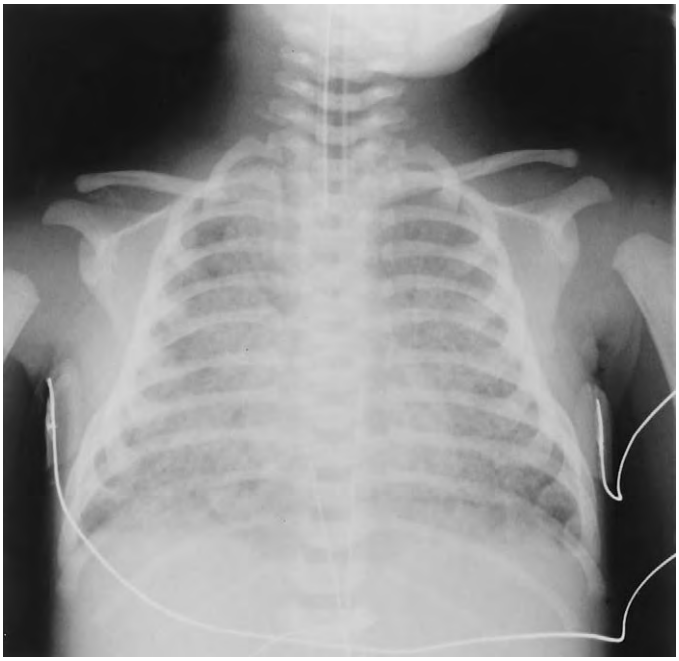

Figure 28-12 Chest radiograph of an infant with meconium aspiration syndrome (MAS). Patchy areas of increased density are observed in both lungs.

secondary bacterial infection. Pneumomediastinum and/or pneumothorax occur in 10% to 15% of infants with MAS who require mechanical ventilation,[143] secondary to small airway obstruction that leads to gas trapping and uneven distribution of inspired gas. The high transpulmonary pressure generated by the infant or required on the mechanical ventilator to achieve adequate ventilation increases the risk. Parenchymal inflammation and damage caused by the meconium may also increase the potential for alveolar rupture. No data on secondary bacterial infection complicating MAS are available in infants, but in experimental animals, meconium enhances bacterial growth in the lung.[142] Because of similarities in the clinical and radiographic manifestations of aspiration of meconium and bacterial pneumonia, it is not always easy to diagnose a superimposed bacterial infection during the acute phase of MAS, necessitating a high index of suspicion. Infants who become infected in utero have a higher incidence of perinatal asphyxia and meconium aspiration.[140]

Although the clinical course is difficult to predict, infants who have large amounts of thick meconium in the trachea and grossly abnormal chest radiographs generally have a more severe subsequent disease course.[152] The clinical course is also influenced by the occurrence of complications, such as PPHN, infection, and pneumothorax, which delay recovery. Although mild cases may require only oxygen supplementation for a few hours or days, infants with severe respiratory failure require mechanical ventilation for several days or even weeks and have a high mortality rate. In a series of infants with MAS, approximately 30% required mechanical ventilation; the overall mortality rate was 4.2%.[143]

Neonates with severe MAS have a marked reduction in dynamic lung compliance.[154] This can be secondary to the changes in lung elasticity caused by the inflammatory reaction produced by the meconium, to inactivation of alveolar surfactant, and to the significant increase in airway resistance or overinflation found in most of these infants.[155,156] Minute ventilation is usually increased because of increased respiratory rate, but increased dead space ventilation reduces alveolar ventilation, leading to carbon dioxide retention.[157,158]

Treatment

PREVENTION

The prevention of MAS must start before birth by taking all the necessary precautions to reduce the risk of fetal distress and avoidance of post-term delivery. Correction of possible cord compression secondary to oligohydramnios and dilution of meconium by the use of intrapartum saline amnioinfusion has been proposed as a means of preventing MAS. Although a meta-analysis of amnioinfusion for prevention of MAS in 2002 noted an overall reduction in MAS and cesarean section, the trials included had small sample sizes and poorly defined outcome measures.[159] More recently, a large multicenter trial with 1998 study subjects found that amnioinfusion did not reduce the risk of moderate or severe meconium aspiration syndrome, perinatal death, or other major maternal or neonatal disorders.[160] The benefits of amnioinfusion may be restricted to settings where routine intrapartum fetal heart-rate monitoring and neonatal resuscitation are not available.[161]

RESUSCITATION

The previous practice of aspiration of meconium from the upper airway at birth has been questioned, with recent studies suggesting that suction of any infant with meconium-stained amniotic fluid on the perineum does not prevent MAS and has no clinical benefit.[162] Meta-analysis of four randomized controlled trials did not demonstrate a benefit for routine endotracheal intubation and suctioning in vigorous term babies born via meconium-stained fluid.[163] Currently, intubation and suctioning of meconium from the airways is recommended only in the unresponsive infant; however, suctioning should cease and resuscitative measures should be commenced immediately if bradycardia becomes evident.

Subsequent Clinical Management

In infants with evidence of respiratory failure, an arterial blood gas analysis and a chest radiograph should be obtained as soon as possible. The inspired oxygen concentration must be adjusted to maintain the PaO_2 above 70 mm Hg or the oxygen saturation above 90%. Some degree of metabolic acidosis is frequently observed as a result of perinatal asphyxia. If persistent, this must be corrected to decrease the risk of pulmonary hypertension. In infants who remain hypoxemic despite the use of high inspired oxygen concentrations or in infants in whom the $PaCO_2$ rapidly rises above 50 to 60 mm Hg, it is necessary to use mechanical ventilation. Because of the reduced lung compliance and increased airway resistance, these infants often require high peak inspiratory pressures. Because most of these infants are active and restless, it is often necessary to use sedation, at least during the first 24 to 48 hours of mechanical ventilation, until the infant is stable and the peak airway pressure of the ventilator can be reduced.[164]

In infants with severe respiratory failure who do not respond to conventional mechanical ventilation, the use of high-frequency ventilation using jet ventilators or oscillators can improve gas exchange and arterial blood gas levels.[165] This is usually indicated when the patient develops pulmonary hypertension with extrapulmonary right-to-left shunting and severe hypoxemia. Inhaled nitric oxide has also been found to provide clinical benefit in the situation of refractory hypoxia. Meconium aspiration can inactivate alveolar surfactant and bolus exogenous surfactant reduces the severity of respiratory disease and decreases the number of infants requiring extracorporeal membrane oxygenation (ECMO).[150] More recently, studies have shown that therapeutic surfactant lung lavage results in better gas exchange and/or pulmonary mechanics than either no lavage[166-168] or bolus surfactant therapy,[167] and that lavage removes considerable amounts of meconium from the lung.[167-170] The practicality and safety of the widespread clinical application of this approach has not been demonstrated.

The risk of bacterial infection is increased in infants with MAS, but the clinical diagnosis of a superimposed infection is difficult. When bacterial pneumonia is suspected because of fever, an abnormal white blood cell count, or deterioration in respiratory function and the appearance on radiograph, blood and tracheal cultures should be obtained and antibiotic therapy should be initiated. There is no clear evidence to justify the use of prophylactic antibiotics in meconium aspira-

tion, but some clinicians elect to administer antibiotics until the acute respiratory failure subsides.

The severity of the respiratory failure should not cause the physician to overlook other complications that frequently occur because of perinatal asphyxia. Central nervous system, cardiovascular, renal, and metabolic function should be monitored closely, and any alteration must be promptly corrected.

Clinical Course and Prognosis

Although most infants with MAS survive without sequelae, long-term follow-up studies have revealed an increased prevalence of hyperreactive airway disease, similar to that found in premature infants with CLD.[171,172]

PERSISTENT PULMONARY HYPERTENSION OF THE NEWBORN

This disorder was originally described by Siassi and coworkers[173] in a group of infants without significant lung disease. Today, PPHN in newborn infants is most often secondary to other pulmonary pathologic conditions such as MAS, sepsis and pneumonia, hypoplastic lung, and alveolar capillary dysplasia. PPHN may also occur after antenatal maternal administration of prostaglandin inhibitors in association with congenital heart disease that blocks pulmonary venous outflow and may be iatrogenic secondary to overventilation.

Epidemiology, Risk Factors, and Pathogenesis

In the normal neonate, pulmonary vascular resistance decreases rapidly after birth in response to an increase in lung volume, oxygen tension, and concentration of vascular dilating prostaglandins.[174,175] This reduction in pulmonary vascular resistance produces a fall in the pulmonary artery and right ventricular pressures that results in the cessation of right-to-left shunting through the foramen ovale and the ductus arteriosus. This normal process can be altered in response to hypoxia, acidosis, infection, or pulmonary hypoplasia and a decreased vascular cross-sectional area. Under such conditions, the pulmonary artery pressure remains elevated to values that may surpass systemic blood pressure, maintaining the right-to-left shunting predominantly through the foramen ovale and, to a lesser extent, also the ductus arteriosus.[176] This causes severe arterial hypoxemia that is relatively unresponsive to increased concentrations of inspired oxygen. The elevated pressure in the right ventricle frequently produces tricuspid regurgitation that increases the likelihood of shunting at the atrial level. Tricuspid regurgitation may be aggravated by the papillary muscle necrosis in the tricuspid valve that occurs in some infants with severe perinatal asphyxia.[177]

The magnitude of the right-to-left shunt in infants with PPHN is determined by the pressure gradient between the two circulations. Therefore, systemic hypotension secondary to sepsis or asphyxia increases the severity of the shunting and the hypoxemia.[178]

Postmortem examination of the pulmonary circulation in a group of infants who died of PPHN demonstrated an increase in vascular smooth muscle and extension into the peripheral vascular bed; thus these infants had an antenatal insult that altered the pulmonary vasculature, which prevented normal adaptation after birth.[179,180] Impaired vascular epidermal growth factor (VEGF) signaling has been implicated in the vascular remodeling process.[181] Other factors that may predispose an infant to PPHN are antenatal exposure to prostaglandin inhibitory drugs[182,183] and polycythemia.[184] Increased concentrations in serum or tracheobronchial secretions of a number of prostanoids[185] and inflammatory mediators such as endothelin-1,[186] leukotrienes (LTC4 and LTD4),[187] thromboxane, and platelet-activating factor have been described in infants with PPHN. All these substances are potent vasoconstrictors and may play a role in the pathogenesis of PPHN.[185,188]

Clinical Presentation and Diagnosis

PPHN occurs only occasionally in preterm infants or in neonates with no lung disease. Most infants with PPHN are born at term and have evidence of perinatal asphyxia and meconium aspiration or neonatal infection (see Table 28-1). In some instances, the infant is hypoxemic from birth, but more often there is a period of adequate oxygenation that may last for minutes or a few hours. During the first few hours after birth, there is a progressive deterioration in arterial oxygen tension that may be accompanied by an increase in carbon dioxide tension. The progressive hypoxemia becomes unresponsive to further increases in inspired oxygen concentration and frequently is disproportionate to the degree of pulmonary involvement. In most cases, large fluctuations in the PaO_2 also occur spontaneously or in response to physical stimulation and activity of the infant. A difference between preductal and postductal oxygenation suggests the presence of a right-to-left ductal shunt. The echocardiographic demonstration of high pulmonary artery pressure, tricuspid regurgitation, and shunting through the foramen ovale and ductus arteriosus confirms the diagnosis of PPHN.[189]

Treatment

The management of PPHN is one of the most difficult challenges in neonatal intensive care. Prevention and correction of predisposing factors such as perinatal asphyxia, sepsis, and polycythemia should be the first steps, including dilutional exchange transfusion, if necessary. Avoidance of unnecessary handling is critical, as this may trigger sudden and severe hypoxia. Correction of hypoxemia and acidosis, both potent pulmonary vasoconstrictors, should also be pursued aggressively. A small degree of metabolic and respiratory alkalemia can result in a marked reduction in shunting and an improvement in oxygenation.[190,191] The arterial oxygen tension must be maintained around 80 to 100 mm Hg (10.5 to 13 kPa) to prevent hypoxemia during spontaneous fluctuations in oxygenation. Moderate hyperventilation to achieve eucapnia, and at most mild hypercapnea and a pH > 7.30 are appropriate. Although hyperventilation to achieve a pH of 7.55 to 7.6 improves PaO_2, it is no longer recommended because of the potential adverse effects resulting from reduced cerebral blood flow,[192-195] potential for gas trapping that in turn impedes venous return and pulmonary blood flow,[196] and the lung injury from the mechanical ventilation. In the more

severe cases of secondary PPHN, the use of high-frequency ventilation can markedly improve carbon dioxide elimination and oxygenation.[193,197]

Cardiovascular support also plays an important role in the management of infants with PPHN. Medications such as dopamine, isoproterenol, and dobutamine are frequently used to increase arterial blood pressure and improve cardiac output.[190,198] Calcium infusion can improve myocardial function in the presence of low plasma ionized calcium levels.[199] Sedation and muscle relaxation are also used in infants whose spontaneous activity interferes with mechanical ventilation, resulting in deterioration of gas exchange.[164] A number of vasodilators have been used in PPHN, but none has been shown to alter the final outcome.[200] The major limitation with medications such as α-adrenergic blockers, calcium channel blockers, and prostacyclin is their lack of specificity as they induce systemic hypotension. Prostaglandin D_2, a selective pulmonary vasodilator in fetal animals, was used in a group of infants with PPHN, but the results were disappointing.[201]

The introduction of inhaled nitric oxide, a potent vasodilator rapidly inactivated in the blood, represented a major advance in the treatment of PPHN[202-204] as oxygenation improves without causing systemic hypotension. Because nitric oxide is a gas that is delivered into the airways, it reaches the better ventilated portions of the lung, preventing the ventilation-perfusion mismatch that can occur when vasodilators are administered systemically. The administration of inhaled nitric oxide (iNO) to infants with PPHN results in a rapid improvement in oxygenation in more than one half of patients and reduces the need for extracorporeal membrane oxygenation.[205-207] More than 30% of infants with PPHN do not respond to iNO, however, and there are problems associated with prolonged administration of and weaning from iNO.[208] More recently, phosphodiesterase (PDE) inhibitors, particularly PDE5 inhibitors such as sildenafil, have shown promise as selective pulmonary vasodilators. Pulmonary vascular smooth muscle cells have very high concentrations of PDE5 receptors.[209] Inhibition of such receptors causes cGMP to accumulate, causing hyperpolarization of the smooth muscle cells and subsequent vasodilation.[210]

Infants who do not respond to management can be treated with extracorporeal membrane oxygenation.[211-213] The survival rate with this mode of therapy in most centers is better than 90%, but because of the possible complications and long-term sequelae, this procedure is still used only as a last resort.[214-216]

Clinical Course and Prognosis

The outcome of neonates with PPHN depends on the underlying condition, the severity of the disease course, and the effectiveness of management. Although most infants survive, many require ventilatory support for long periods, and a few have central nervous system sequelae related to episodes of severe hypoxia and the hypocapnia induced by hyperventilation.[195,217] Some infants develop CLD because of pulmonary damage produced by infection or the aspiration of meconium or because of the mechanical ventilation required to maintain adequate gas exchange.

PULMONARY GAS LEAKS

Lung rupture and gas leak are major complications in infants with respiratory failure, especially in those who need assisted ventilation (see Table 28-1). Rupture of the terminal airways leads to the accumulation of extra-alveolar gas, pulmonary interstitial emphysema, pneumomediastinum, pneumothorax, subcutaneous emphysema, or gas embolization of the lymphatic system and pulmonary and systemic circulations.

PULMONARY INTERSTITIAL EMPHYSEMA (PIE)

PIE is the most common form of barotrauma associated with mechanical ventilation and usually observed as a complication of RDS, although it also occurs in association with aspiration syndromes and sepsis. Although normally confined to intubated subjects, PIE has been described in an infant who received only nasal CPAP,[218] and more rarely, in spontaneously breathing, nonventilated subjects.[219] PIE is important because of the significant pathophysiologic alterations it causes and because it commonly progresses to more severe forms of extra-alveolar gas leak (Fig. 28-13).

Epidemiology, Risk Factors, and Pathogenesis

The incidence of PIE in infants with very low birth weights was reported to be 32%.[220] A significant reduction in the incidence of PIE, as low as 7%, has been reported with surfactant treatment for infants with RDS.[221,222] In patients requiring conventional mechanical ventilation, the use of high rates and short inspiratory times appears to reduce the incidence of gas leak, including PIE.[54,60] In theory, ventilatory modalities such as pressure support ventilation that avoid

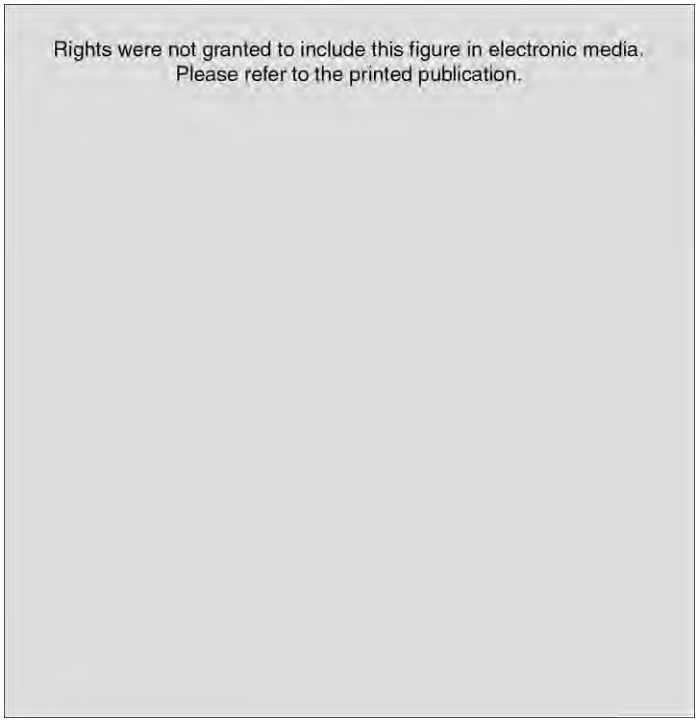

Figure 28-13 Progression of pulmonary gas leak. (From Bancalari E, Goldman SL. In Milunsky A, Friedman EA, Gluck L [eds]: Advances in Perinatal Medicine. New York, Plenum, 1989, p 151.)

active expiration should reduce the incidence of PIE and other air leak phenomena, but evidence is not yet available.

PIE is caused by a dissection of gas from the base of ruptured overdistended terminal airways or alveoli into the pulmonary interstitium. Rupture occurs at the alveolar-capillary junction when shear forces exceed a critical threshold. The amount of interstitial gas is variable. PIE can occur spontaneously in infants with parenchymal lung disease but more frequently occurs as a complication of mechanical ventilation. Neonatal alveoli are less able to compensate for excessive pressure and volume than alveoli in mature lungs. In the adult, interalveolar pores (pores of Kohn) act as relief valves that allow higher intra-alveolar pressures to equilibrate with adjacent alveoli when intra-alveolar pressure is nonuniform. These communicating pores are decreased in number and size in the newborn. Nonuniform transmission of pressure to alveoli during mechanical ventilation means that the newborn is more likely to develop alveolar rupture. The presence of meconium, blood, or other particulate matter that exacerbates uneven aeration also exacerbates this tendency. Experimental work using rabbits suggests that the absolute amount of intrapulmonary pressure generated and mechanical stress resulting from overdistention of alveoli, or of alveolar ducts adjacent to atelectatic alveoli, is directly responsible for the development of PIE.[223] Once rupture occurs, gas enters the adjacent interstitial tissue, where it can dissect along the perivascular (particularly pulmonary venous) sheaths to the hilum of the lung. When the volume of gas in the interstitium is large enough, the resulting perivascular pressure can obstruct the pulmonary circulation.

Diagnosis

The development of mild PIE is rarely associated with demonstrable changes in cardiorespiratory function. When PIE is severe and diffuse, deterioration of the respiratory status occurs with hypoxemia and hypercarbia caused by compression of the pulmonary vasculature by trapped gas. The chest radiograph confirms the diagnosis: The lungs have a fine, bubbly appearance, sometimes with larger lucent areas (Fig. 28-14). In a small, preterm infant with diffuse PIE, transillumination of the chest may be indistinguishable from a large pneumothorax.

Treatment

Management consists primarily of preventing progression to other forms of gas leak by using the lowest effective airway pressures and short inspiratory times in the ventilator. Randomized clinical trials comparing conventional mechanical ventilation with high-frequency ventilation have either failed to show a reduction in the incidence of PIE with high-frequency ventilation,[224-226] or demonstrated effective treatment of PIE[227] and could also reduce the incidence of PIE in infants with severe RDS.[228]

For unilateral PIE, selective intubation of the main stem bronchus on the unaffected side[229] or positioning of the infant with the involved side down[230] may be beneficial. In the case of severe PIE, especially when it has progressed to the formation of large cysts, surgical resection of the affected lobe should be considered.[231]

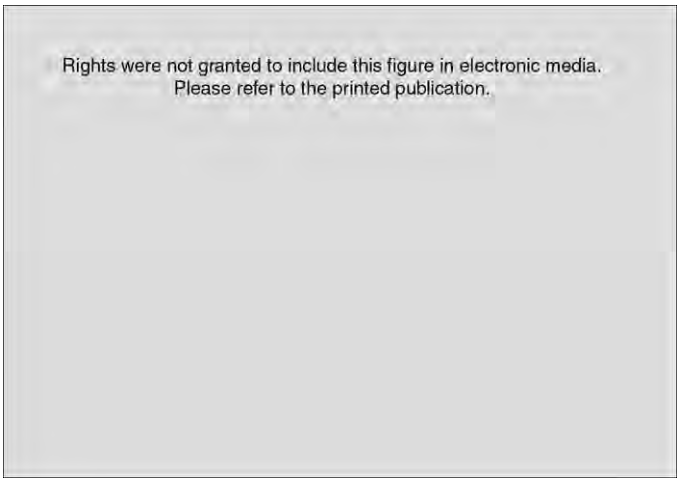

Figure 28-14 Pulmonary interstitial emphysema (PIE). Fine, bubbly appearance of the lungs in an infant with severe respiratory distress syndrome (RDS). (From Bancalari E, Goldman SL. In Milunsky A, Friedman EA, Gluck L [eds]: Advances in Perinatal Medicine. New York, Plenum, 1989, p 154.)

PNEUMOMEDIASTINUM

Pneumomediastinum, a collection of gas within the pleural boundaries of the mediastinum, can occur spontaneously or as a complication of mechanical ventilation.

Epidemiology, Risk Factors, and Pathogenesis

Gas enters the mediastinum after moving along the vascular sheaths toward the lung hilum and then ruptures through the pleura into the mediastinal area. Another cause of pneumomediastinum is traumatic perforation of the pharynx or esophagus.[232] The incidence in well newborns is about 2%[233] but is significantly higher in infants with pulmonary pathologic conditions.[234]

Diagnosis

Pneumomediastinum is symptomatic only if the collection of gas is under sufficient pressure to compress adjacent structures such as the heart or blood vessels, producing cardiorespiratory decompensation. The diagnosis is made radiographically by radiolucency adjacent to the heart border and retrosternal hyperlucency on lateral view.

Treatment

There is no specific treatment for pneumomediastinum.

PNEUMOTHORAX

Pneumothorax is the accumulation of gas in the pleural space between the parietal and visceral pleura. When the pressure of this gas is greater than the atmospheric pressure, the pneumothorax is "under tension." Although pneumothorax can occur spontaneously, it is one of the most common manifestations of pulmonary barotrauma in neonates requiring mechanical ventilation.

Epidemiology, Risk Factors, and Pathogenesis

The incidence of spontaneous, asymptomatic pneumothorax in the newborn has been reported to be 1%.[233] This condition is more frequent in infants with specific lung pathologic conditions that require mechanical ventilation. Before the introduction of surfactant, the incidence of pneumothorax in patients with RDS treated with CPAP alone was close to 20%.[235] In infants with RDS who required mechanical ventilation but did not receive surfactant, the incidence of pneumothorax was 18% when a rate of 60 breaths/minute and a short inspiratory time were used, but the incidence was significantly higher (33%) in infants treated with a slow respiratory rate and longer inspiratory time.[53] The use of high-frequency ventilation in infants with RDS has not affected the incidence of pneumothorax.[225,236]

The introduction of surfactant treatments for the management of infants with RDS has produced a dramatic reduction in the incidence of pneumothorax to a rate as low as 3% to 10%.[221,237,238] Early administration of surfactant seems to be important in reducing the incidence of pneumothorax. When early administration of surfactant was compared with treatment of established RDS in infants of less than 30 weeks' gestation, the incidence of pneumothorax was 7% in the early treatment group compared with 18% in the infants treated several hours after birth.[239,240]

Pneumothorax in the neonate is produced most often by mediastinal gas rupturing through the mediastinal pleura into the pleural space. A large pneumothorax can decrease cardiac output and can increase pulmonary vascular resistance. As the pneumothorax increases in size, compensatory mechanisms can no longer prevent decreases in cardiac output and systemic blood pressure. The increased intrathoracic pressure decreases venous return to the heart and can cause a cardiac tamponade. The accompanying lung collapse also increases pulmonary vascular resistance and contributes to the decrease in cardiac output. Increasing amounts of pleural gas result in a decrease in tidal volume that can initially be compensated for by an increase in respiratory rate—but if severe, it leads to decreased minute ventilation and hypercarbia. As lung volume is decreased and some areas are collapsed, there is an increased ventilation-perfusion mismatch, resulting in an intrapulmonary shunt and hypoxemia.

Intracranial pressure usually increases as a result of an increase in arterial blood pressure, obstruction of venous return, and increased cerebral blood flow. In the premature infant, these factors can increase the risk of intraventricular hemorrhage.[241]

Diagnosis

Clinically, the signs of pneumothorax in the neonate are variable. Although most spontaneously occurring pneumothoraces are asymptomatic, a diagnosis of pneumothorax needs to be considered when significant clinical deterioration occurs in association with lung disease or mechanical ventilation.

Spontaneously breathing infants who develop large pneumothoraces demonstrate the classic signs of respiratory failure, including cyanosis, grunting, intercostal and substernal retractions, tachypnea, and nasal flaring. These signs are sometimes difficult to evaluate in infants whose lungs are ventilated and in whom the only obvious sign of pneumothorax may be abrupt deterioration of the arterial blood gas levels. On physical examination, a pneumothorax is suggested by asymmetrical chest expansion, downward displacement of the liver, and decreased heart and breath sounds on the side of the pneumothorax. The latter sign is particularly unreliable in the small premature infant whose breath sounds are easily heard uniformly all over the chest. A pneumothorax is frequently followed by an increase in respiratory rate, heart rate, and arterial blood pressure.[242] A tension pneumothorax may be associated with shift in the heart sounds to the contralateral side and significant, and often dramatic changes in the vital signs.

The chest radiograph is the best method of confirming the diagnosis. If the radiograph is taken with the infant in a supine position with an anteroposterior view, the pneumothorax can be seen as a crescent-shaped lucency along the lateral aspect of the thorax (Fig. 28-15) without lung markings extending into the lucent area. Care must be taken not to confuse a skinfold or blanket with this type of appearance. These artefacts can frequently be recognized because they extend below the diaphragm. If the lungs do not collapse because of poor compliance or if the accumulation of extrapulmonary gas is anterior, the crescent-shaped lucency may not be present, and the only suggestion of a pneumothorax is a generalized decreased density on the side of the extrapulmonary gas. A medial pneumothorax appears as a lucency just to the right or left of the heart borders. In these cases, the presence of a pneumothorax can be ascertained by obtaining a "cross-table" lateral film. This method should be reserved for the infant who is too unstable to rotate to the decubitus position because

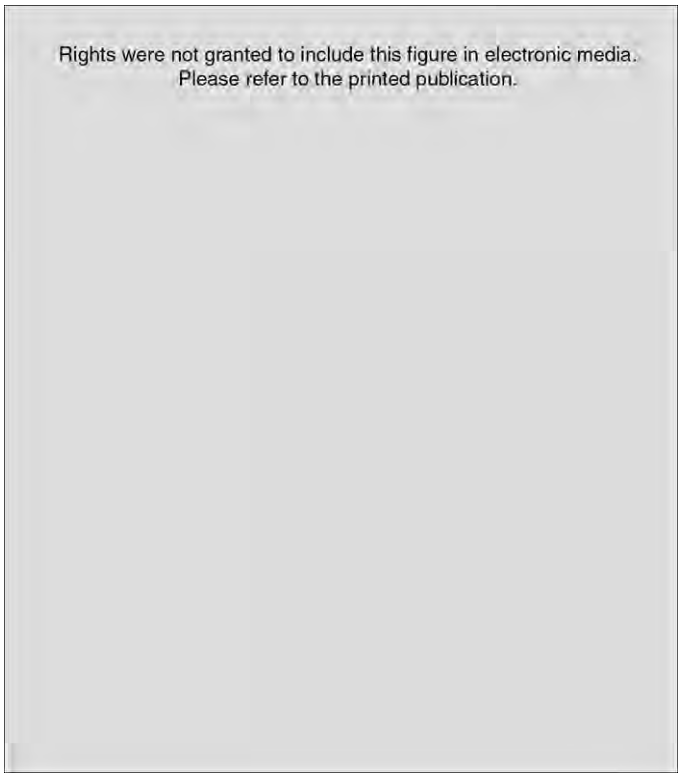

Figure 28-15 Pneumothorax. Chest radiograph shows small crescent-shaped lucency on the left at the level of the apex. (From Bancalari E, Goldman SL. In Milunsky A, Friedman EA, Gluck L [eds]: Advances in Perinatal Medicine. New York, Plenum, 1989, p 156.)

the anterior lucency may be difficult to distinguish from a pneumomediastinum.

The presence of a tension pneumothorax is recognized because the mediastinum is shifted to the opposite side, the intercostal spaces are widened, and the diaphragm is flattened on the ipsilateral side (Fig. 28-16). If bilateral tension pneumothoraces occur simultaneously, there may be no shift of the mediastinum, but the bilaterally increased pressure compresses the heart, resulting in a smaller cardiac silhouette. A noncompliant lung in an infant with RDS may not completely collapse, even with a tension pneumothorax. Transillumination of the chest with a fiberoptic light source is a very useful adjunct for diagnosing pneumothorax,[243] particularly in small premature infants in whom physical examination is unreliable. The thin chest wall of such infants allows for a demonstration of the "halo" of light that indicates extrapulmonary gas. Transillumination of the chest in larger infants with thicker chest walls occasionally gives false-negative results. Thus, a radiographic examination should not be omitted because of a negative transillumination. Treatment should not be delayed for radiographic confirmation in the presence of significant clinical deterioration if a diagnosis of pneumothorax is suspected and supported by transillumination.

Treatment

When the diagnosis of pneumothorax is suspected, the plan for treatment is based on the following considerations: the size of the pneumothorax, the extent of the infant's respiratory deterioration, and the need for positive-pressure ventilation. A pneumothorax diagnosed in an infant with no symptoms does not require specific therapy, but the infant should be observed closely for possible signs of respiratory decompensation.

If the pneumothorax is associated with cardiorespiratory symptoms, immediate treatment is indicated. Evacuation can be accomplished by needle aspiration or by thoracostomy with chest tube insertion. The administration of 100% oxygen can accelerate the reabsorption of gas. This is because breathing 100% oxygen will "wash out" nitrogen from the body, including the tissues surrounding the pneumothorax. This increases the nitrogen gradient, facilitating faster absorption of the nitrogen from the gas collection into the bloodstream. Because of the risk of retinopathy of prematurity, this method should not be used in preterm infants less than 34 weeks postmenstrual age. Needle aspiration is indicated only as a temporizing measure in an infant who has a tension pneumothorax or who requires positive-pressure ventilation. In these cases, the immediate placement of a chest tube is indicated. The thoracostomy tube should then be attached to an underwater seal so that air will not be drawn into the pleural space. If the volume of the pneumothorax is relatively small, the negative pressure maintained by the underwater seal is sufficient to evacuate the extrapulmonary gas. However, if there is a large volume of gas or if there is a continuous gas leak, negative pressure (15 to 20 cm H_2O) should be applied to the system to ensure complete evacuation. When there is no further drainage, the negative pressure can be discontinued, and if no re-accumulation occurs, the chest tube can be clamped and removed in 24 hours.

Figure 28-16 Left tension pneumothorax. Tension is indicated by the contralateral shift of the mediastinum, small heart size, and depressed left diaphragm. (From Bancalari E, Goldman SL. In Milunsky A, Friedman EA, Gluck L [eds]: Advances in Perinatal Medicine. New York, Plenum, 1989, p 162.)

Clinical Course and Prognosis

Pneumothorax is a potentially fatal complication, but if diagnosed and treated promptly, it may have only minimal consequences. The keys to preventing a poor outcome are a high index of suspicion in infants at risk and the proper equipment and personnel for effectively diagnosing and treating the disorder.

PNEUMOPERICARDIUM

Although the pericardial sac is not in direct communication with the pleural space, extrapulmonary gas can collect in the pericardium. Pneumopericardium is an uncommon form of gas leak.

Pathogenesis

The mechanism of gas entry seems to be directly from the pulmonary interstitial air, traveling along the great vessels into the pericardial sac.[244] The physiologic effects of a pneumopericardium are essentially those of cardiac tamponade. Increased pressure around the heart interferes with diastolic filling, resulting in increased central venous pressure and decreased cardiac output. This produces arterial hypotension with a narrow pulse pressure.

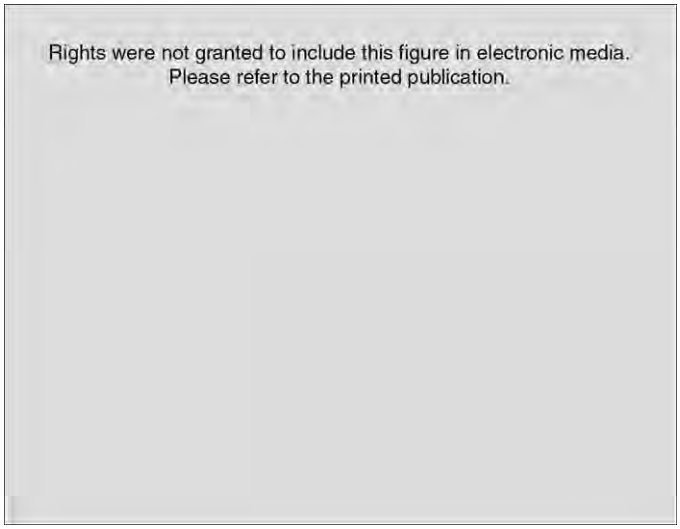

Figure 28-17 Pneumopericardium. The heart is clearly outlined by a collection of gas in the pericardium. (From Bancalari E, Goldman SL. In Milunsky A, Friedman EA, Gluck L [eds]: Advances in Perinatal Medicine. New York, Plenum, 1989, p 163.)

Figure 28-18 Pneumoperitoneum. The wall of the stomach is distinct, indicating the presence of an abnormal collection of gas within the peritoneal cavity surrounding the stomach. (From Bancalari E, Goldman SL. In Milunsky A, Friedman EA, Gluck L [eds]: Advances in Perinatal Medicine. New York, Plenum, 1989, p 164.)

Diagnosis

The clinical signs of pneumopericardium in the neonate are variable, and most are nonspecific. A small pneumopericardium may develop without any significant change in the infant's cardiorespiratory status—being noticed only incidentally on the chest radiograph. When gas is accumulated under tension, an increase in respiratory distress and hypoxemia is observed, and heart sounds become distant with a decrease in arterial and pulse pressure. An increase in the central venous pressure may also be noticed. Pneumopericardium is rarely isolated because it is most commonly associated with other forms of gas leak.

The diagnosis of pneumopericardium must be suspected in any infant in whom there is an acute clinical deterioration while on mechanical ventilation. A decrease in both pulse pressure and mean arterial blood pressure should alert the clinician to this diagnosis. The chest radiograph confirms the diagnosis by showing a gas lucency surrounding the heart on the anteroposterior and lateral films (Fig. 28-17).

Treatment

When a pneumopericardium is symptomatic, immediate drainage is imperative. Decompression can be accomplished by needle aspiration, but continuous drainage via placement of a pericardial catheter is necessary in most cases to prevent re-accumulation of gas. Without treatment, the mortality rate approaches 70%, and even with pericardiocentesis, the mortality rate remains high (20% to 60%).[245]

PNEUMOPERITONEUM

Free gas in the peritoneal cavity, generally considered evidence of bowel perforation, is recognized as a possible complication of ventilator therapy and not necessarily the result of a perforated viscus. In infants ventilated for RDS, the reported incidence was 1.7% before the introduction of surfactant.[246]

Pathogenesis

Although the diaphragm separates the thorax from the peritoneal cavity, there are potential pathways through which gas can cross from one cavity to the other. Free gas in the mediastinum or pleural space can dissect caudally along the perivascular and periesophageal tissue sheaths into the retroperitoneal space and thence into the peritoneum.

Diagnosis

The signs of pneumoperitoneum secondary to pulmonary gas leak are nonspecific. Commonly, there is abdominal distention, which may be severe enough to compromise ventilation by elevating the diaphragm. The clinical setting in which pneumoperitoneum occurs is characteristic: The infant is receiving high ventilatory pressures and usually has evidence of intrathoracic gas leak before the discovery of intraperitoneal free gas. The development of pneumoperitoneum is not usually associated with clinical deterioration unless the volume of gas is massive enough to compromise ventilation. The diagnosis is confirmed radiographically (Fig. 28-18). Unfortunately, no specific radiographic signs accurately define the presence or absence of visceral perforation.

Treatment

Pneumoperitoneum secondary to pulmonary gas leak usually requires no specific treatment. Rather, attention should be directed at preventing or decompressing the intrathoracic gas collection that leads to the pneumoperitoneum. Once gas is present in the peritoneum, no treatment is necessary unless a perforated viscus is suspected or unless there is significant tension that can be relieved by needle aspiration.

GAS EMBOLISM

Intravascular gas embolism is the rarest but most catastrophic consequence of acute pulmonary barotrauma. Gregory and Tooley[247] first reported a case of gas embolism in a newborn who had RDS and who was receiving positive-pressure ventilation.

Pathogenesis

Gas embolism is thought to result from alveolar-capillary fistulas. In spontaneously breathing infants, the pressure in the pulmonary capillary bed is greater than that in the alveolus. However, with the application of positive airway pressure, this gradient is reversed, favoring the movement of gas from the alveolus into the vascular space. Once in the vascular space, the gas can travel to all parts of the body, including the cerebral and cardiac circulations, leading to rapid death from vascular obstruction.

Clinical Features and Diagnosis

Most of the cases reported are of premature infants receiving relatively high airway pressures. Characteristically, these infants have radiographic evidence of other forms of gas leak before the development of gas embolism. Clinically, they have acute cardiovascular deterioration with development of pallor or cyanosis, bradycardia, and hypotension. Often, the diagnosis is made when gas bubbles are withdrawn from an artery or a venous catheter during the clinical deterioration. The diagnosis is confirmed radiographically with demonstration of gas shadows within the heart chambers and vascular tree (Fig. 28-19).

Treatment, Clinical Course, and Prognosis

Massive gas embolism is invariably fatal; hence, treatment must be viewed as preventive: The lowest possible ventilatory pressures should be used to prevent alveolar rupture and gas leak.

WILSON-MIKITY SYNDROME

Wilson-Mikity syndrome was first described in 1960 and is characterized by late-onset progressive respiratory distress in small preterm infants. In contrast to CLD, it manifests in infants without severe initial respiratory distress syndrome.[248,249] The respiratory symptoms usually begin between 1 and 4 weeks of age and last several weeks or months, after which most infants recover gradually. Radiographically, the lungs have a cyst-like appearance with diffuse streaks of increased density resembling the changes observed in infants with CLD. On histologic examination, the lungs show areas of hyperinflation alternating with areas of collapse and septal thickening, but in contrast with infants with CLD, these infants do not show significant changes in the airway epithelium. The etiology and pathogenesis of Wilson-Mikity syndrome are not known, but congenital infections have been mentioned as possible causes. This condition is seldom diagnosed today in spite of the fact that the survival rate of very small infants has increased.

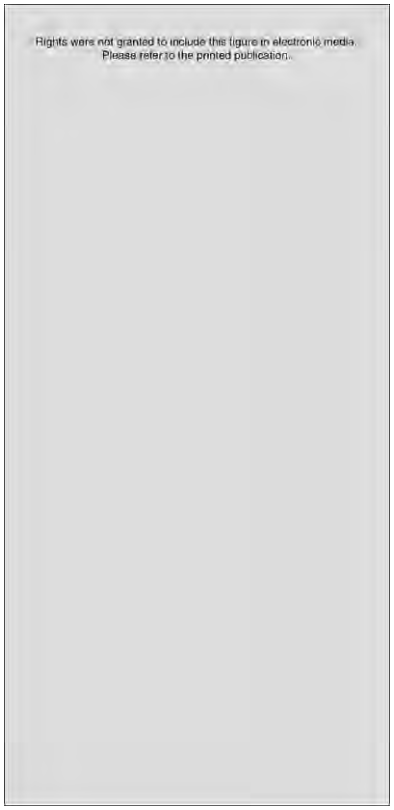

Figure 28-19 Gas embolization. Postmortem radiograph of a premature infant who died suddenly while requiring high ventilatory pressures. Gas can be seen within the heart and in some intra-abdominal veins. (From Bancalari E, Goldman SL. In Milunsky A, Friedman EA, Gluck L [eds]: Advances in Perinatal Medicine. New York, Plenum, 1989, p 129.)

CURRENT MAJOR CONTROVERSIES AND CHALLENGES IN CLINICAL MANAGEMENT OF NEONATAL ACUTE RESPIRATORY DISEASE

- Role of oxygen in initial resuscitation and its contribution to subsequent CLD
- Noninvasive versus invasive mechanical ventilatory support for the extremely preterm infant with RDS
- Pros and cons of new ventilatory modalities and strategies including pressure-support ventilation, proportional assist ventilation, and volume- versus pressure-limited mechanical support
- Pros and cons of inhaled nitric oxide, postnatal corticosteroids, adjuvant vitamin therapy, and new anti-inflammatory agents on the development of the structurally and functionally immature lung and other body organs
- Routine suction of the pharynx and trachea in the infant born through meconium-stained fluid

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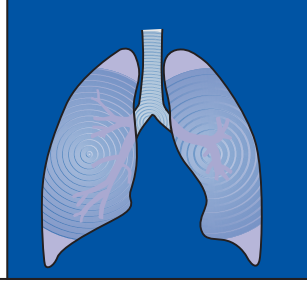


CHAPTER 29 Chronic Respiratory Complications of Prematurity

Sailesh Kotecha

TEACHING POINTS

- Chronic lung disease (CLD) is a common disease of preterm infants.
- Lung growth abnormalities are important in development of CLD
- Risk factors for CLD include extreme prematurity, male sex, white race, surfactant deficiency, oxygen toxicity, barotrauma, chorioamnionitis, sepsis, patent ductus arteriosus, and fluid overload.
- The mainstay of treatment for CLD is oxygen, but the ideal oxygen saturation is unknown.
- Drug management of CLD is empirical.
- Long-term respiratory outcome, especially in surfactant-treated infants, remains unclear.

CHRONIC LUNG DISEASE: BACKGROUND

Terminology

The term *chronic lung disease* (CLD), used to describe the aftermath of prematurity and its treatment on the respiratory system, is deliberately vague. It implies a wide spectrum of disorders affecting the upper and lower respiratory tract—the result of the complex interaction of antenatal and postnatal factors. Although the use of the term *disease* may seem to indicate the possibility of a clear all-or-none definition, CLD encompasses a range of clinical, physiologic, pathologic, and developmental problems that extends from marginally significant at one extreme to fatal at the other. The vagueness of the term hides the ignorance of many aspects of the pulmonary outcomes of prematurity.

Unlike the well-defined condition *bronchopulmonary dysplasia* (BPD),[1] CLD can be defined a number of ways to suit particular purposes. It is worth exploring the history of the ideas of the respiratory consequences of prematurity to draw attention to the themes that permeate this chapter.[2]

CLD has risen in importance since the advent of effective care for preterm babies. Until the 1960s and the introduction of mechanical ventilation, the survival of infants of very low birth weight (VLBW) was rare. (A VLBW infant weighs less than 1500 g at birth.) No chronic disease was therefore possible. When Northway and colleagues[1] described the chronic clinical and radiologic features of CLD in the preterm survivors of mechanical ventilation and high inspired oxygen therapy, defining bronchopulmonary dysplasia, they created a series of controversies that continue today. The most vehement arguments raged over the importance of barotrauma and oxygen toxicity as causes of lung injury in the neonate. The ignorance of the mechanisms and consequences of CLD has moved to a more sophisticated level because the multiple, interacting causes exert effects that vary in both their pathophysiologic basis and clinical features throughout infancy, childhood, and adolescence.

To some extent, the definitions of CLD reflect the applications of the term (Table 29-1). It has become clear that BPD (chronic oxygen dependency with certain characteristic radiologic features at 28 days of age) has become a less useful term because of the survival of infants at ever-lower gestational ages. Nevertheless, the term *bronchopulmonary dysplasia* or *"new" bronchopulmonary dysplasia* is used more frequently in North America to signify the changing pattern of the disease from both a clinical and pathologic perspective. Most infants who weigh less than 1000 g at birth are still oxygen dependent after 4 weeks. Thus, the continually varying level of risk of an adverse long-term outcome for VLBW infants is still defined according to a single criterion: the need for oxygen therapy.[3] The suggestion of Shennan and coworkers[3] that 36 weeks of gestational age represents the best compromise seems realistic. This cutoff point may vary with local need, secular trends, and changes in the epidemiology of CLD.

Comparisons between units are difficult not only because of differing local practices but also different definitions. A consensus regarding definition would permit comparisons between centers and with historic data. At a recent workshop sponsored by the National Institute of Child Health and Human Development, it was proposed that babies should be considered to have CLD if they had been oxygen dependent for at least 28 days and then be classified as suffering from mild, moderate, or severe BPD according to their respiratory support requirements at a later date.[4]

Diagnostic Overlap

Chronic lung disease includes not only BPD but also several purely neonatal disorders such as Wilson-Mikity syndrome (Table 29-2). Clinically and radiologically, this disorder is very similar to classic BPD (Northway type IV), except for a lack

Table 29-1
Definitions of Chronic Lung Disease

Application	Definition
Recognition of Clinical Abnormality	
Individuals	Definition based on the presence or quantification of clinical features such as hospital readmission or abnormal lung function in infancy
Groups	Statistical definition based on the quantification of excess morbidity
Risk Prediction for Clinical Intervention	Criteria dependent on the risk of possible interventions (e.g., the need for a fraction of inspired oxygen at 40% at 4 weeks would justify low-risk intervention; the prediction of intermittent positive-pressure ventilation at term might justify a very risky procedure)
Audit	
Clinical efficacy	All-or-none definitions such as bronchopulmonary dysplasia (BPD), which may be useful
Financial cost of care	Statistical definition based on excess respiratory morbidity (e.g., excess "bed days" as a result of all respiratory causes in premature infants)
Long-Term Health Care Planning	Definitions according to risk of need for long-term management, such as need for domiciliary oxygen therapy
Death Certification	Histopathologic criteria

Table 29-2
Clinical Disorders That Are within the Spectrum of Chronic Lung Disease (CLD) or That Contribute to Morbidity

Disorders	Comment
Neonatal disorders	
Developmental abnormalities	Pulmonary hypoplasia, intrauterine infection
BPD	
Type I	Small "gray" lungs on chest radiograph
Type II	Classic Northway type IV
Wilson-Mikity syndrome	Similarity to type II BPD, without preceding RDS
Chronic pulmonary insufficiency of prematurity	Similarity to type I BPD, without preceding RDS
Recurrent pulmonary aspiration	Gastroesophageal reflux, which often accompanies CLD
Disorders of Later Infancy in Which Morbidity Rate May Be Greater in Preterm Infants	
Wheezing disorders	Excess lower respiratory tract morbidity, which is seen in infants born prematurely and can be considered epidemiologically as a form of CLD
Defects of host defense	Very rare incidence, apart from cystic fibrosis
Developmental anomalies	Excess incidence of congenital heart disease in infants with CLD

BPD, bronchopulmonary dysplasia; RDS, respiratory distress syndrome.

of mechanical ventilation in its early postnatal course. Some pathologists deny any specific histologic features. Within the restricted category of BPD, at least two types are recognized: type 1 with "gray" lungs on chest radiographs and type 2 with classic radiologic changes.[5] There are other clinical distinguishing features (see Table 29-2). The role of developmental lung disorders such as pulmonary hypoplasia and of common clinical problems such as gastroesophageal reflux (GER) with aspiration is clearly complex. Such problems often contribute to CLD, but unless they are strikingly obvious, they do not usually warrant an independent diagnostic label. Recognizing their contribution may be important in understanding the etiology of CLD, its management, and its prognosis.

Diagnostic overlap is even more of a problem in later infancy, when infants of preterm birth tend to have greater morbidity in a range of clinical situations (see Table 29-2). For instance, because at least 30% to 60% of preschool children suffer from recurrent lower respiratory illness, mostly with wheezing,[6-8] the symptom is common in children born prematurely. Preterm infants are, in fact, at increased risk,[9-12] but it would be fruitless to try to define a level of morbidity that distinguishes "ordinary" wheezing lower respiratory illness from CLD. In clinical practice and increasingly in clinical epidemiology, a problem-oriented approach is more useful than one based on categorical diagnostic labels. The same argument applies to the other disorders in Table 29-2. This chapter uses the term *chronic lung disease* to encompass both a range of well-characterized syndromes and an overall increase in respiratory tract morbidity in infancy and later life.

EPIDEMIOLOGY, PATHOLOGY, RISK FACTORS, PATHOGENESIS

Epidemiology

The prevalence of CLD varies widely. Crude figures, even when adjusted for birth weight, are difficult to interpret and, hence, are of only limited value except as starting points for further exploration. Inaccuracy of terminology and diagnostic overlap produce so much "noise" that signals relating to important risk factors are difficult to discern. In the well-known eight-center, comparative study of VLBW infants in the United States,[13] strict diagnostic criteria were applied. Even so, major differences in the prevalence of CLD were observed that were not explained by different mortality rates within the institutions or by differences in birth weight, race, or gender. The authors speculated that the differences in 28-day oxygen requirements, which varied between 21% and 42%, might be accounted for by early postnatal management practices. At the center with the lowest incidence, nasal continuous positive airway pressure was instituted early for all symptomatic infants, and mechanical ventilation (without muscle paralysis) was commenced only when the partial pressure of carbon dioxide (P_{CO_2}) had risen to 60 mm Hg. Local variations in management may, therefore, have influenced the long-term outcome.

In another large, multicenter study in the United States, the incidence of CLD varied from 3% to 33% of all preterm infants and up to 50% of those who had respiratory distress syndrome (RDS).[14] By taking a complete, clearly defined VLBW population, Kraybill and associates[15] eliminated selection and diagnostic bias but came to the conclusion that although most of the variation between centers was due to differences in birth weight, about one third was due to other

BOX 29-1 Factors Determining the Prevalence and Variations in Diagnostic Criteria of Chronic Lung Disease

Population base of community
- Social factors
- Environmental factors
- Age and health structure of community
- Ethnic mix of population

Referral patterns of neonatal unit
- Obstetric population (high or low risk)
- Obstetric practices
- Postnatal referrals from units with less expertise

Morbidity of patients
- Early morbidity
- Maturity of population
- Complication rate
- Early mortality rate

Quality of care
- Quality and quantity of medical and nursing staff
- Quality of equipment
- Use of protocols based on scientific data

factors, differences in treatment being the prime suspect. Their overall incidence of classic BPD in VLBW infants was 22%. A number of the general factors that could affect the incidence of CLD are listed in Box 29-1.

Against this uncertainty, secular trends in birth weight–adjusted prevalence have clearly occurred. Within single institutions, increased survival of VLBW infants has been associated with a rise in CLD in the whole population (but not necessarily as a proportion of survivors), whereas for larger infants, the figures have fallen markedly.[16] Interestingly, despite or perhaps because of longer survival times, the prevalence of CLD has not fallen in the very smallest babies, those who weighed less than 750 g at birth.[17] Although much of the change in prevalence may be accounted for by the factors listed in Box 29-1, specific changes in perinatal care have brought overall survival benefits to preterm babies, increasing the risk in some cases of severe CLD.[18] The reduction in RDS by obstetric and early neonatal interventions has played a major part (see Chapter 28).

Early perinatal interventions have been exhaustively reviewed.[19-21] Corticosteroids have been used to accelerate lung maturation for many years, but their effect on the incidence of CLD is inconsistent and at most marginal,[19] although survival is significantly enhanced. Although long-term adverse effects have not been demonstrated in humans,[19] a number of animal studies have shown persistent,[22] transient,[23] or no effects[24] from fetal corticosteroid exposure. There are little data on human lung growth.[25]

One of the main advantages of population studies is the identification of risk factors, which can then be subjected to detailed investigation, often by randomized, controlled trial. The potential for bias in identifying risk factors from small, poorly controlled samples is largely a consequence of the network of interrelated risks in neonatal medicine

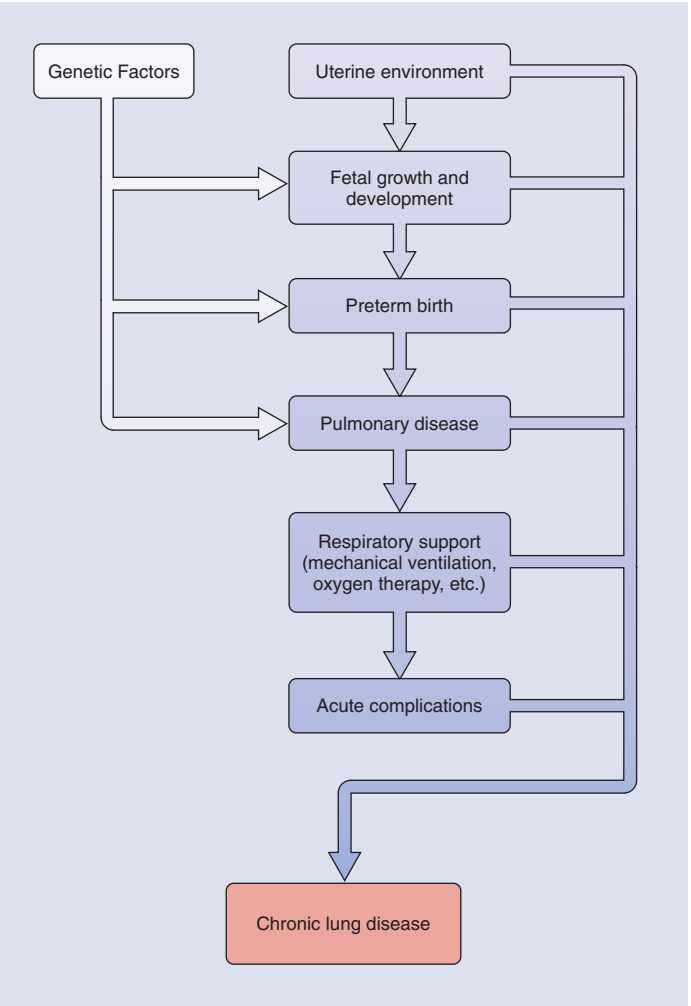


Figure 29-1 There is a great deal of interaction among risk factors in chronic lung disease (CLD).

(Fig. 29-1). The possibilities of bias are numerous and explain some of the conflicting results that have been reported from outcome studies. Many early studies identified mechanical ventilation and oxygen therapy as major risk factors for BPD on the basis of comparative outcome studies of infants whose lungs were mechanically ventilated compared with controls whose lungs were not ventilated. Such studies were confounded by the interaction of factors illustrated in Figure 29-1 and biased by the selection of unrepresentative samples of the population. The analysis of Kraybill and coworkers[26] illustrates some pitfalls. A crude analysis of the risk factors for oxygen dependency at 28 days of age in babies weighing less than 1000 g at birth indicated significant risks associated with low gestational age, male gender, high rate of ventilation at 96 hours of age, and low arterial P_{CO_2} at 96 hours of age. However, logistic regression analysis left male gender and low arterial P_{CO_2} as the only independent factors (the latter being a weak association).

The age at which the risk of an adverse outcome is determined may be important, not only because lung pathology, symptoms, and lung function may become less obvious with time,[10,27,28] but also because it is possible that the risk factors for acute lung damage (classic BPD) may differ from those of CLD later in childhood. The CLD could, for instance, be

determined to a greater extent by disturbed long-term growth related to prematurity itself,[29,30] whereas acute lung damage might result from mechanical ventilation.[31]

Secular trends in prevalence almost certainly affect the assessment of risk because classic BPD is more common and may have a different spectrum of risk factors in VLBW infants, who are increasingly represented in the most recent studies. This can lead to bias if there is a parallel change in some important aspect of management, such as the earlier introduction of lipid-based intravenous feeding regimens.[18] Even the definition of risk factors may be important. One cannot, for instance, assume that low birth weight (LBW) and prematurity are equivalent, because Rona and colleagues[32] showed in a cross-sectional study that at school age, decreased lung function was the predominant outcome for children of LBW for age, whereas prematurity led to an increase in symptoms, confirming the longitudinal data of Chan and coworkers.[33] Finally, neonatal death from respiratory causes may itself introduce major selection bias into the analysis of the risk of CLD by removing from the equation the possible major risk factors for the most severe form of CLD.

The analysis of risk should be based on studies of complete populations, using simple clinical variables to avoid bias[34] and appropriate types of statistical analysis to eliminate confusion.[26] It may then be possible to start to predict risk[26,35-38] for early intervention or to identify specific factors with a view to identifying remediable causes of BPD.[18,26,33,34]

The public health burden of CLD has yet to be accurately calculated. Studies revealing that certain percentages of preterm babies cough, wheeze, or require readmission to the hospital are of little intrinsic interest unless they provide information that can be used in planning or calculating the cost of health care provision. Domiciliary oxygen therapy clearly has such implications.[39,40] The effect of therapeutic or preventive regimens using surfactant and corticosteroids on the overall cost of neonatal care has been assessed.[41] The budgetary and ethical results of this study are at variance: It is cheapest to give no antenatal steroids or postnatal surfactant because of the high early mortality rate, but clinically and ethically it is better to use both because the chance for healthy long-term survival is then far greater.

MODELS

The epidemiologic model used for this chapter is represented in Figure 29-1. Its applications have already been discussed. As a framework for understanding the interactions of growth and repair that underpin CLD and are described by techniques in pathology, the evolution of this disorder is considered in four overlapping stages representing early inflammation, its resolution, repair and modeling, and finally lung growth and development (Fig. 29-2). The earliest stages relate to acute neonatal lung disease and its management (see Chapter 28). The evidence to support this general scheme (see section on pathology) is based on a combination of histopathologic data collected in infants who die, supported by cytologic findings from bronchoalveolar lavage in infants whose lungs are ventilated, and by developmental physiology later in life. Animal models have provided support for this analysis.[42]

The value of this model lies not only in its contribution to understanding the pathogenesis of CLD but also in its management. Because the disorder has such a huge clinical spectrum—from fatal cardiorespiratory failure in the neonate to the mildest symptoms and dysfunction in the school child who had a premature birth—and because it covers such a wide age range, therapeutic schemes must be tailored to the various clinicopathologic stages. It is convenient to separate the management of the acute stage in the neonatal unit from the management of CLD in the infant at home. By the end of the first year, when repair and remodeling may be largely completed and growth tracks along the channel thereby determined,[43] management issues again alter, focusing on symptom management and health maintenance rather than potentially preventive measures and health enhancement.

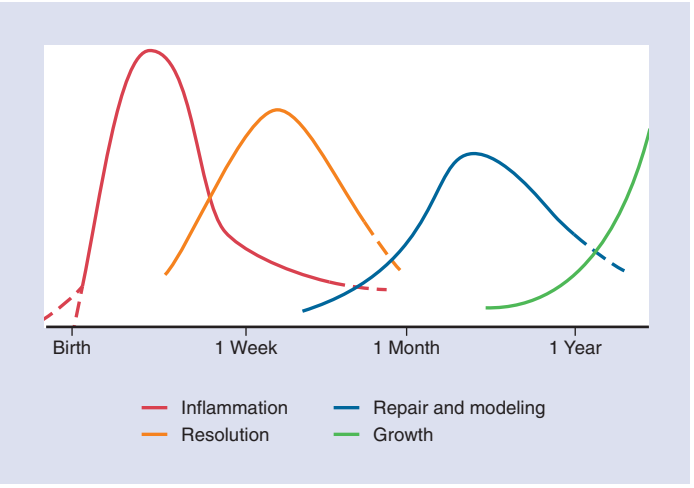
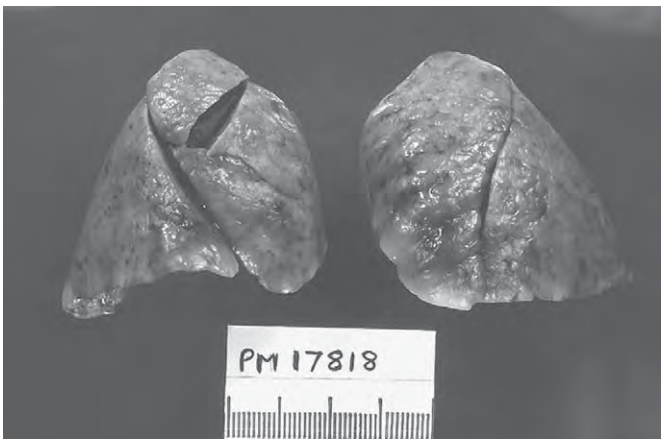


Figure 29-2 Speculative model of the clinicopathologic phases of chronic lung disease (CLD).

Pathology

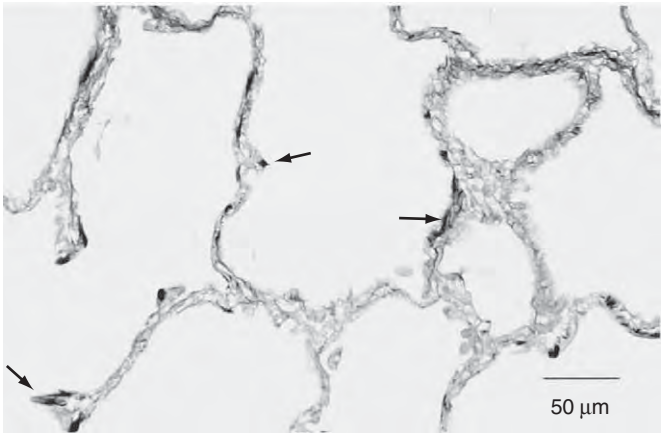
Pathological changes described in infants who have died from respiratory failure have evolved as CLD has changed from a disease of more mature infants to one of extremely preterm infants. Macroscopically, during acute RDS, the lung is firm with a smooth surface that, during the second week, becomes more irregular if CLD is evolving; the lung weighs approximately 25% to 75% more than expected.[44] By the third and fourth weeks, the lung surface has a cobblestone appearance as a result of variable underlying alveolar distention and collapse. As the reparative process progresses, deep fissuring into the lung depths may occur (Fig. 29-3A). The fissuring may resemble the major normal fissures of the lung. During the second year of life, a smooth surface contour returns, with only the deepest fissures remaining.

Histologically, classic BPD was characterized as an early exudative inflammatory phase followed by a subacute fibroproliferative phase of resolution and finally a chronic fibroproliferative phase[44] characterized by growth and remodeling. Microscopically, during the inflammatory phase, the most frequent finding is extensive residual hyaline membranes.[45] During the subacute, fibroproliferative stage of resolution, which occurs from the second to fourth weeks of life, there is progressive replacement of the hyaline membrane with interstitial and perialveolar fibrosis. The septal walls are thickened and myofibroblast proliferation is seen by electron microscopy.[45] Type II pneumocyte hyperplasia lines the



A

B



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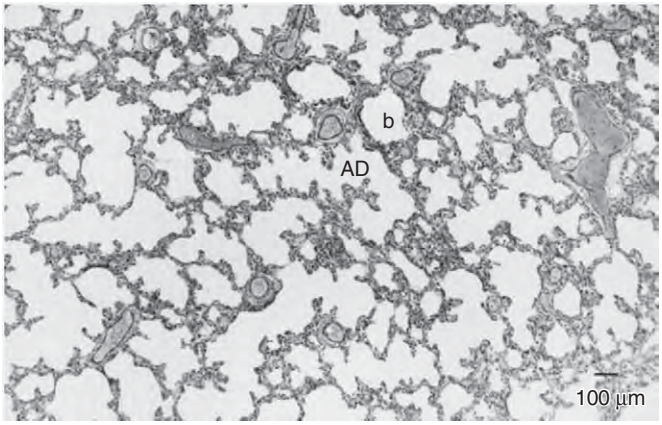


D

Figure 29-3 **A,** Macroscopic appearance of the lungs of a 5-week-old infant with chronic lung disease (CLD) born at 27 weeks' gestation. Note the solid, edematous lungs with nodular surfaces and rib markings secondary to mechanical ventilation. **B,** Lung tissue biopsy showing enlarged airspaces in 8-month-old infant born at 28 weeks' gestation treated with antenatal corticosteroids and postnatal surfactant. Some are alveolar ducts (AD) that show scattered alveolar structures (*arrow*) lacking additional branching, resulting in acinar simplification (hematoxylin-eosin stain). **C,** Same tissue stained with van Gieson elastica that shows a remarkable number of layered elastic fibers within the thinned alveolar walls (*arrows*). Elastic fiber deposition is also seen in the tips of alveolar ducts (*arrows*) and within the alveolar walls. **D,** For comparison, lung tissue from a term +5 month infant showing numerous secondary crests and alveolar structures within the airspaces and alveolar ducts (AD), yielding increased acinar complexity (hematoxylin-eosin stain). (**B** through **D** reprinted from Coalson JJ: Pathology of new bronchopulmonary dysplasia. Semin Neonatol 8:73-81, 2003, with permission.)

restructured alveolar walls. During the ensuing month, remodeling occurs. Hyaline membranes are no longer seen, but interstitial fibrosis of varying severity is evident. Emphysematous areas are interspersed with areas of collapsed alveoli.

More recently with survival of the most preterm infant, the disease process has resulted in less of a fibroproliferative disorder and more of dysregulated lung growth.[46] In particular, far less fibrosis is observed and far more simplified, enlarged alveoli/saccules are prominent (Table 29-3; see Fig. 29-3). The population most at risk of developing CLD is at the 24 to 26 weeks of gestation—this is the canalicular stage of lung growth. Alveolarization occurs at a later date but by being born early, dysregulated lung development occurs. Margraf and coworkers studied eight infants between 24 and 30 weeks of gestation at autopsy and noted a markedly decreased alveolar count for these infants who died between 2 and 28 months of age when compared to control infants who died from nonrespiratory causes between 2 weeks and 4 years of age.[47]

Table 29-3
Evolution of Pathology In Bronchopulmonary Dysplasia

"Old" CLD
• Altered inflation pattern of atelectasis and overinflation
• Severe airway epithelial lesions (hyperplasia, squamous metaplasia)
• Airway smooth muscle hyperplasia
• Extensive fibroproliferation
• Prominent vascular hypertensive lesions
• Decreased internal surface area and alveoli
"New" CLD
• Decreased, large and simplified alveoli (alveolar hypoplasia, decreased acinar complexity)
• Decreased, dysmorphic capillaries
• Variable interstitial fibroproliferation
• Less severe arterial/arteriolar vascular lesions
• Negligible airway epithelial lesions
• Variable airway smooth muscle hyperplasia

CLD, chronic lung disease.
From Coalson JJ: Pathology of new bronchopulmonary dysplasia. Semin Neonatol 8:73-81,2003, with permission.

Many of these studies predate the introduction of antenatal corticosteroids and exogenous surfactant treatment. Husain and colleagues investigated 14 surfactant-treated and 8 untreated lungs at autopsy from infants with CLD and 15 age-matched controls. They reported mild to moderate septal fibrosis but no necrotizing bronchiolitis in the surfactant-treated infants. They also observed simplified dilated alveoli/saccules much in keeping with dysregulated lung growth with abnormal acinar development.[48] In another elegant study by Thibeault and colleagues parenchymal elastic tissue was quantified in control infants and infants with varying severity of CLD.[49] They reported an increase in volume density of parenchymal elastic tissue with gestation in control infants but this was markedly increased in the CLD group, with the increase being greatest in the infants with the highest respiratory scores (integrated area under curve of average inspired oxygen × mean airway pressure). The septal thickness was increased in the most severe form of CLD. Although many of the factors including transcription factors associated with normal lung development are known especially in animal models, our understanding of these factors in the developing human lung is rudimentary and, indeed, almost nonexistent in the injured human preterm lung.

An alternative theory for the dysregulated lung growth seen in infants who develop CLD is that their vascular development may be abnormal, which leads to abnormalities of lung growth. In a series of experiments in rodents, Abman and colleagues demonstrated that chronic inhibition of vascular endothelial growth factor (VEGF) receptors led to pulmonary hypertension, as well as abnormal lung growth.[50] The angiogenic growth factor VEGF is a potent endothelial cell growth and permeability factor and highly expressed in the lung. Expression of different VEGF isoforms and their receptors (Flt-1 and Flk-1) appear to be developmentally regulated, with increased expression toward term coincident with the phase of active microvascular angiogenesis. VEGF and its receptors are significantly decreased in CLD, possibly leading to failure to expand the capillary network. Interestingly, addition of nitric oxide to the rodent model led to improved alveolarization.[51] It is likely that injury to either epithelial cells or endothelial cells will disrupt the normal pattern of lung development and maturation.

In summary, the pattern of acute lung injury observed in the lungs of infants who die from CLD has altered significantly with the survival of the most preterm of infants. The previously observed fibroproliferative disorder is replaced with one of decreased alveolarization, enlarged rudimentary gas exchanging air sacs that appear to undergo dysregulated alveolar growth. Whether these infants will develop clinical emphysema in young adulthood is currently speculative but is of great concern.

Risk Factors

Although the etiology of CLD is unknown, since the earliest description of BPD by Northway,[1] many of the risk factors have been identified. Multivariate analysis has demonstrated that CLD is more common in the extremely premature infant when compared with mature infants, and other independent risk factors include male gender, white race, surfactant deficiency, oxygen toxicity, barotrauma resulting from mechanical ventilation (including air leaks), chorioamnionitis, sepsis, patent ductus arteriosus (PDA), and fluid overload. The significance of many of these risk factors is unknown, but animal models have been used to identify the importance of some. In particular, several groups have focused their attention on the relative importance of oxygen toxicity and barotrauma to the pathogenesis of CLD and, more recently, on the role of antenatal infection in the development of CLD. As discussed earlier, these factors might be important causes of acute lung damage, but with healing by remodeling and growth, the long-term risk of CLD depends on the degree of prematurity and the degree of disruption of the normal pattern of alveolarization in late fetal life and infancy.

OXYGEN TOXICITY

Oxygen has long been recognized as being toxic to the lung. The extents of its effects are determined by its concentration, and the susceptibility of the host. The latter is greatly influenced by the stage of development of the subject. In adults, the administration of 100% oxygen to the lung for prolonged periods leads to the development of acute respiratory distress syndrome (ARDS). An initial destruction of endothelial cells is followed by epithelial type 1 cell necrosis. This results in an alveolar leak, resulting in diffuse exudation of plasma into alveolar spaces. Accompanying this cell injury is the release of proinflammatory cytokines and subsequent recruitment into the lung of inflammatory cells. Release of cytokines such as IL-6 results in a systemic acute phase response. These pathophysiologic changes result in the clinical correlate of ARDS, characterized by severe respiratory failure with diffuse pulmonary infiltrates in the absence of congestive heart failure.[52]

It has long been recognized that neonates of most species are more resistant to the toxic effect of hyperoxia than are adults. Classically in infant CLD, the prematurity, hyperoxia, and ventilator-induced lung injury have been regarded as prerequisite risk factors. This observation has been demonstrated in animal models with the increased survival of newborn rats exposed to 100% oxygen when compared to adult counterparts who all perish within 1 week of exposure.[53]

More recent studies have demonstrated the link between hyperoxia and inflammation in the developing animal lung. Warner and colleagues utilized the newborn mouse as a model of hyperoxic lung injury as alveolar development progresses in the early postnatal period.[54] Exposure of these animals to 85% oxygen for 1 month resulted in 40% mortality. Survivors demonstrated decreased alveolar septation with increased terminal airspaces similar to those found in CLD. Lung lavage studies have shown that hyperoxia results in a neutrophilic infiltrate, peaking 2 weeks after exposure to hyperoxia. Analysis of neutrophil mRNA revealed an upregulation in expression of proinflammatory cytokines IL-1β and macrophage inhibitory protein (MIP-1α).

The association between hyperoxia and CLD is believed to stem from oxidant stress. The increased availability of oxygen results in leaking of reactive oxygen species (ROS) from the mitochondrial electron chain. This oxygen load cannot be dealt with by the immature antioxidant enzyme system present in preterm infants when compared to term infants.[55] The formation of these oxygen radicals also results

from the process of hypoxia/reoxygenation, whereby the conversion of xanthine dehydrogenase to oxidase results in the generation of superoxide.[56] Another source of ROS, once inflammation has been initiated, is from activated neutrophils recruited to the lungs in RDS. Via the NAPDH oxidase pathway, these cells produce and release hydrogen peroxide, superoxide, and hydroxyl radicals.

A number of pathways exist by which ROS exert their effect. A major determinant is the direct toxicity they possess, inherent from their ability to react with cellular constituents. In particular, lipid peroxidation leads to cellular membrane disruption, followed by cellular necrosis. The variety of intracellular constituents released has chemotactic properties, resulting in the recruitment of neutrophils to the lung.[57] Evidence for increased lipid peroxidation in early CLD infants has been demonstrated by Pitkanen[58] by the measurement of the expired lipid by-products, ethane and pentane.

Supplementing the immature antioxidant system of the preterm infant has been attempted using a number of pharmacologic agents including vitamin E, vitamin A, and superoxide dismutase (SOD).[59,60] Vitamin A supplementation has been associated with a modest reduction in CLD among survivors at 36 weeks. However, administration is via repeated intramuscular injections.[61,62] No clinical improvement has been demonstrated after the use of vitamin E in infants less than 1500 g.[59]

Animal studies have shown a reduction in lung injury after intratracheal administration of antioxidants including SOD, alpha-tocopherol, and *N*-acetylcysteine.[63,64] Human studies have demonstrated a reduction in inflammatory mediators with the use of CuZn SOD, but as yet no improved clinical outcomes have been demonstrated conclusively—other than reduced admissions for respiratory illnesses in the first year of life.[65,66] This limited effect may be secondary to limited ability to deliver these agents to the lung. Newer methods of delivery may show promise, in particular, recombinant human CuZn SOD used in combination with a surfactant vector.[67,68]

VENTILATOR-INDUCED LUNG INJURY

In their pathologic description of CLD, Taghizadeh and Reynolds[69] found a significant association between the most severe pathologic changes of CLD and peak inspiratory pressures of more than 35 cm H_2O during mechanical ventilation. Using newborn piglets, Davis and colleagues[70] investigated the relative contribution made to the pathogenesis of CLD by barotrauma and oxygen toxicity. Of the four groups investigated, the groups exposed to 100% oxygen with or without hyperventilation developed the most significant lung injury. Animal lungs normally ventilated in air developed no injury, and the group hyperventilated in air developed intermediate lung injury. The conclusions are that hyperoxia causes the most significant inflammatory and histologic changes but the barotrauma alone may also result in a lesser degree of lung injury. However, the importance of barotrauma to the development of CLD is provided by several studies. Premature lambs whose lungs were supported by mechanical ventilation developed more severe lung injury than lambs allowed to mature while supported by their placentae.[71] Similarly, using preterm lambs, Penn and coworkers[72] have demonstrated the susceptibility of tracheal segments to mechanical ventilation. Because bronchomalacia is one of the long-term adverse outcomes of CLD, this form of barotrauma could be very important. It is likely that the smaller airways are similarly affected by mechanical ventilation. It may be that volutrauma may be more important than barotrauma as suggested by Hernandez and colleagues, who limited chest wall expansion (volume) by plaster casting the chest walls and noted that increased volutrauma may cause significantly more lung injury than barotrauma.[73] Acute lung injury may even commence at birth owing to volutrauma from inflationary breaths because five sustained breaths at 8, 16, and 32 mL/kg resulted in a dose-dependent lung injury in preterm lambs.[74]

Many studies of different ventilatory modes have shown improved physiologic outcome, but systematic review of such trials has failed to identify any ventilatory method that has a significant impact on CLD. Interpretation of ventilation trials is complicated by differing uses of ventilatory modes because this may affect their efficacy. For example, high frequency oscillatory ventilation (HFOV) has been used either with a low-volume strategy in which pressures are minimized to decrease lung injury or a high-volume strategy to optimize alveolar recruitment. Meta-analysis of the results of eleven trials in which infants were randomized to receive HFOV or conventional ventilation in the first 24 hours after birth has shown that HFOV is associated with modestly decreased CLD.[75] Some ventilatory modes have not undergone such rigorous testing. CPAP is often used in preference to mechanical ventilation, which necessitates tracheal intubation. Decreased lung injury has been documented in a baboon model using CPAP, but only small clinical studies have addressed this question.

ANTENATAL AND POSTNATAL INFECTION

Chorioamnionitis, the histologic inflammation of the placenta, is common in mothers who deliver prematurely.[76] The presence of chorioamnionitis has been reported to be protective against the development of RDS[77] but is a significant risk factor for the development of CLD and also of cerebral palsy.[78] Although only 30% of preterm infants with RDS had histologic evidence of chorioamnionitis compared to 82% without RDS, 63% exposed to chorioamnionitis developed CLD compared to 21% who were not.[79] It appears that the destiny to develop CLD is triggered in utero, as shown by the observation of Yoon and associates of increased proinflammatory cytokines in the amniotic fluid of women who deliver preterm infants who develop CLD when compared to preterm deliveries in which the infant does not develop CLD.[80]

The importance of antenatal inflammation in the development of CLD has been demonstrated using animal models. Intra-amniotic injection of *Escherichia coli* endotoxin to pregnant ewes has been shown to cause chorioamnionitis and, subsequently, lung inflammation with increased inflammatory cytokines in the newborn preterm animal.[81] Once delivered, these newborn preterm lambs develop less RDS, have better lung compliance, and increased surfactant proteins when compared to control animals. In spite of such improvements, the lung histology showed decreased alveolarization with fewer but larger alveoli when compared to control animals. In addition, preterm lambs born to mothers exposed antenatally with intra-amniotic endotoxin generated a greater

inflammatory response when mechanically ventilated compared to ventilated unexposed control animals. These findings suggest that antenatal inflammation is effective in rapidly maturing the fetal lung and, in particular, upregulating surfactant production, resulting in reduced incidence of RDS. However, this is at the expense of decreased alveolarization. Antenatal inflammation may also prime the preterm lung to respond with increased lung injury when subjected to mechanical ventilation and/or oxygen therapy.

An organism that has received particular attention in the development of CLD is *Ureaplasma* spp. *Ureaplasma* spp in humans is found on mucosal surfaces, primarily of the respiratory and urogenital tracts. It is present in the lower genitourinary tract of 40% to 80% of women of child-bearing age and is vertically transmitted to the fetus in 46% to 89% of cases—with the highest transmission rates being among preterm infants.[82] *Ureaplasma* spp colonization of the preterm lung has been associated with the development of CLD with a relative risk ratio of nearly 3 in a recent publication by Schelonka and colleagues[83]; unfortunately, an adequately randomized controlled trial to determine if eradication of *Ureaplasma* colonization of preterm lungs decreases the rate of CLD has not been performed.[84,85]

Postnatal infection has also been implicated in the pathogenesis of CLD. A study of 119 ventilated preterm infants with a birth weight less than 1000 g reported systemic sepsis to be a risk factor for CLD.[86] Of the 64 infants who had a positive blood culture with clinical or laboratory signs of sepsis, 35 (55%) developed CLD, compared to 9 (16%) without sepsis (odds ratio 4.4). This study also reported that a patent ductus arteriosus was a significant risk factor for CLD (odds ratio 6.2). If both these risk factors were combined, the odds ratio markedly increased to 48.4. Nosocomial infection such as *Staphylococcus epidermidis* has also been associated with the development of CLD with 64% of infants with *S. epidermidis* sepsis developing CLD compared to 24% of controls.[87] Ventilated preterm neonates frequently have endotracheal secretions colonized with gram-positive bacteria, particularly *S. epidermidis*. In some cases gram-negative bacilli, such as *Klebsiella pneumoniae, Enterobacter cloaca,* and *E. coli* can also colonize endotracheal secretions. Such colonization has been reported to significantly increase the incidence of CLD.[88]

Viral infections, particularly with adenovirus or cytomegalovirus (CMV), have been implicated in the development of CLD. Sawyer and coworkers identified 32 infants born with a birth weight less than 2000 g as being infected with CMV over a 5-year period.[89] Of these, 24 (75%) went on to develop CLD compared to 12 of 32 (38%) matched controls. It was believed that the CMV infection was acquired postnatally. Although adenovirus has been implicated in the development of CLD, it has not yet been confirmed by other groups.[90]

PATENT DUCTUS ARTERIOSUS AND FLUID OVERLOAD

An association has been noted by many workers between PDA and CLD.[91-93] The presence of a PDA has been associated with pulmonary inflammation—possibly via increased pulmonary blood flow.[94] However, a controlled, randomized study of prophylactic ligation of PDA did not demonstrate a significant improvement in oxygen dependency.[95] A multicenter, multivariate, risk-adjusted, case-control study reported an association between an increased fluid intake within 96 hours of birth and oxygen dependency at 30 days of age.[96] Similarly, in their prospective study, van Marter and associates[92] compared the medical practices of three different centers managing preterm infants with birth weights less than 1751 g. They reported that the center with the highest incidence of CLD administered higher-than-expected rates of colloids during the first 4 days of life. It has been proposed that increased fluid intake, either by direct means or by an increase in the incidence of PDA, may worsen any coexistent pulmonary edema, thereby reducing pulmonary compliance. The subsequent increase in ventilatory requirements, including oxygen toxicity and barotrauma, may further exacerbate the ongoing acute lung injury. However, when Lorenz and colleagues[97] randomized 88 infants weighing 750 to 1200 g to receive either low or high fluid intake, no difference was noted in the relative incidence of CLD between the two groups. Similarly, Kraybill and coworkers[26] did not find an association between the development of CLD and weight loss, furosemide, or pancuronium therapy in 147 surviving infants weighing 751 to 1000 g.

OTHER RISK FACTORS

The incidence of CLD is related to the gestational age of premature infants, with the incidence increasing as gestation decreases. However, because not all premature infants develop RDS or CLD and near-term infants may develop CLD, it appears that the immaturity of the lungs predisposes the infant to the development of CLD. It is, therefore, not surprising to note an association between infants with LBW and CLD because these are the infants most likely to have immature lungs. For reasons that are unclear, male infants are more prone to both RDS and CLD. Similarly, the incidence of CLD is decreased in people of color. Both gender and race are independent factors for the development of CLD. An increased incidence of CLD has been reported in infants from families with atopy.[98-100] This association was not confirmed by Chan and colleagues.[101]

Another area receiving attention is the role of genetic factors in the development of CLD. Many polymorphisms especially of surfactant proteins, pro- and anti-inflammatory cytokines, and of growth factors are being investigated. A recent study showed that twin preterm infants are at increased risk of developing CLD and that genetic factors may play a large part in the development of CLD.[102]

Pathogenesis

Animal models and lung lavage studies in human preterm infants have established a vast array of data of cells, cytokines, and growth factors for infants who develop CLD.[103] Often the significance or importance of such findings is unclear. Techniques to look at evidence for inflammation in living human preterm infants have relied principally on bronchoalveolar lavage (BAL). This methodology involves the instillation of saline via a catheter wedged into a lobar bronchus followed by the aspiration of terminal airway and alveolar contents.[104,105] This contrasts with the technique of tracheal aspiration, which predominantly samples the larger proximal airways. As with histologic samples, an inflammatory infiltrate has been repeatedly demonstrated in BAL from preterm

infants with lung disease. It has consistently been shown that persistence of neutrophils in the lung beyond 7 to 10 days of age is associated with the development of CLD (Fig. 29-4).[106-108] Although there were no differences in lymphocyte numbers noted in the study by Murch and coworkers, activated macrophages denoted by expression of the RM/3-1 marker were similarly found to be increased in the BAL of babies with CLD, peaking at 1 week of age and subsequently reducing in numbers over the following weeks.[107] This contrasted with neutrophil numbers in the same lavage samples, whereby progressive CLD was marked by an excess number of neutrophils over macrophages. This supports earlier work demonstrating an increased presence of macrophages at 96 hours in babies with uncomplicated RDS, as well as those with developing CLD, but with a relative paucity in macrophages in CLD patients at 4 weeks of age.[109]

Neutrophil recruitment is followed by resolution of lung injury by the recruitment of alveolar macrophages and of removal of senescent neutrophils by the process of apoptosis or programmed cell death. Alveolar macrophages, the cells of resolution, commence the process of repair and remodeling and also remove apoptotic neutrophils. Recent observations show that neutrophil apoptosis is delayed in the lungs of infants who develop CLD. There is some evidence to show that this delayed neutrophil apoptosis may be related to the gestational age of the preterm infant who is at most risk of developing lung injury.

The migration of neutrophils to the area of injury is mediated by a series of processes (Fig. 29-5). The adherence of neutrophils to the endothelial wall by attachment of the neutrophil ligand L-selectin, to P- and E-selectins expressed on endothelial surfaces, produces slowed movement of neutrophils at these vessel sites, termed *rolling*. The expression of L-selectin by endothelial cells is upregulated at inflamed areas owing to the effect of TNF-α and IL-1. Subsequent firm adherence of neutrophils and migration across the endothelium is partly mediated by the β_2-integrins (e.g. CD11b/CD18), which are upregulated on the neutrophil surface after activation, usually in response to IL-8. The β_2-integrins attach firmly to the receptor, ICAM-1 (intercellular adhesion molecule) expressed on endothelium.[110] In addition, the lipid mediators platelet activating factor (PAF) and leukotriene B4 (LTB4), together with complement, all of which are produced as part of an inflammatory response, act to increase vascular permeability.

Initiation of the inflammatory response is mediated by the proinflammatory cytokines TNF-α, IL-1 and IL-6. TNF-α, which possesses the ability of promoting the expression of IL-1β and IL-6, can be produced in response to infective agents via LPS, or injurious agents such as ventilator-induced lung injury or hyperoxia. Antenatal inflammatory response is believed to be related to infection in the amniotic fluid by

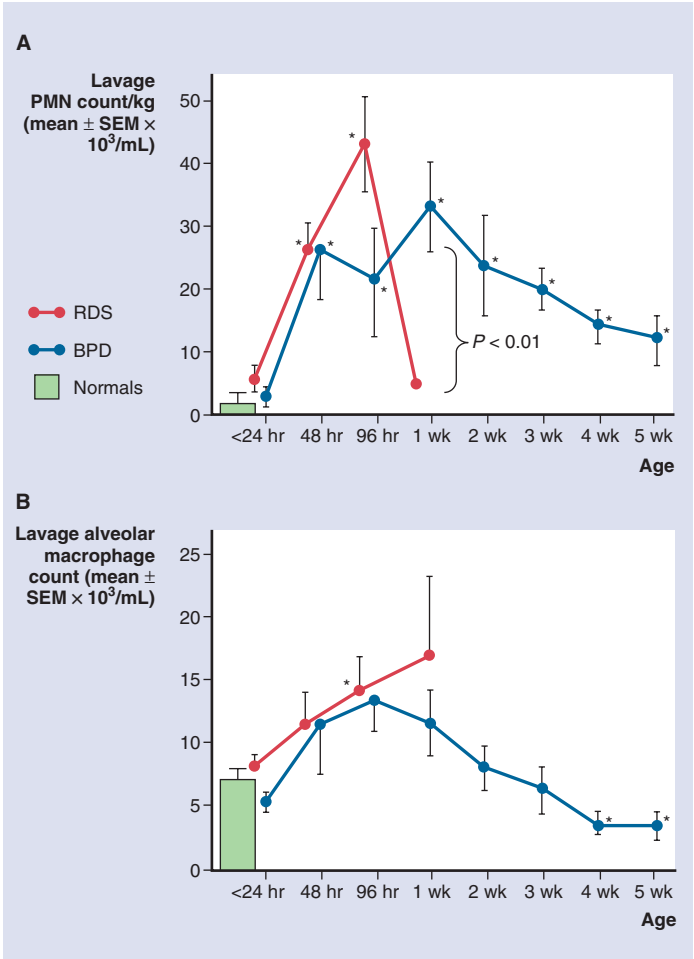


Figure 29-4 **A,** Absolute neutrophil (PMN) count divided by body weight in kilograms (mean ± standard error of the mean [SEM] (×200) 10^3/mL) at each lavage. **B,** Absolute alveolar macrophage count (mean ± SEM ± 10^{-5}) at each lavage. Asterisks indicate significant difference from normal control subjects ($P < 0.05$) by analysis of variance and Duncan's multiple range test. (Redrawn from Ogden BE, Murphy SA, Saunders GC, et al: Neonatal lung neutrophils and elastase/proteinase inhibitor imbalance. Am Rev Respir Dis 130:817-821, 1984.)

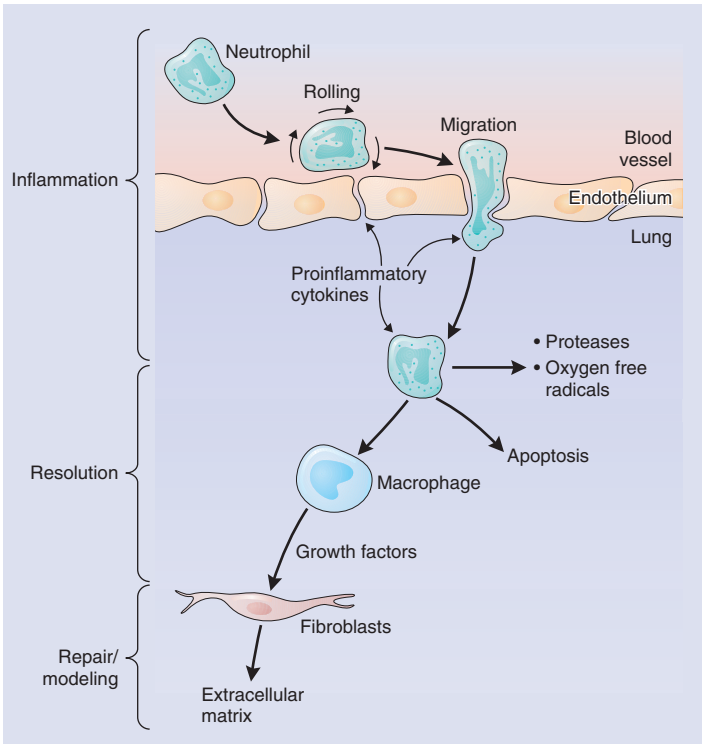


Figure 29-5 Speculative model for the pathogenesis of chronic lung disease (CLD) at the cellular level.

organisms such as *Ureaplasma urealyticum*, which have been linked to the development of CLD,[111,112] in particular the *new* form of CLD, which can occur in the absence of hyperoxic insult. Raised concentrations of TNF-α in BAL from patients who developed CLD have been found at 14 days of age, but have also been described as early as 3 days of age—with increased presence of immunoreactive cells in BAL.[113-115] IL-1 has been shown to be predictive of CLD in the first week of life.[114,116-118]

IL-8 is a neutrophil chemoattractant and has been consistently demonstrated to be raised in association with CLD when compared to infants who recover from RDS. We noted a significant rise in IL-8 BAL concentration at 10 days in CLD,[108] findings supported by Groneck and coworkers[119] and Baier.[120] Munshi noted a significant rise in IL-8 in babies with RDS progressing to CLD as early as 1 to 3 days postnatally.[121] Differences may be partly explained by the use of tracheal aspirates rather than bronchoalveolar lavage, resulting in sampling from central airways rather than distal lung.[122] The accumulation of IL-8 appears predominantly confined to the lungs. Serum concentrations of IL-8 do not appear to differ between CLD and RDS subjects and are an order of magnitude below lavage concentrations.[108]

The proinflammatory cascade is regulated to prevent an uncontrolled inflammatory response. In part, this is provided by the presence of a group of anti-inflammatory mediators that provide a counterbalance to the proinflammatory agents. These include IL-4, IL-10, IL-13, transforming growth factor-β (TGF-β), soluble TNF-α receptors (sTNFR1 and R2) and interleukin 1 receptor antagonist (IL-1RA). There appears to be an inadequate anti-inflammatory response to the proinflammatory cytokines in the development of CLD; whether this is, in part, due to gestational immaturity of the infants most at risk of developing CLD is unclear.

The activity of recruited neutrophils has been estimated by study of their released local effectors, principally elastase (see Fig. 29-5). The proteolytic properties of this enzyme are likely to impair the septation process in the lung necessary for normal alveolar development. The activity of elastase is counterbalanced by the presence of alpha$_1$-antitrypsin (alpha$_1$-AT). At birth, the ratio of elastase and alpha$_1$-PI in the BAL of normal controls and infants with RDS is similar. In infants who progress to develop CLD, however, a raised elastase/alpha$_1$-AT ratio develops within the first 48 hours of life and is maintained for several weeks.[109] This reflects increased elastase production by neutrophils, reduced macrophage contribution to the alpha$_1$-AT pool, and inactivation of alpha$_1$-AT by the oxidizing effect of toxic oxygen radicals.[123] Matrix metalloproteinases (MMPs) are a specialized subgroup of proteinases that form an important link in controlling tissue degradation during lung injury. A relative increase on MMP-9/tissue inhibitor of metalloproteinase (TIMP)-1 with decreased TIMP-1 has been noted in the tracheal fluid of infants who develop CLD.[124]

TGF-β has been associated with the development of CLD. Studies have demonstrated an increased presence of TGF-β protein in lavage from the lungs of infants who develop CLD within the first week of life.[125] These remain elevated in chronically ventilated babies with a need for home oxygen.[126] Physiologic release of TGF-β is intended to be short-lived, however, the maintenance of an inflammatory stimulus (e.g., hyperoxia, infection) leads to an exaggerated response that is perpetuated by the ability of TGF-β to stimulate its own secretion.[127]

Other growth factors such as epidermal growth factor (EGF), platelet-derived growth factor (PDGF), keratinocyte growth factor (KGF), and vascular endothelial growth factor (VEGF) have also been implicated in the pathogenesis of CLD. VEGF is of particular interest because it promotes vascular endothelialization. Chronic inhibition of vascular endothelial growth factor (VEGF) receptors led to pulmonary hypertension, as well as abnormal lung growth.[128] Expression of different VEGF isoforms and their receptors (Flt-1 and Flk-1) appear to be developmentally regulated, with increased expression toward term coincident with the phase of active microvascular angiogenesis. VEGF and its receptors are significantly decreased in CLD, possibly leading to failure to expand the capillary network. Interestingly, addition of nitric oxide to the rodent model led to improved alveolarization.[129] It is likely that injury to either epithelial cells or endothelial cells will disrupt the normal pattern of lung development and maturation.

CLINICAL FEATURES AND COURSE OF CHRONIC LUNG DISEASE OF PREMATURITY

Newborn Unit

In infants in whom classic BPD evolves, Northway[1] recognized four stages of clinical, radiologic, and pathologic change. Stage I is typified by the clinical, radiologic, and pathologic features of RDS (see Chapter 28). During stage II, which occurs during days 4 to 10, either the infant's respiratory status improves or the condition progresses to stage III. In infants who recover from RDS, a reduction in inspired oxygen levels, peak inspiratory pressures, and minute volume is possible. After weaning from mechanical ventilation and a variable period of supplemental oxygen (most frequently administered via a head box or, if prolonged, by nasal cannulas), the infant is weaned to room air. In infants whose condition does not improve, the lungs become less compliant, and ventilatory requirements may increase. Pulmonary interstitial emphysema and other air leaks, including pneumothorax and pneumomediastinum, may develop. The chest radiograph shows increasing opacification with or without air leaks. In infants who die during this stage, thick exudation into the airways with patchy bronchiolar and alveolar epithelial cell necrosis is seen at autopsy.

During stage III, occurring between the second and third weeks of age, the infant remains oxygen dependent. The respiratory status may slowly improve or progress to respiratory failure, particularly if it is complicated by chronic pulmonary interstitial emphysema, infection, or hemodynamically significant PDA. Compensated respiratory acidosis and hypoxemia are noted from the results of arterial blood gas tests. The chest radiograph shows cystic emphysematous areas interspersed with areas of reticular strands, atelectasis, and consolidation. Histologically, at autopsy, areas of emphysematous alveoli are seen adjacent to areas of atelectatic alveoli. Healing commences, and the necrotic bronchial and bronchiolar epithelial cells are replaced by mucosal metaplasia and hyperplasia.

In stage IV, occurring after 4 weeks of age, the infant is in stable or progressive respiratory failure. An infant whose respiratory status is stable is weaned from mechanical ventilation and supplemental oxygen over the ensuing weeks and months; many of these infants require long-term domiciliary supplemental oxygen. However, in an infant whose condition continues to deteriorate, ventilatory needs increase, requiring increased amounts of inspired oxygen, peak inspiratory pressure, and minute volume. The condition may be complicated by right-sided heart failure and pulmonary hypertension. The prognosis is poor. The chest radiograph usually demonstrates persistent CLD with hyperinflated and cystic lungs, particularly in the lower lobes, and in the most severe cases, striking areas of atelectasis and scarring. The pathologic features have been described.

In many infants with "new" CLD who remain oxygen dependent, the radiograph does not have the classic appearance of stage IV disease. More frequently the chest radiograph shows homogeneous or patchy, ill-defined pulmonary opacities lacking any coarse reticulation ("small gray lungs"). This radiographic appearance has been classified as type I CLD with type II disease, showing similar radiographic changes to Northway's stage IV bronchopulmonary disease[5] (Fig. 29-6). This simpler classification is useful at 1 month of age because type I disease has a better prognosis than type II disease, which more frequently follows pulmonary interstitial emphysema. Many other radiographic features, including segmental atelectasis resulting from mucus plugging and upper lobe shadowing secondary to repeated aspiration, are commonly seen (see Fig. 29-6).

Infant and Preschool Child

A useful and practical definition of CLD is a simple one of oxygen dependency at 36 weeks' corrected gestation.[3] Therefore, the typical infant diagnosed as suffering from CLD is usually a preterm infant who has needed supportive mechanical ventilation, including supplemental oxygen, during the neonatal period for RDS. Clinically, features of obstructive airway disease are often evident. An abnormally increased respiratory rate with retractions and a variable degree of hypoxemia (in air) are noted. The arterial P_{CO_2} may be raised. At discharge, these infants may require domiciliary oxygen. The infant may feed poorly, and weight gain is usually inadequate. Vomiting and GER are common. The chest radiograph may show changes compatible with CLD, including cystic, consolidated, fibrotic, and atelectatic areas or may simply show "small gray lungs" (see Fig. 29-6A). Pulmonary function tests demonstrate an increased airway resistance, low dynamic compliance, and a variable thoracic gas volume with gas-mixing inefficiency (see later section). Echocardiography may demonstrate right ventricular hypertrophy with evidence of pulmonary hypertension and tricuspid regurgitation.

The differential diagnosis of obstructive airway disease in infancy is dealt with in Chapter 10. In addition to intrathoracic disorders, the differential diagnosis includes a number of upper airway disorders such as laryngomalacia and tracheomalacia, subglottic stenosis, laryngeal webs, vascular rings, and enlarged tonsils and adenoids.[130,131] Surgical procedures on the upper respiratory tract were performed in 30% of VLBW infants in one study.[131]

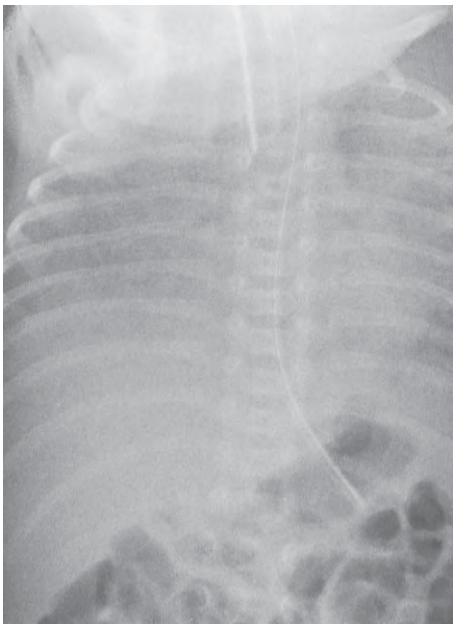
Exacerbations of respiratory symptoms are common in infants born prematurely, especially those with CLD. Potentially, the most serious exacerbating factor is viral infection. In a series of 40 infants who were born prematurely and who needed mechanical ventilation for respiratory insufficiency, 70% had one or more episodes of pneumonia or bronchitis during the first 2 years of life.[132] A direct relation was noted between the presence of CLD and respiratory infections. In a 4-month prospective study of children younger than 2 years of age with CLD, 27 of 30 children had one or more respiratory illnesses.[133] Respiratory syncytial virus was isolated from 59% of the children, and 70% of these required hospitalization. Adenovirus is particularly troublesome because it may result in bronchiolitis obliterans, which may make CLD irreparable. A full immunization program, including the recommenaded use of monoclonal antibody against RSV (palivizumab) and immunization against influenza, is vital for preterm infants. Other causes of exacerbations include aspiration events, heart failure, and "wheezy" episodes. Apneic events or sleep-disordered breathing with hypoxemic spells frequently complicate the situation.

Sudden infant death has been reported more frequently in infants with BPD. A recent population-based study showed that the proportion of SIDS attributable to prematurity increased from 12% to 34 %.[134] One small study suggested an odds ratio of 8 (11% mortality) in comparison with healthy infants weighing less than 1000 g at birth.[135] In the author's experience of 100 very severe cases of CLD in which the infants were dependent on domiciliary oxygen therapy, one infant died suddenly and unexpectedly. In a multicenter trial of corticosteroids for CLD, there was a 3.4% mortality (7 of 209) from sudden unexpected death in infancy.[136]

Adolescent and Adult

A large number of infants with CLD who survive to childhood, adolescence, and adulthood have some degree of pulmonary dysfunction. Most studies of these populations are biased by extreme selectivity, inadequate control data, and small numbers. Yu and associates[137] studied 16 survivors of CLD at a mean age of 8.4 years (range, 7.2 to 9.6 years) and reported an 81% prevalence of wheezing. Respiratory symptoms are most troublesome in the preschool years and seem to decline thereafter.[138] One study of a population-based cohort of 120 LBW children and 100 full-term controls studied at the age of 7 years found troublesome cough with colds to be the only persistent symptom[33]; wheeze was no longer a problem. Exercise tolerance has been studied in small numbers of children. "Normal" preterm children have no limitation,[139] but 10-year-old survivors of BPD are commonly reported to develop exercise-induced asthma, hypoxemia, and hypercapnia.[140] This was further supported by Halvorsen and colleagues, who reported increased use of bronchodilators, decreased FEV_1, and increased bronchial hyper-responsiveness in young adults (mean age 17.7 years) who had CLD in infancy.[141]

Most adult survivors of CLD have a degree of pulmonary dysfunction, including hyperinflation, airway obstruction, and airway hyper-responsiveness.[2] However, LBW infants who never had any neonatal respiratory abnormalities have a degree of respiratory dysfunction when they reach middle



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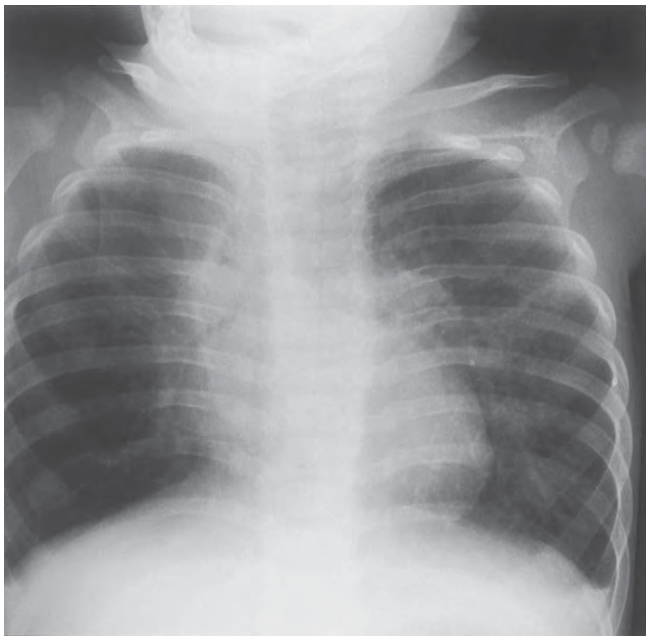

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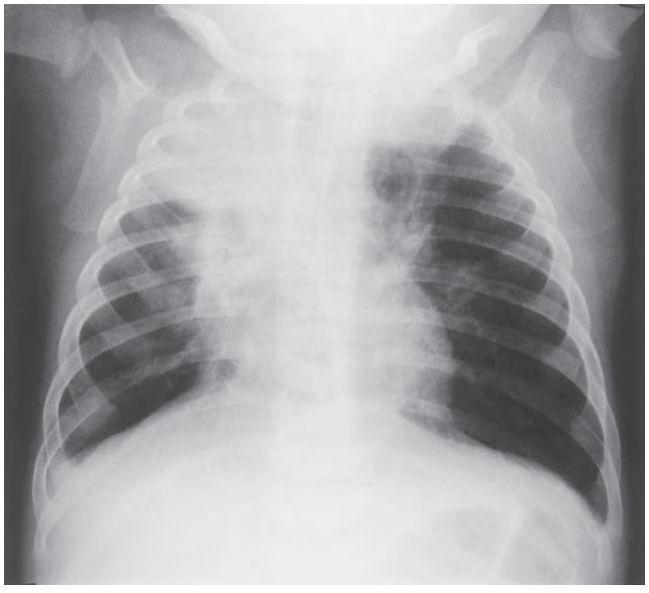

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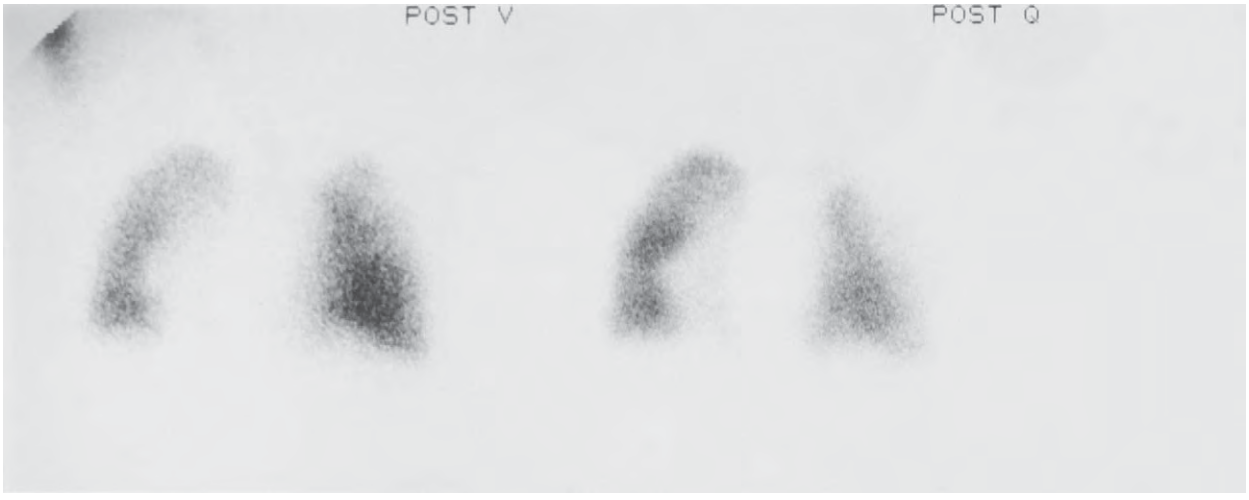


D

Figure 29-6 Chest radiographs in chronic lung disease (CLD) of prematurity. **A,** Type I CLD (small gray lungs) in an infant born at 27 weeks' gestation who is 4 weeks of age. **B,** Type II CLD with classic changes in a very low birth weight (VLBW) infant at 2 weeks of age. **C,** Segmental atelectasis *(right upper lobe)* resulting from mucus plugging in an infant born at 27 weeks' gestation who is 4 months of age. **D,** Patchy, matched defects of ventilation ($\dot{V}$) by krypton-81m inhalation and perfusion ($\dot{Q}$) by technetium-99m infusion in a child with severe CLD. POST, posterior view.

childhood.[27-30,130] Lung function tends to improve with age, however.[27] The long-term outcome is unknown, but recent evidence linking fetal and infantile somatic and pulmonary development with CLD in adulthood suggests that chronic airway disease with accelerated aging processes may be in store for infants with CLD.[142,143]

ACQUIRED UPPER RESPIRATORY TRACT COMPLICATIONS

Disorders of the intrathoracic airways are important and common in infants with CLD. They include subglottic stenosis, laryngeal granulomas, laryngomalacia and tracheomalacia, vocal cord paralysis, and laryngeal perforation resulting from direct endotracheal tube trauma. In one series of 196 bronchoscopies in 132 neonates with respiratory complications, the most common findings were laryngomalacia or tracheomalacia (24%), tracheal obstruction resulting from stricture or granulation tissue (17%), obstructive mucus plugs (17%), tracheobronchitis (8%), and laryngeal perforation (2%).[144] Vocal cord paralysis secondary to thoracic surgery should be considered.

The true incidence of subglottic stenosis is unknown and probably varies according to local practice. In one study, it was reported in 5 from 845 newborns who required artificial ventilation.[145] Arguments rage concerning the cause of upper airway damage. Direct laryngeal and tracheal trauma is likely to lead to shedding of the respiratory epithelium with subsequent re-epithelialization and squamous metaplasia, scarring, and contraction (Fig. 29-7).[44,146]

Large airway damage includes stricture, granuloma, cyst formation, and excessive collapsibility resulting from bronchomalacia.[147-149] A number of animal studies show how airway collapsibility (compliance) decreases with age.[150] Airway collapsibility may be exacerbated by bronchodilators, which reduce airway smooth muscle tone, and conversely stabilized by active smooth muscle contraction induced by methacholine.[137] There are major species differences. Tracheomegaly may result from positive pressures applied to compliant airways, possibly exacerbated by using bronchodilators at earlier stages of disease.

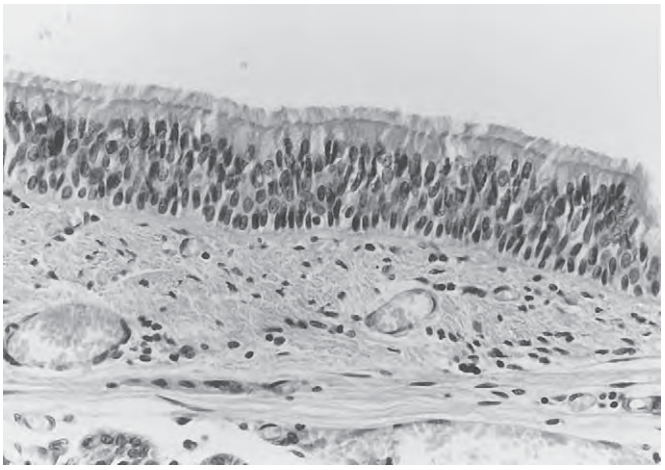
The management of upper airway pathology may require lateral neck and chest radiographs, barium swallow, MRI scans and echocardiography to exclude extrinsic obstructive lesions, and direct visualization by laryngoscopy or bronchoscopy to identify specific abnormalities. Tracheobronchography with dilute, nonionic contrast medium is a safe procedure but less frequently used. In the infant whose lungs are intubated, weaning may be facilitated by a 24-hour course of corticosteroids. Postextubation stridor was reduced in a double-blind trial, with a suggestion that late subglottic stenosis was reduced.[151] Management of subglottic stenosis remains controversial, but the experience in Liverpool, United Kingdom, suggests that conservative treatment with tracheostomy achieved success in 73% of patients; corrective surgery and laser treatment are reserved for the more difficult cases.[152] Tracheobronchial stenosis is less amenable to effective treatment.[153]

EXTRAPULMONARY COMPLICATIONS

Growth and Nutrition Problems

Several controlled and uncontrolled studies have demonstrated suboptimal growth in survivors with CLD. Although weight and length are appropriate for gestational age at birth, they are commonly at or below the third percentile at 40 weeks' corrected gestation. As the pulmonary status improves, accelerated growth is seen in infants who recover from CLD. Infants with CLD may fail to grow satisfactorily because of increased work of breathing, hypoxemia, GER, poor feeding with inadequate nutritional intake, heart failure, neurodevelopmental handicap, and socioeconomic factors (including inadequate parenting skills and emotional deprivation).

Hypoxemia appears to be particularly detrimental to growth in infants with CLD. Groothuis and coworkers[154] noted that when oxygen was abruptly and inadvisably discontinued by the parents of 7 infants, weight gain dramatically



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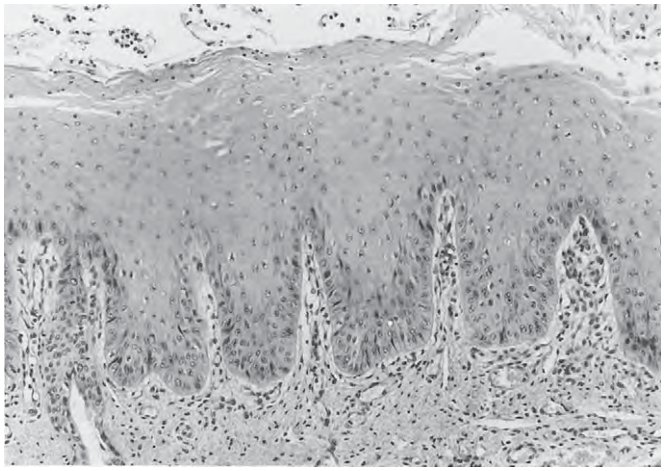

B

Figure 29-7 **A,** Photomicrograph showing grade 0, normal, ciliated tracheal epithelium (hematoxylin-eosin stain). **B,** Photomicrograph showing grade 4, mature, keratinizing, stratified squamous epithelium that is markedly thickened. It was taken from an infant with severe chronic lung disease (CLD) (hematoxylin-eosin stain).

decreased to a mean of 1.4 g/day compared with 16.0 g/day in 15 infants who continued to receive supplemental oxygen. Growth restarted when oxygen recommenced, but infants failed to catch up with their peers. Although the BOOST trial did not find retarded growth in the lower range of oxygen saturations (91% to 94% versus 95% to 98%), it remains to be seen if this still holds true for oxygen saturations of less than 90%.[155] Factors other than hypoxemia are important because under other circumstances (e.g., cyanotic congenital heart disease), growth may be satisfactory with lower values of oxygen saturation than values that occur in CLD.

Infants with CLD have increased energy expenditure, particularly resulting from increased work of breathing secondary to abnormal lung mechanics. Improved growth may be obtained by increasing the caloric intake of these infants and, if necessary, by increasing the caloric density of their food. Vomiting, heart failure, and feeding difficulties may contribute to undernutrition and growth failure.

Gastroesophageal Reflux

GER, which is common in infants with CLD, has recently been extensively reviewed by Vandenplas.[156] It may manifest by obvious vomiting, poor feeding, failure to thrive, or irritability, but in some cases, even mild possetting is absent. Pulmonary effects include deteriorating lung function, hypoxic spells, and overt radiographic evidence of aspiration. Other complications may include anemia, hematemesis, esophageal stricture, laryngospasm, chronic stridor, and apnea.[157-159] Hrabovsky and Mullett[153] demonstrated that symptoms were usually evident by 4 to 6 weeks of age and that 14 of 22 infants with CLD (64%) had GER. An improvement in growth and a decrease in oxygen requirement were noted in infants with CLD who had surgery for symptomatic GER.[160,161]

Esophageal pH monitoring for 24 hours and radionuclide scan on occasion are the most useful investigations for diagnosing GER.[162] Barium swallow and meal should be performed if mechanical obstruction is suspected. Hypertrophic pyloric stenosis is, for example, more common in preterm than in term infants. Examining the bronchoalveolar lavage fluid for lipid-laden macrophages is of limited value.

Cardiovascular Complications

Heart failure is common in infants with CLD and is often overlooked. Contributory factors include pulmonary hypertension, right and left ventricular hypertrophy, right-to-left shunting through the foramen ovale (particularly as the right atrial pressure rises as a consequence of pulmonary hypertension), and systemic hypertension. Persistent PDA often complicates the early course of CLD and contributes to respiratory failure. A high index of suspicion is required in these patients because there are many similarities between exacerbations of pulmonary dysfunction resulting from infection and those resulting from cardiac failure and because one condition may lead to the other. Poor feeding, tachypnea, increased oxygen requirements, and inappropriate weight gain may be present. Hepatomegaly is a late sign and is difficult to elicit in infants with obstructive airway disease. Treatment with additional supplemental oxygen, fluid restriction, and diuretics may be necessary.

The possibility that unsuspected congenital heart disease may predispose to CLD should always be considered.[163] Of the author's 75 patients with severe CLD who were dependent on domiciliary oxygen therapy, 2 had structural heart disease requiring surgical procedures within the first year of life. In both cases, clinical status improved markedly in the postoperative period. Another factor in the development of pulmonary hypertension in CLD is the presence of systemic pulmonary shunt vessels, which have been described by two groups.[164,165] Histologically, these have been demonstrated as dilated bronchial arteries.[166] The relevance of these vessels is unclear, as is the appropriate means of management.

Pulmonary hypertension is the most important cardiovascular complication of CLD. It can lead to cor pulmonale, which was in the past a major cause of death in CLD. There are two components: variable oxygen sensitive (hypoxic) vasoconstriction and a relatively fixed component. Recent observations suggest that even in the presence of high concentrations of inspired oxygen, a further variable element can be uncovered by the use of inhaled nitric oxide. The underlying structural basis for pulmonary hypertension has been described by Hislop and colleagues[167] and Hislop and Haworth.[168] At the severe end of the spectrum, treatment with prostacyclin, nitric oxide, sildenafil, and calcium blockers may be tried but has variable success.

Noninvasive diagnostic methods of investigation include echocardiography with continuous-wave Doppler flow measurements and (rarely) radionuclide angiography. Cardiac catheterization is risky and should be performed only if required for the diagnosis of structural disease or a life-threatening complication.

In the past, M-mode echocardiography was extensively used to investigate the natural history and management of pulmonary hypertension in CLD.[169,170] Halliday and colleagues[169] established the importance of an oxygen-sensitive element to pulmonary hypertension, with a clear implication that adequate oxygenation was an important aspect of management. Abman and coworkers[171] used cardiac catheterization to study oxygen-dependent infants with CLD and made the very important observation that there were great individual differences in the response to oxygen (Fig. 29-8). Even mild degrees of hypoxemia were associated with unacceptable pulmonary artery pressure in some individuals. A very poor prognosis (50% mortality rate) was found in 10 infants with pulmonary hypertension who were unresponsive to oxygen therapy.[164]

Cardiac catheterization has been used in a number of studies.[171-174] These studies have indicated significant disparities between the measurements made during catheterization and M-mode and Doppler ultrasound techniques.

Advances in echocardiography suggest that indirect methods of assessing pulmonary artery pressure using Doppler time intervals (e.g., the ratio of pulmonary artery acceleration time and right ventricular ejection time)[175] or the more direct method for determining right ventricular pressure in the presence of tricuspid regurgitation[176-178] may be reliable and practical for monitoring children and their responses to oxygen therapy in clinical practice. Newer methods of echocardiography including tissue Doppler studies and assess-

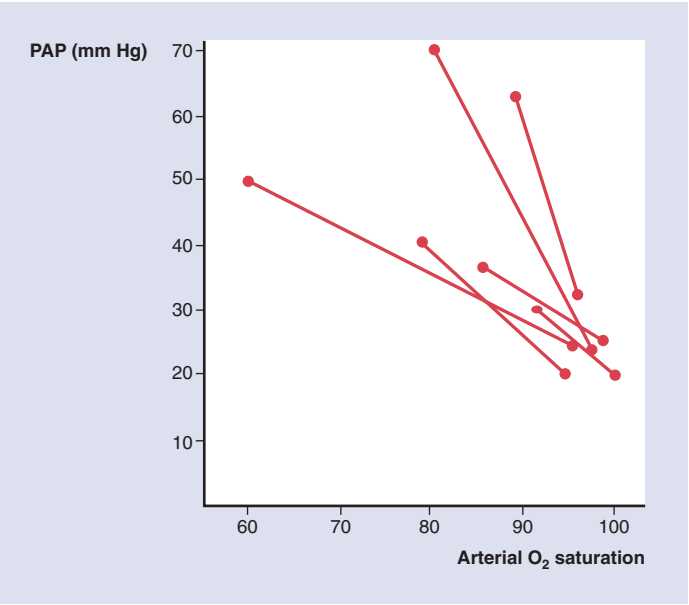

Figure 29-8 Relationship of mean pulmonary artery pressure (PAP) to systemic arterial oxygen saturation in infants with bronchopulmonary dysplasia (BPD), measured during cardiac catheterization. There are great individual differences in both the degree of oxygen-sensitive (reversible) pulmonary hypertension and the fixed component that remains when hypoxia is abolished. (Redrawn from Abman SH, Wolfe RR, Accurso FJ, et al: Pulmonary vascular response to oxygen in infants with severe bronchopulmonary dysplasia. Pediatrics 75:80-84, 1985.)

ment of strain and strain rates show promise but have not been applied to the newborn as yet.[179]

Neurodevelopmental Problems

Because infants with CLD come from the smallest, sickest population of preterm infants, it is not surprising that neurodevelopmental problems are relatively common. Although direct comparability among studies is impossible, most studies appear to suggest that half the survivors are free of any handicap at follow-up but that half are either moderately or severely handicapped, cerebral palsy being the most frequent condition reported. Furthermore, 4% of survivors in studies reviewed by Bregman and Farrell[180] were blind as a result of severe retinopathy of prematurity. This is likely to be an underestimate because many studies exclude from follow-up any infants with significant retinopathy of prematurity. Similarly, not all studies reported the presence of sensorineural hearing loss, but the prevalence appears to be approximately 4% in survivors of CLD.[180]

Of particular importance in CLD are feeding problems and control of breathing. Many infants with CLD exhibit dysphagia. This rarely has an obvious mechanical or even neurologic cause but seems to be an acquired behavioral problem, probably on the basis of swallowing difficulties during weaning from tube to oral feeds. Hypoxia during feeding may complicate matters.[181,182] Later in infancy, fear of lumpy foods may complicate feeding.

Sleep-disordered breathing is generally secondary to mechanical disturbances and is enhanced by upper airway floppiness or obstruction. However, hypoxic arousal mechanisms may not work as well in preterm infants,[183] which in a condition known to be associated with a greater likelihood of hypoxemia,[182,184] is clearly a potentially life-threatening complication.

CLINICAL PULMONARY PHYSIOLOGY

Background

LUNG DEVELOPMENT AND DISEASE

Disturbances in lung mechanics and gas exchange in CLD must be measured against the changing pattern imposed by growth and development (see Chapter 3). Abnormalities of lung function may be the result of CLD or its complications, may be causally related (see Fig. 29-1), or may be independently associated with CLD (see Table 29-2). Disturbed physiology changes with time[27]; follow-up studies have reached early adulthood,[2] but it is likely that abnormalities persist for the patient's lifetime, possibly accelerating the aging process itself.[152]

Physiologic Measurement

Functional assessment has several purposes and requires methods appropriate to the age group concerned. The most important and widely used physiologic measurements relate to gas exchange and especially oxygenation, because appropriate oxygen therapy appears to be the key to the successful long-term outcome of established CLD.

Gas Exchange

PATHOPHYSIOLOGY

By definition, hypoxemia is a feature of BPD and, therefore, is a feature of the early stages of CLD. The degree of severity varies with the stage of disease, so in the severest cases of CLD in the neonatal unit, artificial ventilation with 100% oxygen is required. The factors leading to hypoxemia follow:

1. Mechanical disturbance leading to alveolar underventilation, as indicated by raised values for the arterial P_{CO_2}, and in the chronic state, a compensatory increase in the bicarbonate concentration (positive base excess)
2. Ventilation-perfusion mismatching, which can be measured by calculating the degree of right-to-left shunting, assuming that there is no extrapulmonary shunt
3. Extrapulmonary shunt through the foramen ovale in the presence of pulmonary hypertension in the first few months of life
4. Abnormalities of control of breathing, leading to episodic breathing, apnea or hypopnea, or chronic underventilation

In practice, these processes interact to produce the characteristic instability of arterial oxygenation from which children with CLD seem to suffer (Fig. 29-9).

There are several important consequences of hypoxemia (Table 29-4). The most important is pulmonary vasoconstriction; although a structural basis for increased pulmonary vascular resistance is undoubtedly present in many children with CLD,[168] a reactive, oxygen-sensitive element is almost always detectable.[164,169,171,177] The mechanism of the reversible element of pulmonary vascular resistance is unclear. Even in

Table 29-4
Consequences of Hypoxemia in Chronic Lung Disease

Target	Acute Effects	Long-Term Effects
Airways	Increased airway resistance	Smooth muscle hypertrophy
Pulmonary vasculature	Increased pulmonary vascular resistance with or without shunt via the foramen ovale	Cor pulmonale
Central nervous system	Arousal or apnea with sleep disturbance	Sudden unexpected death Growth failure

the presence of 100% oxygen during mechanical ventilation, a reversible element can still be demonstrated by a response to inhaled nitric oxide. The large individual differences in the degree of pulmonary vascular oxygen responsiveness among individuals[171] (see Fig. 29-8) imply either the need to measure the effect in each infant or to maintain a level of oxygenation above which hypoxic vasoconstriction is abolished in all infants with CLD. There is presumably a critical level of pulmonary hypertension at which right atrial pressure exceeds left atrial pressure, leading in young infants to shunting across the foramen ovale. The long-term benefits of a reduction in pulmonary vascular resistance include better right ventricular function[185] and probably (although unproved) increased long-term survival.

Acute hypoxic airway narrowing has been demonstrated in two physiologic studies.[186,187] Because the large airways are normally exposed to ambient concentrations of oxygen, the effect must occur in peripheral airways, where gas mixing in CLD may be poor, leading to localized hypoxia, or the effect must be the result of hypoxemia. The contribution of hypoxic airway narrowing to clinical disease is unknown but clearly represents a potential vicious cycle when added to any underlying disorder of lung mechanics in CLD (see Fig. 29-9).

Control of breathing may be disturbed in some infants with CLD. Sleep-disordered breathing with more frequent and prolonged pauses than normal is found, in general, in babies born prematurely.[188-190] The hypoxic arousal response was abnormal in 8 of 12 infants in one study of CLD.[183] The significance of the finding is unclear, but these results could provide an explanation for sudden unexpected death in CLD.[134,135] Recent studies showed that spontaneous desaturations during sleep are more likely if the usual level of oxygenation is low—a complex way of demonstrat-ing that the oxygen-hemoglobin dissociation curve is not linear.[184,191] Whether growth failure in hypoxic infants with CLD is related to sleep disruption is unclear.[154]

The pattern of hypoxemia during sleep, feeding, and wakefulness changes with age during infancy. Early in infancy, oxygen-dependent babies with CLD become more hypoxic during feeding,[181,182] but from about 6 months of age, their lungs generally oxygenate better. Postural effects on oxygenation are also more marked in young infants, with falls in the PaO_2 of 7.5 to 15 mm Hg in the supine position in infants recovering from RDS.[192,193] Acute viral infections may be associated with transiently worse hypoxemia, especially if lower respiratory tract symptoms develop. A decline in the arterial oxygen saturation occurs even 1 to 2 days before the onset of upper respiratory tract symptoms in oxygen-dependent infants. The mechanism is unknown but provides a useful warning. Other major complications such as pulmonary aspiration and heart failure may be detected by worsening respiratory symptoms with increased hypoxemia. Whether chronic mild hypoxemia may persist to school age or is exacerbated by exercise remains to be confirmed.[140]

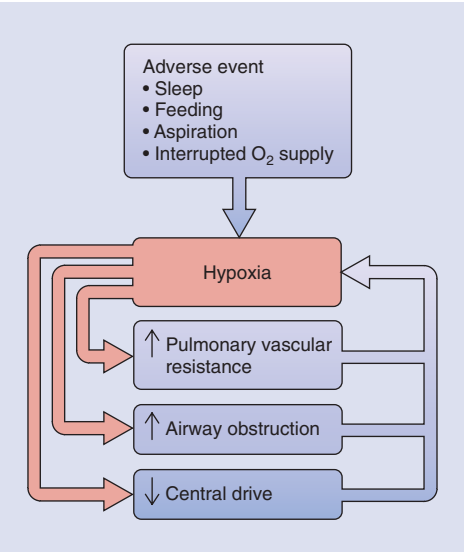

Figure 29-9 Interacting cycles of hypoxia. The cycles may be broken by termination of the adverse event or by arousal of the infant.

Clinical Measurement

Full arterial blood gas measurement is indicated only during the early phase of severe CLD with respiratory failure or during an acute exacerbation. Radial artery puncture through anesthetized skin should be performed by an expert, ideally while the infant sleeps. The disturbance caused by the infant often renders all but the value of the base excess useless. Because the latter is measurable from a capillary sample, in the absence of an indwelling arterial cannula, arterial sampling is an unrewarding exercise that should be performed only if the information obtained is likely to affect clinical decision making.

The advent of oximetry has rendered most other techniques obsolete. Certainly, transcutaneous monitors are useful only for detecting trends.[194] The effects of age and sleep state need to be taken into account.[195] Recording oximeters provide the information relevant to the management of oxygen therapy. However, operators should be familiar with their mode of operation (beat-to-beat or averaging) and the detection of motion artifact. For domiciliary use, oximetry is preferable to the more complex and less relevant transcutaneous monitors.[40,196,197]

Lung Mechanics and Lung Volumes

NEONATAL INTENSIVE CARE

For technical reasons, there have been few measurements of lung volumes during neonatal intensive care. Newer techniques such as the use of SF6 remain largely research based and have yet to reach the clinical arena.[198,199] Although diffi-

cult, measurements of lung mechanics have been made, most commonly as part of trials of medication therapy or techniques of mechanical ventilation. Both static compliance (using the occlusion technique) and dynamic lung compliance (using an esophageal balloon) are low at this stage. The precise interpretation of these data is unclear because compliance is volume dependent and dynamic compliance is frequency dependent; both measurements are therefore influenced by the technique of mechanical ventilation itself. Some of the problems inherent in intensive care measurements have recently been reviewed.[200,201]

Resistance cannot reliably be measured by the single-breath technique under intensive care conditions because of the alinear characteristics of the respiratory system and endotracheal tube.[202] Very high pulmonary resistance values have been demonstrated by the esophageal balloon technique, even allowing for the endotracheal tube. The main value of such observations has been in relation to clinical trials of diuretics, bronchodilators, or corticosteroids (see later section). By briefly applying a powerful negative pressure of about 100 cm H_2O to the endotracheal tube, Motoyama and colleagues[203] devised a system for producing maximal expiratory flow-volume curves in infants whose lungs are ventilated and used the technique to demonstrate bronchodilator responsiveness.

The site of airway obstruction cannot be determined from this type of study. Anatomically, there are abnormalities of both the large central airways and the small peripheral airways with major dynamic changes in resistance that are demonstrable (see later section). From a practical viewpoint, few simple techniques can reliably provide information about lung mechanics during intensive care.[201] Responses to therapeutic interventions and changes in disease state can be determined more precisely using ventilatory or gas-exchange measurements[204] or their combination in such indexes as the ventilatory efficiency index.[205] A sequential trial of intermittent positive-pressure ventilation guided by a pulmonary mechanics monitor failed to demonstrate a reduction in CLD.[206]

INFANTS

A wide range of physiologic measurements have been made on freely breathing infants with CLD, but again, there are many technical limitations[201,207]—especially in infants who require continuous oxygen therapy. The short-term variability of lung function tests is great in infants with CLD.[208] Sedation for lung function testing often worsens hypoxemia. Interpretation of data is affected by the normalization procedures used to compare infants with CLD to healthy infants or to compare one age group or disease state with another. If, for instance, body weight is used to correct lung volume or compliance measurements, differences in body mass index (weight/length) affect the results. Most simple normalization procedures implicitly assume a linear relationship (without any intercept) between lung function and body size; this is rarely the case. However, subject comparisons over short periods of time are not affected by these constraints, so short-term clinical trials are possible.

Lung volumes measured by helium dilution or nitrogen washout underestimate the functional residual capacity (FRC) in the presence of poor gas mixing. Values of FRC are invariably reported as low in the first 6 months of life in infants with CLD compared with those in healthy infants or controls whose lungs are ventilated,[28] exceeding the normal value by 12 months. The author has found helium equilibration times to be as long as 12 minutes in severe CLD; measurements taken over shorter times tend to underestimate the FRC. Plethysmographic lung volumes, which detect all of the gas within the chest, are higher than normal,[209,210] again recovering to normal by 12 months. One direct comparison of the two methods[211] illustrates this discrepancy, showing that preterm infants whose condition was symptomatic (although not specifically with CLD) had a greater difference and, therefore, by implication more "gas trapping" than full-term infants or infants whose condition was asymptomatic. "True" lung volume cannot, therefore, be determined. Nevertheless, changes in lung volume over short periods have been used to measure response to treatment, although the physiologic interpretation of the change may be highly speculative.

During the latter part of infancy, FRC normalizes or may even exceed normal values,[208-212] suggesting true hyperinflation. The increase in FRC may result from worsening obstructive airway disease or a loss of elastic recoil as a consequence of alveolar underdevelopment and, hence, over-enlargement and remodeling of the lungs with removal of excess collagen and elastin.

Lung mechanics has been extensively measured in groups of infants with and without CLD. Respiratory system compliance is always low,[208] returning toward normal by 1 to 3 years of age.[208,213] The weighted spirometer technique is worth considering in infants.[214] Resistance values are mostly high, an indication of the severity but not the site of airway obstruction.[211] Changes in resistance (or its reciprocal, conductance) with age can be judged only in relation to changes in lung volume with growth and disease. Specific airway conductance is low in infancy (about 60% of that predicted) and increases only a little in CLD over the first 3 years of life to about 70% of that predicted.[208,212,215] In healthy VLBW infants, plethysmographic airway resistance is lowest at about 6 months of age, improving thereafter.[210,216] Airway function seems to "track" from 12 months to 9 years in preterm infants.[43]

Flow-volume curves occurring during tidal breathing and generated by the squeeze technique in infants with CLD are clearly abnormal, exhibiting severe flow limitation, even at rest. Measured values of maximum flow at FRC of around 50% of the reference value with little improvement over the first year have been reported by Tepper and associates.[217]

The concept of a single value for compliance or resistance hides the fascinating process of dynamic airway function. Changes in cross-sectional area and, hence, resistance and changes in wall elastance and, hence, maximum sustainable flow[218] may be brought about because of structural abnormalities in the airways, such as bronchomalacia[147] or airway wall thickening with glandular or smooth muscle hypertrophy,[44] because of developmental changes,[150] or because of the administration of bronchodilator or bronchoconstrictor agents. With the use of computed tomography scans, dynamic tracheal narrowing during tidal breathing is far greater in infants with CLD (63%) than in control infants (9%).[148] These observations have been confirmed using different techniques.[149]

The work of breathing in CLD is markedly increased as a result of mechanical factors combined with an increase in overall metabolic rate.[219] This is not a simple relationship between pulmonary mechanics and total metabolic rate.[220]

SCHOOL-AGE AND OLDER CHILDREN

Many studies of preterm babies have been taken through to school age, although the numbers with classic BPD in these groups is small.[29,30,33,101,130] The general conclusions are that preterm babies at school age have reductions in the 1-second forced expiratory volume and forced vital capacity, which are largely matched, suggesting mainly restriction rather than obstruction as the basic mechanical problem. There is an increase in the total lung capacity and the ratio of residual volume and total lung capacity (to 0.4 to 0.45 compared with a predicted value of 0.22), a reduction to about one half in specific airway conductance. These studies suggest that children with BPD are little different from the other preterm cohort members whose lungs have or have not been ventilated and that prematurity is the main determinant of functional impairment at school age. To interpret earlier studies in which selected groups of children with BPD differed from healthy control children as implying that there are long-term effects from BPD is to be swayed by selection bias.

One longitudinal physiologic study that demonstrated tracking in airway function from the age of 8 to 12 months through 9 years[43] is explained by the model illustrated in Figure 29-10. The resolution and remodeling of acute lung injury are largely complete by 1 year, and further changes in lung function represent subsequent growth. At school age, the physiologic findings of restrictive disease with a large residual volume are compatible with a reduced alveolar component, perhaps resulting from the disturbed alveolarization associated with prematurity. This hypothesis awaits confirmation because no methods for measuring alveolar number or surface area in the living child are available, although newer methods show promise.[221]

Northway and colleagues[222] have provided data on lung function in late adolescence that indicate persistent, largely reversible airway obstruction affecting the large and small airways and persistent overinflation resulting from small airway disease. The latter could represent narrowed peripheral airways or a loss of elastic recoil. Airways responsiveness to methacholine or a β-agonist was found in 52% of the group, and fixed obstruction was found in 24%. This contrasts with the findings in preterm and term controls, in whom 31% and 17% of the airways, respectively, were reactive to methacholine but there was no fixed obstruction.

The presence and interpretation of airway responsiveness in children who were born prematurely is controversial. In a small study, Bertrand and coworkers[99] found increased methacholine responsiveness in children born prematurely and their mothers, suggesting that premature labor was itself due to excessive familial smooth muscle responsiveness, a finding confirmed by Riedel and associates.[100] These findings were not confirmed in a population study of LBW infants and their mothers,[101] although a marginal increase in bronchial responsiveness was reported in the LBW group to a much lesser degree than might be expected in groups with asthma. This may simply be a reflection of altered airway caliber or airway wall thickness.

For clinical purposes, the most valuable measurements in school children are based on forced expiration; these measurements are supplemented by bronchodilator challenge to assess acute reversibility. Marked deviation from normal is an indicator for more detailed assessment with plethysmography, which is supplemented as indicated by specialist imaging (computed tomography or ventilation-perfusion scans). Exercise testing may reveal additional abnormalities such as exercise-induced asthma or exercise-induced hypoxemia and hypercapnia.[140]

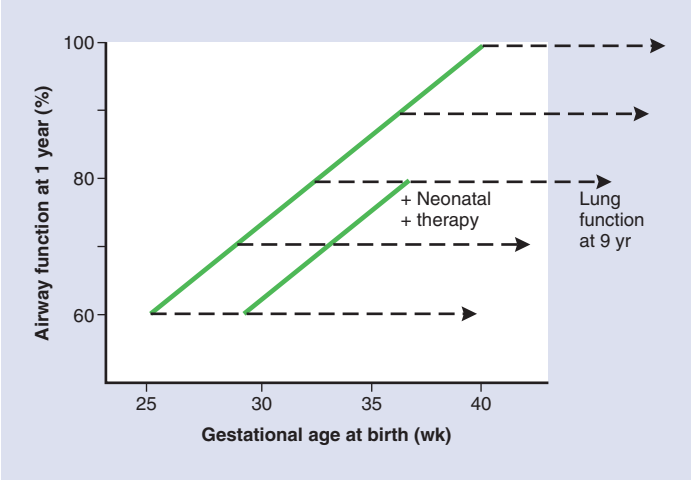

Figure 29-10 Tracking of infant lung function. Airway function at 1 year of age depends on gestational age (or birth weight) and to a lesser extent on neonatal therapy *(green lines)*. Thereafter, airway function seems to "track."

MANAGEMENT

General Aspects of Management

BACKGROUND

CLD is rare in infants weighing more than 1500 g at birth. Because pulmonary disability occurs in the smallest, sickest infants, it is almost always accompanied by other disorders; sensory and neurodevelopmental handicaps, growth impairment and nutritional difficulty, congenital anomalies, and cardiovascular problems are among the most prominent. Only the aspects that have a bearing on pulmonary disease are considered in this chapter, but it is a prerequisite of good care that management should be carried out by a team and not by a disparate group of independent experts. Discharge from the hospital requires careful joint planning by hospital and community health professionals, even for infants who do not require domiciliary oxygen therapy, aerosol therapy, or tube (gavage) feeding. Avoidance of cigarette smoke, minimal contact with other preschool children,[223] attention to immunization programs, and ready access to the hospital in an emergency are all important. There is no evidence that apnea monitoring is of any value, although some parents demand a monitor for their own peace of mind. Where a monitor is provided for high-risk infants (e.g., those who have had apneic attacks, have GER, or are oxygen dependent), cardiopulmonary resuscitation should be taught and simple suction equipment may be necessary. Domiciliary oxygen therapy and monitoring are discussed later.

Hospital visits should be kept to a minimum. This means that the pulmonologist, follow-up team, nutritionist, speech therapist, physical therapist, home-care nurse, and possibly the pediatric cardiologist or echocardiographer should all be available for consultation at a joint clinic.

The rational management of CLD presupposes an understanding of the mechanisms of the disease and its resolution. This information is rarely available. Management also requires data from clinical trials of sufficient power to provide valid results. Much of clinical practice is still based on consensus or local custom, but where possible, the conclusions of scientifically valid data are preferred to anecdotal studies to back up management schemes. Several thorough reviews of CLD and its therapy have recently been published.[224-227]

GROWTH AND NUTRITION PROBLEMS

The frequent occurrence of poor growth in CLD has been discussed (see section on clinical features). Contributory factors may include behavioral feeding problems, swallowing disorders, GER, chronic hypoxemia, and heart failure. Excessive use of diuretics to control respiratory or heart failure may impair growth, presumably as a result of a critical reduction in the extracellular fluid volume or total body sodium levels, even in the absence of hyponatremia. There are no nutritional deficiencies that are specific to infants with CLD. Corticosteroid therapy also has growth-suppressing effects.

After remediable causes have been identified and treated, caloric supplementation can be achieved by increasing feed density. Carbohydrate supplements alone may exacerbate respiratory failure by increasing the metabolic rate; lipid/carbohydrate combinations should be used. A speech therapist skilled in infant feeding problems may be able to retrain the child who has a behavioral or neurologic feeding disorder. It is the author's impression that very small stature in infants with severe, chronically oxygen-dependent CLD is a manifestation of a fundamental disorder of somatic growth, of which failure of resolution of neonatal lung "injury" leading to CLD may be a component.

GASTROESOPHAGEAL REFLUX

The relationship between GER and respiratory symptoms in infants is not easy to disentangle. GER is certainly common in preterm infants in general and in infants with CLD in particular[156,228] (see section on clinical features). Obvious xanthine-resistant apnea, massive aspiration, recurrent vomiting, or failure to thrive may draw attention to it. A causal relationship between GER and hypoxic spells in CLD has never been demonstrated, although both are common in CLD. It is the author's experience that GER is a sequel to, rather than a cause of, obstructive apneic spells.

Some clinicians prefer to institute simple medical management (e.g., posture, food thickening with carob extract and agar-based demulcents), pursuing further investigations if this fails. Failure of simple medical therapy should be followed by the addition of drugs such as gaviscon, domperidone, histamine$_2$ receptor blockers or proton pump inhibitors—although evidence of their efficacy in preterm infants with GER or CLD is limited. Diarrhea is a common side effect. H_2-blockers or proton pump inhibitors should be used if there is evidence of esophagitis. Fundoplication should be considered if life-threatening symptomatic reflux continues despite such medical therapy. Several observational studies have shown improvement in such patients.[157,160,161]

CARDIOVASCULAR COMPLICATIONS

Clinical features that suggest impending heart failure, usually secondary to severe pulmonary hypertension, include excessive or sudden weight gain and increased breathlessness or hypoxemia (or an increase in oxygen requirement) and on physical examination, edema and hepatomegaly. Chest radiographs may show cardiac enlargement.

Oxygen therapy is the mainstay of management. In the absence of an echocardiographic assessment to demonstrate the presence and reversibility of pulmonary hypertension and to determine the appropriate target level of arterial oxygen saturation in individuals, clinicians should aim for a target level of 94% to 96%.[164,171] Many subjects can be safely managed, at least for short periods, below this range, provided that they are not highly sensitive to hypoxic vasoconstriction. Diuretic therapy should be instituted or increased if the features of heart failure occur. For short-term therapy, furosemide is useful; long-term use may lead to nephrocalcinosis.[229] A combination of a thiazide with a potassium-sparing diuretic (spironolactone or amiloride) is more appropriate for long-term treatment. Excessive sodium excretion may cause alarming hyponatremia within the first week of treatment, whereas subsequent growth failure relieved only by sodium supplementation is often a problem. The separate effects of diuretic therapy on pulmonary function are considered later.

Pulmonary vasodilators have very unpredictable effects in babies with severe oxygen-unresponsive pulmonary hypertension.[172] These infants should be individually evaluated by a pediatric cardiologist either during cardiac catheterization or by using reliable echocardiographic measurements. Pulmonary artery vasodilators such as prostacyclin, inhaled nitric oxide, sildenafil, and calcium channel blockers such as nifedipine may be considered for severe pulmonary hypertension on an individual basis. Responses to these drugs during cardiac catheterization may be necessary. These drugs may have actions additive to oxygen, e.g., on the systemic vascular resistance or any abnormal systemic pulmonary shunt vessels.[165,166]

Systemic hypertension has been recorded in oxygen dependent infants with CLD; it is occasionally severe enough to lead to left ventricular hypertrophy. In one study, 13 of 30 infants had a systolic pressure higher than 113 mm Hg,[230] and 6 received antihypertensive therapy for a mean of 3.7 months. The hypertension resolved. Electrocardiography may not be sensitive enough to detect left ventricular hypertrophy. Echocardiography should be performed in hypertensive children with CLD. The cause of systemic hypertension is unknown, but corticosteroid treatment, segmental renal disease, renal vascular complications of prematurity, long-term inotropic support (or even theophylline therapy), and possibly hyperoxia might be contributory factors. Left ventricular hypertrophy is a common finding at autopsy.[44] Unsuspected congenital heart disease was found in association with CLD by two groups.[163,174] This sort of observation implies that severe CLD should be seen as a marker of other, causally important anomalies or defects.

Respiratory Management

For almost all modes of respiratory therapy, there are no definite indications, no objective methods of evaluating the response in individuals (except in the very short term), and no randomized clinical trials of adequate power. Moreover, when any of these defects has been remedied, the information applies only to a specific stage of CLD (e.g., ventilated BPD or wheezy infants), and the results cannot be generalized throughout this evolving disorder. Despite many Cochrane reviews and meta-analyses, the call from most of these publications is for better-powered, designed, randomized, controlled trials to address clinically relevant questions rather than shorter-term benefits of unknown value.[231-240]

BRONCHODILATORS

One of the striking pathologic features of CLD is airway smooth muscle hypertrophy.[241] It would seem reasonable to expect bronchodilator agents (β-agonists, anticholinergic agents, and methylxanthines) to be effective. Little is known, however, of the ontogeny of β-receptors or muscarinic-receptor subtypes in preterm babies or even healthy infants, so no one can predict the long-term outcome of stimulating these receptors during a period of rapid pulmonary development. The β-agonist controversy should promote caution. Neuroendocrine cell hypoplasia suggests a role for nonadrenergic, noncholinergic mechanisms in CLD.[242,243]

Moreover, there is reason to suppose that airway smooth muscle tone may be important in stabilizing the compliant airway of the neonate to minimize dynamic changes during breathing (see previous section). The removal of this tone could render airways more collapsible, with adverse effects on expiratory flow during spontaneous breathing, or more distensible, with the potential for enhanced tracheomegaly during positive-pressure ventilation (see later section). Bronchodilation might also remove the potential focal protective function of narrowed airways.[244] There is no logical basis for their use, except that these drugs are often effective in relieving airway obstruction in other situations.

In addition to these unknowns, the appropriate dose and means of administration of bronchodilators have not been determined (see Chapter 16). For ventilator-dependent infants, the most effective method for delivering aerosol is probably by metered dose inhaler (MDI) and small volume spacer (such as the Aerochamber).[245-247] Jet and ultrasonic nebulizers are extremely inefficient.[248-251] For older infants whose lungs are extubated, all methods of delivery are certainly inefficient.[252] The choice of device has recently been reviewed.[253] The nose acts as an all-too-effective filter.[254] In wheezy infants, in general, nebulized bronchodilators often have transient adverse effects on oxygenation and airway function.[255-259] The effect is not seen when an MDI is used.[260] Changes in air entrainment during infancy mean that drugs administered by jet nebulizer are available in relatively high doses to young infants.[261]

A recent well-designed multicenter randomized control trial starting caffeine within 10 days of birth in infants with a birthweight between 500 and 1250 g showed that 350 (36%) of 963 treated infants alive at 36 weeks' corrected gestation were on supplemental oxygen compared to 447 (47%) of 954 infants receiving placebo (adjusted odds ratio ± 95% confidence interval 0.63 (0.52 to 0.76), $P > 0.001$).[262] The mechanisms of this benefit are unclear. Beyond the early neonatal period, there is only one satisfactory study of methylxanthines, which found that in 4-month-old oxygen-dependent infants, 4 days of oral theophylline therapy gave significant benefits in lung mechanics and work of breathing.[263] The open, placebo-controlled study of a single oral dose of caffeine[264] showed significant short-term mechanical benefits during mechanical ventilation. One other brief open study of theophylline gave a marginal result.[265]

Whether given by nebulizer or by the oral or subcutaneous route, in every study, β agonists have produced short-term improvements in lung mechanics as measured by a variety of techniques. Several studies of single doses of nebulized salbutamol given to ventilator-dependent infants younger than 1 month of age have shown clear benefits in terms of respiratory system compliance and resistance.[266-268] In infants who have CLD and whose lungs are mechanically ventilated, reversible airway disease was demonstrated by changes in maximum forced expiration after nebulized metaproterenol[203] and by measurements of classic lung mechanics.[269] The only full-scale clinical trial of bronchodilators in preterm infants concerns symptomatic (i.e., wheezy) infants who were born prematurely, not infants specifically with CLD.[270] This was an open, sequential study of β_2-agonists administered by MDI. Symptomatic and physiologic improvements were demonstrated. De Boeck and colleagues investigated both albuterol and ipratropium in clinically stable 1-year-old infants with CLD and did not note a significant decrease in pulmonary resistance with either drug, but individual infants either improved or deteriorated.[271] It is interesting that a recent Cochrane review of the use of bronchodilators in CLD only included the study by Denjean and colleagues for prevention of CLD and none was included for established CLD.[268]

The results for the nebulized anticholinergic agents atropine and ipratropium bromide are similarly positive but of limited significance. There is evidence that ventilator-dependent babies with CLD respond to single doses of nebulized ipratropium bromide,[269] but again, long-term randomized trials in CLD are lacking. One double-blind, randomized trial in older preterm infants whose conditions were symptomatic was effective,[272] although the same authors caution its use in infants whose condition is asymptomatic.[273] There is weak evidence for synergy between β_2-agonists and anticholinergic agents.[274]

In practice, salbutamol (albuterol) or ipratropium bromide given by MDI and small volume spacer may be used for ventilator-dependent infants, older infants with CLD who have severe airway obstruction, and wheezy infants with CLD. There is little to support the use of bronchodilators in acute viral episodes in infancy in general and even less in acute viral exacerbations of CLD.

There are no dosage regimens, but the author has noted that salbutamol (albuterol), 100 to 200 μg every 4 to 6 hours, and ipratropium bromide, 20 to 40 μg every 6 hours, do not seem to cause undue tachycardia or any detectable side effects. The efficacy of treatment can be judged only by general clinical features or the ventilatory efficiency index during mechanical ventilation.[204] Short-term measurements of lung function may lend support but are generally too vari-

able over days or weeks to guide long-term therapy in individual cases.

ANTI-INFLAMMATORY AGENTS

Data on sodium cromoglycate (cromolyn sodium) are sparse and consist of one open study on ventilator-dependent infants that suggested cytologic improvement,[275] a pilot study that showed no benefit,[276] and one properly conducted, double-blind, randomized, controlled trial in older preterm infants symptomatic at follow-up.[277] In the last study, there was a significant reduction in symptoms after 3 weeks of treatment by MDI and spacer.

The pharmacologic effects of corticosteroids on the lungs can be considered at the molecular or cellular level, at the functional or physiologic level, and at the level of clinical disease. There are data on all these outcomes of corticosteroid therapy in preterm infants. The common theme of most studies is the anti-inflammatory action of corticosteroids. There are, however, several other potentially relevant actions, some studied only in animal models, including enhancement of β-receptor density, increased transduction of the genes for several antioxidant enzymes, altered gene expression for a variety of cytokines and growth factors, enhanced surfactant production, and suppression of inducible nitric oxide synthase. Recent data linking the early use of corticosteroids in the neonatal unit with neurodevelopmental abnormalities including cerebral palsy are of clear concern and have been reviewed recently by Grier and Halliday.[278]

Clinical trials of systemic corticosteroids in developing CLD or established CLD (BPD) have been thoroughly reviewed by series of Cochrane reviews, with most reviews pleading for more appropriate studies to be adequately performed especially for established CLD.[231-236] The only clear evidence for the use of corticosteroids remains the ability of these drugs to facilitate extubation of ventilator-dependent infants. Most clinicians are much more cautious than earlier due to the association of these drugs with adverse neurodevelopment.[278-280] In contrast to ventilated preterm infants, adequate studies of the use of both systemic and inhaled corticosteroids in established CLD are lacking.

Administration and dosage regimens are poorly worked out. Dexamethasone is the most popular corticosteroid in neonatal practice, and parenteral (usually intravenous) administration is the usual route. Recent attempts to evaluate other corticosteroids such as hydrocortisone have been affected by significant side-effects.[281,282] Although unable to recruit the intended number of participants, the DART study showed promise using a lower dose of dexamethasone (0.89 mg/kg over 10 days) but the need for either a second course or of rescue therapy with dexamethasone was increased in the treated group.[283] Despite known differences among corticosteroids in the degree of penetration into the lungs after parenteral administration, no study of this important aspect of therapy has been reported in young infants.

Pulmonary mechanics have been reported in a number of small, mainly sequential observations.[284-288] Individually, these studies have major flaws, but their consistency is remarkable. Within 12 to 72 hours, falls in respiratory resistance of about 30% and increases in compliance of 60% to 70% are typically seen (Fig. 29-11).

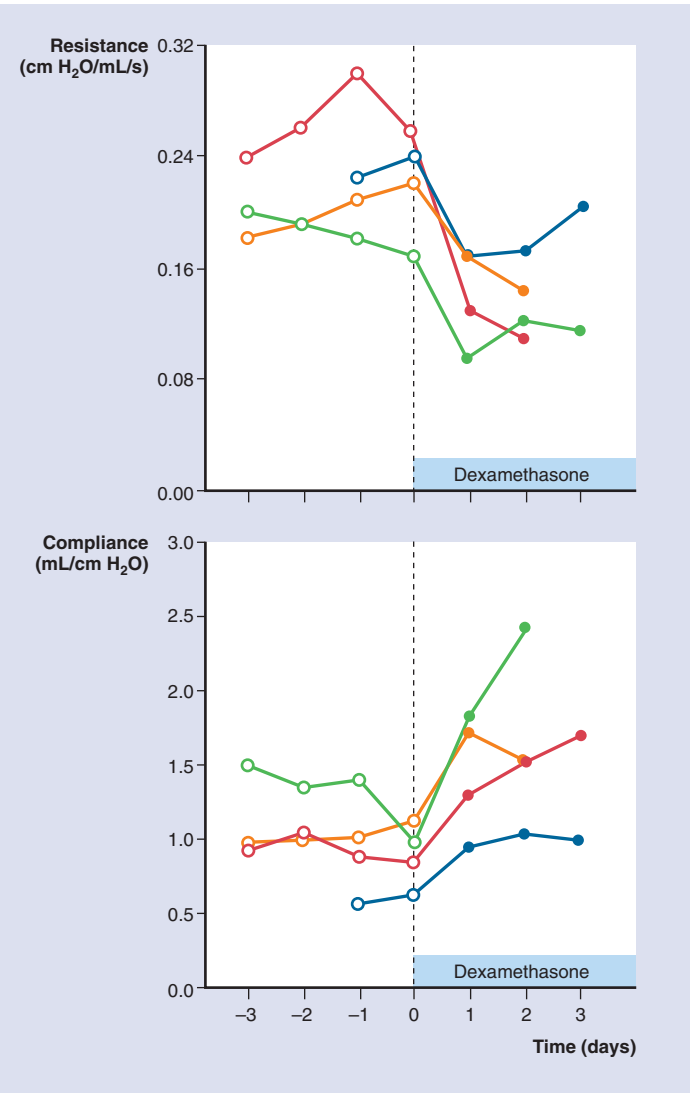

Figure 29-11 Dexamethasone and ventilator-dependent chronic lung disease (CLD) at 3 weeks. Changes in lung mechanics occur within 24 hours. Data shown for individual patients. (Redrawn from Brundage KL, Mohsini KG, Froese AB, et al: Dexamethasone therapy for bronchopulmonary dysplasia improved respiratory mechanics without adrenal suppression. Pediatr Pulmonol 12:162-169, 1992.)

Attempts to understand the mechanism of corticosteroid action in CLD have led to a bewildering number of measurements of cytokines and other cell products in bronchoalveolar lavage fluid or tracheal aspirate. This is definitely a growth area. Sadly, the majority of observations were not designed to answer any useful hypotheses. Again, there are methodological defects in many studies: inadequate control data, sequential observations, lack of attention to the expression of bronchoalveolar lavage fluid concentrations (by reference to a reliable denominator), and very variable and small patient groups. The most comprehensive and carefully conducted study showed parallel changes in tracheal fluid neutrophil cell counts, cell products, lung mechanics, and clinical status within 3 days of starting dexamethasone therapy in a randomized, controlled trial.[285]

The use of topical corticosteroids to prevent CLD has also been reviewed by a Cochrane review.[236] By far the largest study by Cole and associates used a high dose of inhaled

beclomethasone (starting dose of 1000 μg/kg/day with an estimated 4% delivery at the endotracheal tube, i.e., 40 μg/kg/day) for 4 weeks in 253 preterm infants between 3 and 14 days of age. Although a decrease in inflammatory cytokines was noted,[289] the rate of CLD (either oxygen dependency at 28 days or at 36 weeks' corrected gestation) with treatment was not decreased, although a subsequent need for systemic corticosteroids was reduced.[290] The potential range of devices, medications, and doses is huge, although there are now sufficient data from human and model lung experiments to devise regimens for clinical trials.[228-230]

Corticosteroids are often used in older infants and children, but very little data are available to support their use except where clear clinical benefits are observed in symptomatic infants. In the most recent Cochrane review of the use of inhaled corticosteroids in established CLD by Lister and coworkers only one study published as an abstract was included in their analysis.[236,291] In the study, by Dunn and colleagues,[291] nonventilated infants of at least 36 weeks' corrected gestation and who were oxygen dependent were included. Budesonide (1 mg) was administered by an Airlife Misty-Neb jet nebulizer three times a day for 7 days. A significant reduction in oxygen requirements was observed by the authors. In another study of 18 preterm infants at a mean postnatal age of 10.5 months, the use of inhaled beclomethasone for 6 weeks was associated with an improvement in respiratory tract symptoms and functional residual capacity.[292] Because this study did not specify the number of infants with oxygen dependency, it is difficult to extrapolate the results to infants with established CLD.

Adverse effects of corticosteroids are obviously a major concern. Brief and probably insignificant systolic hypertension, hyperglycemia, and neutrophilia are reported in many of the dexamethasone trials. Of more concern is the evidence of adrenal suppression of up to 1 month's duration even after 1 week of therapy.[293,294] Gastrointestinal perforation has been reported.[295,296] Whether this rare complication can be safely prevented by the routine use of H_2-blocking agents during dexamethasone therapy remains to be investigated.

One of the most worrisome potential effects of corticosteroids on the growing lung is suppression of alveolar development. There are certainly effects on somatic growth and lung morphology from brief exposures of neonatal rats to modest doses of dexamethasone.[297,298] Measurements of lung function in infants and children exposed to antenatal dexamethasone do not suggest any persistent adverse effects.[299,300] However, the studies are small, are open to bias, and depend on an assumption that lung function is equivalent to lung growth. Transient growth suppression is demonstrable by knemometry, with apparent catch-up after cessation of steroid treatment.[301]

In practice, the approach adopted by most is to consider the clinical need (e.g., wheezing) and clinical response to the use of inhaled corticosteroids in infants with established CLD and to continue treatment in those who respond but to cease treatment when an adequate response is not observed. Pulmonary function tests may be useful but remain largely a research tool for this group of infants. As this set of children forms a large group in the community, there is a clear need for adequately powered, randomized, controlled trials to examine the role of both systemic and inhaled corticosteroids in infants with established CLD.

DIURETICS

In addition to their cardiovascular indications (see previous section), diuretics are frequently used to treat the pulmonary problems of CLD. The role of diuretics has been extensively documented by several Cochrane meta-analyses.[238-240] Their efficacy is based on experimental reductions in pulmonary vascular resistance and in extravascular lung water in experimental animals by furosemide treatment. In CLD, there is evidence of a disturbance in water balance[302,303] and peribronchial edema.[304] The mechanism of clinical improvement in response to diuretics is unclear. Local actions on the distribution of lung water and on the pulmonary vasculature may be as important as renal effects on total body water levels. For instance, furosemide has a number of such actions. Potential actions on the airway epithelium are especially interesting because they open the possibility that aerosol therapy may be effective, thus avoiding troublesome renal actions.[305]

There is striking uniformity of the results of clinical trials with furosemide (1 mg/kg once or twice a day intravenously or 2 mg/kg twice a day orally) despite the variety of trial designs and methods of measuring outcome. All results demonstrate an increase in pulmonary or respiratory system compliance, and some also demonstrate falls in resistance and oxygen requirement over intervals of between 1 hour and 8 days of therapy.[305-307] The rapid onset suggests a local effect,[305,308] a conclusion supported by the presence of changes in lung mechanics in the absence of measurable diuresis.[307]

Three of four studies on the combination of thiazide and spironolactone (chlorothiazide, 20 mg/kg, or hydrochlorothiazide, 1.5 to 2 mg/kg every 12 hours, with spironolactone, 1.5 mg/kg every 12 hours by mouth) showed significant improvements in compliance with variable improvements in resistance and oxygen requirement, albeit to a less marked extent than the changes found after furosemide.[309-311] One study using a lower dose[312] found no significant effect, despite diuresis. There are no dose-ranging studies. In the author's clinical experience (with chlorothiazide, 10 to 20 mg/kg twice a day and spironolactone 1 to 2 mg/kg twice a day), some adjustments of dose are often necessary.

The conclusion from these small studies is that diuretics are effective over periods of up to 8 weeks. Long-term side effects may be troublesome. Furosemide enhances calcium excretion and often leads to nephrocalcinosis and osteopenia. Electrolyte imbalance is common, and serum electrolyte measurements must be performed twice a week. Alternate-day therapy should be considered, although it is uncommonly used in practice. The combination of thiazide and spironolactone leads to lower calcium levels and potassium loss but may cause troublesome hyponatremia soon after the onset of therapy.

A trial of diuretic therapy for 1 to 2 weeks is indicated for the following:

1. Chronic ventilator-dependent cases
2. Infants on very low-flow oxygen therapy (100 mL/min or less) who are to be discharged home shortly
3. Sudden deterioration or sudden weight gain

There is no standard weaning process. The author simply allows infants to outgrow their therapy and withdraw when the dose has fallen below the accepted therapeutic range.

MISCELLANEOUS THERAPIES

Anti-infective agents are commonly used to treat episodes of "sepsis" in the neonatal intensive care unit. Most infective pulmonary exacerbations later in childhood have a viral etiology—respiratory syncytial virus being an especially virulent agent.[145] The use of the monoclonal antibody against RSV (palivizumab) appears to be efficacious in decreasing the severity of RSV in vulnerable infants.[313] Antibiotics are indicated only for specific reasons: high index of suspicion of bacterial disease, host defense defect, and cystic fibrosis-like pattern of illness with frequent severe exacerbations. There are no clinical trials to back up these assertions. Complete immunization including influenza during winter periods is vital for infants with CLD.

RESPIRATORY FAILURE

The management of CLD consists largely of attempting to identify remediable causes of respiratory failure or (in milder cases) respiratory dysfunction and trying to tackle them. Respiratory failure itself, defined as the failure of the respiratory system to adequately exchange oxygen and carbon dioxide for whatever reason, often needs to be tackled directly by mechanical ventilation and oxygen therapy. The classification and causes of respiratory failure in general are discussed in Chapter 19.

Upper airway obstruction is often overlooked as a cause of weaning failure in infants whose lungs have been intubated for a prolonged period. If laryngeal or subglottic edema is suspected, a short course of corticosteroids may be effective.[314] In modern neonatal practice, clinically significant structural (as opposed to transient) upper airway damage appears to be less common.

MECHANICAL VENTILATION

Mechanical ventilation has a role in the etiology of acute lung injury (see previous section), but its role in CLD is speculative. The safest technique has not been established despite large clinical trials and an array of modern modes of mechanical ventilation. There are even less data to guide the neonatologist in the ventilatory management of established CLD.[315] No clinical trials of techniques of mechanical ventilation have been reported. Because small numbers of infants with established CLD are likely to require mechanical ventilation, adequately powered clinical trials are unlikely to be performed in the immediate future. Devices would be welcome that could allow the clinician to avoid intubation. There has been some resurgence of interest in continuous or intermittent negative extrathoracic pressure.[316]

OXYGEN THERAPY

Appropriate oxygenation is essential. Too little oxygen is clearly harmful, but excess has adverse effects too. These include toxic effects on the airway epithelium, including inhibition of ciliary action; possibly systemic hypertension; and the physical, emotional, and economic costs on the child, family, and society for unduly prolonged treatment.

Although the optimal oxygen saturation is unknown, it is likely to be higher than 90%. Win Tin and colleagues (U.K.) in a retrospective analysis of their data suggest that oxygen saturations as low as 70% may not be harmful to preterm infants, but this needs to be confirmed with an adequately powered prospective study which at the time of writing has been funded (BOOST2). The STOP-ROP and BOOST trials showed that oxygen saturations of between 91% and 94% may be preferable to oxygen saturations of between 95% and 98%—with the former not being associated with poor growth and the latter associated with greater need for home oxygen and respiratory illness.[155,317] It is unknown whether brief hypoxic spells during feeding or interruption of the oxygen supply or during apneic pauses has a cumulative long-term effect on cardiovascular function, neurodevelopmental progress, or growth regulation. It seems prudent to supply sufficient oxygen to prevent even brief changes in saturation below 90% because this provides a safety margin at the upper end of the oxygen-hemoglobin dissociation curve for those "natural" variations in breathing resulting from feeding, posture, the sleep state, crying, and upper respiratory infection that may depress the partial pressure of arterial oxygen and, therefore, the arterial oxygen saturation.[181-184] There are no data from controlled trials, only some observational support, to justify these figures.[191]

There are several techniques for administering oxygen to infants with CLD.[318] Each has its advocates. Head-box delivery of oxygen is less frequently used and most prefer delivery with nasal cannulae. Humidification is unnecessary in most instances of infants with established CLD.

Domiciliary therapy[40,196,197,319-321] is most conveniently and cheaply provided by an oxygen concentrator with a low-flow meter (range about 100 to 1000 mL/min or 25 to 200 mL/min), but back-up cylinders and portable devices are also needed for emergencies and for mobility. A liquid oxygen-based system is indicated if higher flow rates (of greater than 1 L/min) are required. The supervision of a dedicated home care nursing team in collaboration with other community health professionals is advantageous.

Monitoring is vital. The limitations of transcutaneous devices have been discussed. They may be useful in the hospital but are too inaccurate, slow responding, and technically demanding for domiciliary use. Oximeters in averaging mode have allowed safe and stable domiciliary therapy and have arguably been responsible for the enormous recent improvement in long-term prognosis. The frequency of monitoring may vary depending on the stability of the patient's condition.

Implicit in oxygen monitoring is the need for regular echocardiographic assessment of the pulmonary circulation because one of the primary aims of oxygen therapy is to reduce pulmonary vascular resistance to normal levels. The author recommends an echocardiographic evaluation before discharge from the hospital and at 3-month intervals thereafter until oxygen therapy ceases. Measurements are made on each occasion of right ventricular systolic times (ratio of right ventricular acceleration time and ejection time) and, where possible (50% of cases), right ventricular systolic pressure from the tricuspid regurgitant jet both in and out of oxygen therapy during sedated sleep. The information is particularly useful during weaning from oxygen therapy.

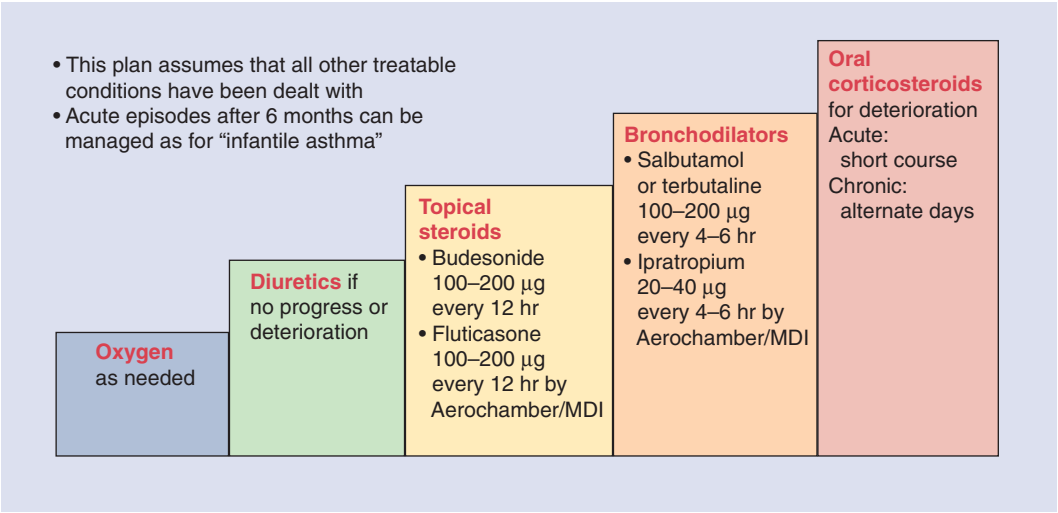

Figure 29-12 Suggested stepwise management plan for oxygen-dependent infants whose conditions are symptomatic.

The indications for referral to the hospital for reassessment or readmission include:

1. Sudden or gradual decline in arterial oxygen saturation requiring a marked increased in oxygen flow
2. Frequent catheter blockage resulting from nasal obstruction
3. Hypoxic spells or an acute life-threatening event

Monitoring should continue for 2 to 3 months after withdrawal of oxygen because secondary deterioration may occur and is often precipitated by a viral respiratory tract infection. It is probable that oxygen saturation never reaches truly "normal" values (98% to 100%) in children who have had prolonged severe CLD in infancy.

MANAGEMENT PROTOCOLS

With individual institutions, management protocols evolve by consensus and experience backed by scientific data. As such, change is inevitable. Protocols should be seen as advisory and not prescriptive. Examples of a consensus approach to the management of ventilator-dependent respiratory failure and symptomatic infantile CLD are given in Figure 29-12.

Domiciliary management demands the sort of guided self-management approach that has become the norm in the management of asthma (see Chapter 59). Thus parents can be provided with information, training (in oxygen administration, cardiopulmonary respiration, and the use of inhaler devices), and written instructions that allow them to vary their child's therapy according to clear guidelines and within agreed limits. Open access is essential for parents of infants with children on home oxygen to either an emergency room or preferably to inpatient wards with expertise in respiratory management of infants with oxygen dependency.

Future Directions

The short-term outcome of preterm birth has already improved considerably by interventions such as antenatal corticosteroid therapy and the early use of surfactant for babies at risk of RDS (see Chapter 28). Given the fact that the long-term outcome at school age appears to be more closely related to prematurity itself than to acute lung injury, the prospects for preventive intervention, assuming that prematurity cannot be prevented, are more speculative. Areas that may benefit from further intense study include:

- Prevention of premature labor (e.g., better understanding of the role of antenatal infection)
- Use of current knowledge to improve respiratory outcomes (e.g., does targeted treatment to eradicate *Ureaplasma* spp. prevent the development of CLD?)
- Better understanding of the mechanisms that can lead to better management (e.g., mechanical ventilation to avoid pulmonary inflammation)
- Identification of optimal oxygen saturations while avoiding adverse events—including poor growth, pulmonary hypertension, and adverse neurologic outcome
- Although corticosteroids are the main available drug treatment to facilitate extubation from mechmical ventilation, identify ideal dosage, timing, and length of treatment for corticosteroids. Seek suitable alternatives to dexamethasone treatment.
- Alternative therapies to corticosteroids include the use of proteins such as alpha$_1$ antitrypsin, CC10; antibodies monoclonal antibodies toward proinflammatory cytokines or adhesion molecules
- Better assessment of lung growth using more powerful techniques of magnetic resonance imaging
- Better assessment of pulmonary hypertension using modern imaging techniques of echocardiography
- Long-term follow-up studies to assess if CLD predisposes to premature respiratory morbidity in adulthood

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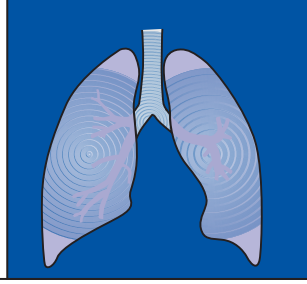

CHAPTER 30

Apnea of Prematurity, Sudden Infant Death Syndrome, and Apparent Life-Threatening Events

Christian F. Poets

TEACHING POINTS

- Factors involved in the pathogenesis of apnea of prematurity (AOP) are the infant's low lung volume, diaphragmatic fatigue, the unique response of the preterm infant to hypoxia, and the propensity to upper airway obstruction.
- Treatment should be incremental, starting with prone positioning followed by methylxanthines and nasal continuous positive airway pressure (CPAP) or intermittent positive pressure ventilation (IPPV).
- Primary prevention such as the supine sleep position, room but not bed sharing, pacifier use, use of a sleeping bag, and adherence to a smoke-free environment will prevent >90% of SIDS cases, even though its pathophysiology remains unknown.
- Pathologic studies in SIDS suggest that the final pathway leading to SIDS involves large intrapulmonary pressure swings. These could result from upper or lower airway obstruction or asphyxic gasping.
- Numerous disorders may materialize as an apparent life-threatening event (ALTE), with hypoxia being a common end point in many. Management involves careful history taking and the use of a memory monitor to gather objective data if further events occur.

APNEA OF PREMATURITY

Apnea of prematurity (AOP) is a developmental and thus self-resolving disorder, which nonetheless can cause serious problems. Attempts to improve its treatment require an understanding of its pathophysiology, and this will be the focus of this chapter. Equally important, but completely unclear, are treatment indications (i.e., how much intermittent hypoxia and bradycardia can be tolerated without putting an infant at risk of neurodevelopmental impairment, and will this risk be reduced or even enhanced by some of the treatments currently available?).[1]

Almost every infant born at less than 29 weeks of gestation exhibits AOP.[2] No study, however, has yet identified a threshold in either frequency or severity of accompanying bradycardia or hypoxemia above or below which there is an increased risk for neurodevelopmental impairment. Most studies even suggested that within the frequency and severity of AOP tolerated in their institution, there is little indication that AOP, by itself, leads to impaired neurodevelopment.[3-7] This is surprising, given that *after* hospital discharge, infants with 5 or more apneas (>20 seconds) or bradycardias during at least 175 hours of documented home monitor use scored 5 points less on the Mental Development Index (MDI) at 1 year of age than those without such monitor alarms.[8] Other studies found that infants who had received theophylline or doxapram during their initial hospital stay had worse neurodevelopmental outcome (see later),[9,10] but these latter analyses cannot distinguish whether it is the symptom (AOP) or its treatment that is responsible for the neurodevelopmental impairment.

Given the lack of good outcome data, indications for treatment or a step-up in its intensity are bound to be arbitrary. From a physiologic point of view it is not the apnea but its effect on oxygenation and/or heart rate that is relevant to the well-being of an infant. For example, in German guidelines for AOP, this threshold has been set at six or more bradycardias (to <80/minute) or desaturations (to <80% pulse oximeter saturation [SpO_2]) occurring in a 6-hour period, with a reduction being suggested if less than two occur in the same period.[11] It has to be kept in mind, however, that these thresholds strongly depend on the averaging time used in the instrument with which they were measured (Fig. 30-1). Thus, their role is more in helping to standardize treatment than in defining a uniform threshold that is relevant to outcome.

Pathophysiology

RELATION BETWEEN APNEA, BRADYCARDIA, AND DESATURATION

One of the most striking findings in recordings of respiration, heart rate and SpO_2 in preterm infants is the close temporal relationship between apnea, bradycardia, and desaturation.[12] Early studies suggested that the bradycardia resulted from a chemoreceptor reflex elicited by the rapid development of hypoxemia during apnea.[13,14] Subsequent investigators, however, claimed that the fall in heart rate commenced too early during the apnea to be attributed to apnea-induced hypoxemia, and suggested instead that bradycardia was

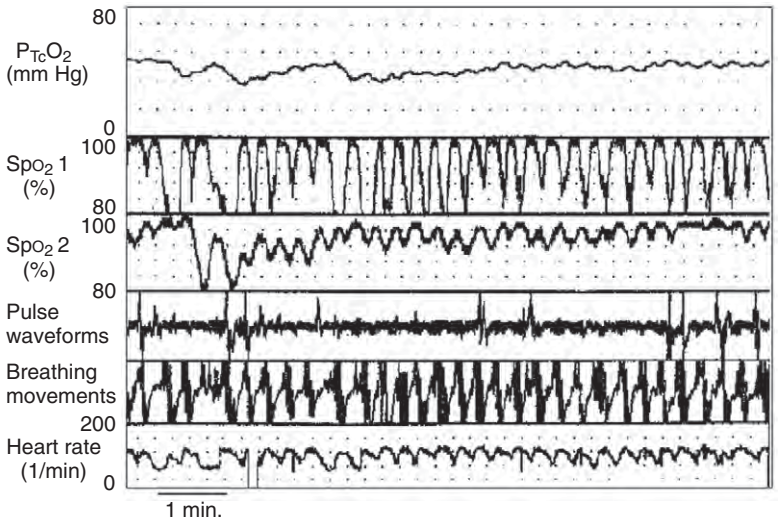

Figure 30-1 Influence of averaging time of the pulse oximeter on rates of intermittent hypoxia. Two pulse oximeters (Nellcor N200) are attached to the right and left foot of a preterm infant during periodic apnea. The upper pulse oximeter saturation trace (Spo_2 1) was recorded in a beat-to-beat mode, the lower one (Spo_2 2) in a 6-second averaging mode. Note that with the oximeter set in a non-averaging mode, 15 alarms to ≤80% Spo_2 would have been counted, in contrast to only two with the 6-second averaging mode. Unaccounted for, this purely technical difference might have resulted in different treatment decisions. Abbreviations: $P_{Tc}O_2$, partial pressure of transcutaneous oxygen tension; Spo_2, pulse oximeter saturation.

caused by a reflex response to the cessation of lung inflation.[15,16]

In an analysis of the relation between these three phenomena in 80 preterm infants (mean gestational age [GA] at study 36.3 weeks), most bradycardia (86% and 83%, respectively) was accompanied by hypoxia (SaO_2 < 80%) and apnea (>4 seconds) and commenced almost always *after* the onset of both apnea and hypoxia (median interval, 4.8 and 4.2 seconds, respectively). This was predominantly because the interval between the onset of apnea and that of desaturation, corrected for the time it takes for the blood to travel to the pulse oximeter sensor, was extremely short (median 0.8 seconds; Fig. 30-2).[17]

These temporal observations support the concept that hypoxemia causes bradycardia (e.g., via stimulation of peripheral chemoreceptors).[18] But why was it apparently not the hypoxemia per se, but its coincidence with an apneic pause that resulted in the development of bradycardia? The answer to this may be found in cross-perfusion experiments in dogs, where the fall in heart rate was far more pronounced if there was a combination of both apnea and hypoxemic excitation of arterial chemoreceptors than with either apnea or hypoxemia alone.[19] Thus, the appearance of bradycardia during apnea may be dependent on there being no overriding effect from the pulmonary inflation reflex, which is known to cause an increase in heart rate.[19] One possible explanation for the comparatively high frequency of bradycardia in preterm infants is, therefore, that bradycardia is primarily caused by hypoxemia, and that the resultant effects on heart rate are potentiated if there is no lung inflation. This would also explain why, despite a similar severity of the accompanying hypoxemia, bradycardia is more common with central than with mixed or obstructive apnea.[20]

Changes in Lung Volume During Apnea

A surprising finding in the aforementioned study[17] was the brevity of the interval between the onset of apnea and that of desaturation. It is tempting to speculate that there would have been far less bradycardia had the hypoxemia not occurred so early during apnea. It remains unclear, however, whether this early onset of hypoxemia was due to preceding hypoventilation, nonapneic mechanisms, or both. Hypoventilation was suggested to precede apnea[21] by Adams and colleagues, who found that 62% of events with Spo_2 less than 80% were preceded by breaths with a tidal volume of less than 50% of baseline.[21]

Figure 30-2 Example of the close temporal relation between apnea, bradycardia, and desaturation. The delay caused by the time it takes for the blood to travel from the lung to the pulse oximeter sensor attached to the foot can be estimated from the delay between the first breath following an apnea and the onset of the recovery in Spo_2 (C). This was subtracted from the interval between the onset of apnea and that of desaturation (A) and from the interval between the onset of bradycardia and that of desaturation (B; see text). (Reprinted with permission from Poets CF: Pathophysiology of apnea of prematurity: implications from observational studies. In Mathew OP: Respiratory Control and Its Disorders in the Newborn. Dekker, New York, 2003, pp 295-316.

A nonapneic mechanism that could explain the early onset of hypoxemia during apnea is a low lung volume. This is particularly relevant to young infants, whose relaxation volume is only 10% to 15% of total lung capacity and thus very close to residual volume, predisposing them to the development of airway closure.[22] To compensate for this disadvantage, both term and preterm infants actively maintain their end-expiratory lung volume above relaxation volume (which is one reason for their high respiratory rate),[23-25] whereas lung volume falls if respiration ceases.[26] During repeated measurements of functional residual capacity (FRC) in 48 "healthy" preterm infants (mean GA at study 36.6 weeks) during unsedated sleep, breathing movements and SpO_2 were recorded throughout and analyzed for apneas (>4 seconds), sighs, and desaturations ($SpO_2 < 90\%$) during the last 2 minutes prior to each FRC measurement.[27] Apneas resulted in a significant decrease in FRC: mean FRC was 20.0 mL/kg following an apnea, 26.0 mL/kg after a sigh ($P < 0.001$), and 23.9 mL/kg if there had been neither a sigh nor an apnea ($P < 0.05$). The interval between the apnea and the FRC measurement had no effect on FRC. Thus, apneas resulted in a persistent reduction in FRC, which was restored by a sigh. These findings provide further evidence for the hypothesis[28,29] that one of the main functions of sighs in preterm infants is to reverse falls in lung volume caused by apneas.

What does this have to do with the interval between apnea and desaturation? The FRC serves as a buffer to stabilize oxygenation during brief periods of apnea. Lung volume is an important determinant of the speed with which desaturation develops during voluntary breathholding,[30] and preapneic lung volume was found to have a strong influence on the hypoxemia that occurs during sleep apnea in adults.[31] Preterm infants also show such a relationship: the lower the lung volume *following* an apnea, the more rapid is the fall in SpO_2 *during* the apnea.[27]

A clinical scenario where the potential influence of lung volume on oxygenation becomes particularly evident is periodic apnea. During this respiratory pattern, SpO_2 was observed to fall twice as fast as during isolated apneas (8.4% versus 4.3% per second, $P < 0.005$).[12] Although other factors (e.g., a fall in mixed venous SO_2[32] may also play a role, the main reason for the more rapid fall in SpO_2 likely is a progressive fall in lung volume during the repeated apneas.

Another potential consequence of the reduction in lung volume occurring during spontaneous apneas is a further inhibition of respiration via activation of the Hering-Breuer deflation reflex. In term infants this vagally mediated reflex, which acts around FRC, terminates expiration while initiating inspiration. In preterm infants, however, induction of this reflex via chest compression resulted in a shortening of inspiratory time and a tendency to have short apneas (2 to 5 seconds).[33] A similar inhibition of breathing may result if lung volume falls spontaneously, for example, during apnea.

These considerations provide a theoretical basis for the effectiveness of strategies that increase or stabilize lung volume in reducing the frequency and/or severity of both bradycardia and desaturation in preterm infants.[34] In fact, Thibeault and coworkers[35] observed as long as 40 years ago that recurrent apnea may be abolished by increasing FRC via the application of negative extrathoracic pressure. The same effect can also be achieved by continuous positive airway pressure (CPAP; see later).[36]

The Role of Feeding and Gastroesophageal Reflux (GER)

A frequent observation in infants with AOP, first noted over 80 years ago,[37] is that symptoms increase during and after feeding. The hypothesis that this association could be a result of "the full stomach interfering with the action of the diaphragm" was put forward in 1936.[38] Since then the effects of feeding on respiration have been studied extensively.[39-49] It is now clear that some preterm infants, particularly those with bronchopulmonary dysplasia (BPD), may become severely hypoxemic during and immediately after bottle feeding,[38-42] and that gavage feeding may also cause a significant reduction in blood oxygen levels.[43-46] Hypoxemia *during* feeding may be caused by a reduction in minute ventilation due to an immature coordination between breathing, sucking, and swallowing,[42,46-48] activation of the laryngeal chemoreceptor reflex,[49] gastroesophageal reflux (GER), diaphragmatic fatigue,[50] or combinations of these mechanisms. Hypoxemia *after* feeding was suspected to be due to a reduction in lung volume and an increased work of breathing resulting from gastric distention.[47] If this were true, avoidance of gastric distention via slow or continuous gavage feeding should ameliorate the problem.

However, in a study on the effect of bottle feeding, as compared to slow and fast (10 min) gavage feeding, on AOP, there were 3 times more falls in SpO_2 to less than 80% with bottle than with bolus gavage feeding, but no further reduction with slow gavage feeding. With all three feeding techniques there were significantly more desaturations in the hour the feeds were given. The deleterious effects of bottle feeding were most evident during the hour of feeding, but desaturation frequency remained significantly higher than with gavage feeding during the following 2 hours. In contrast, there was no significant effect of feeding technique on the frequency of apnea or bradycardia.[51]

Although the deleterious effects of bottle feeding on respiration may be avoided by postponing bottle feeds in infants with severe AOP, it is puzzling that slow gavage feeding offered no advantage over bolus feeds, because it should have prevented gastric distention.[52] This hints toward GER as an explanation for the observed increase in desaturation with feeding

A relation between GER and AOP has long been suspected[53,54] but was difficult to prove because most GER in this age group is nonacidic and, thus, undetectable by pH-monitoring, which is the current standard for GER detection. Using the multiple intraluminal impedance (MII) technique, however, which allows pH-independent reflux detection,[55] the frequency of apnea, bradycardia, or hypoxia occurring within ±20 seconds of a reflux episode (RE) was *not* found to be significantly different from that found during reflux-free epochs.[55] Also, RE occurred similarly often within 20 seconds before or after an apnea. Thus, it appears that both cardiorespiratory events and GER are common in preterm infants but, with few exceptions, do not appear to be temporally related.[55,56]

Thus, the widespread practice[57] of giving antireflux medications to infants with AOP most likely is futile. It remains unclear, however, why AOP is so closely associated with feeding. One alternative explanation is diaphragmatic fatigue. Diaphragmatic work increases significantly after gavage feeding, whereas FRC decreases,[47] but whether this is sufficient to cause diaphragmatic fatigue in relation to feeding remains, at present, unknown.

Chest Wall Distortion, Anatomic Dead Space, and Diaphragmatic Fatigue

What is the evidence that diaphragmatic fatigue plays any role in the pathophysiology of AOP? Because of their highly compliant chest wall, preterm infants are disadvantaged with regard to their respiratory mechanics. Chest wall distortion, clinically apparent as paradoxical breathing, is common in infants and is especially visible in preterm infants. It has been suggested that this distortion increases the volume displacement of the diaphragm during inspiration.[50,58] In longitudinal studies, Heldt showed that the minute volume displacement of the diaphragm was almost twice as large as pulmonary ventilation at 29 to 30 weeks GA and fell to approximately 90% of pulmonary ventilation at 36 weeks GA. Concomitantly, diaphragmatic work was almost halved.[59] The author speculated that this additional workload may represent not only a significant energy expenditure in these infants but may also contribute to the development of diaphragmatic fatigue and apnea.[59] Further contributing to this fatigue is the fact that, because of their relatively large head size, anatomic dead space is approximately 45% of tidal volume in newborns compared to 25% in adults.[21,25]

Circumstantial evidence that muscle fatigue may indeed be involved in neonatal apnea stems from the time course of apnea in term and preterm infants. This was already noted over 40 years ago to become more problematic toward the end of the first week of life,[60] whereas chemoreceptor resetting, which otherwise might also explain this phenomenon, is essentially complete within approximately 24 to 48 hours of birth.[61] Periodic apnea also starts usually only after day 2 of life, reaching a maximum during the second and third week.[62] In our own studies, preterm infants studied at around 4 weeks of age showed more desaturation than those studied during their first week of life, but at a lower postconceptional age: although the 95th centile for desaturation frequency was 8 per 12 hours in the latter group, it was 61 in the former.[63] A similar relation between postnatal age and desaturation rate was found for term infants (Fig. 30-3).[64] A mechanism through which labored breathing may produce apnea in preterm infants is the intercostal-phrenic inhibitory reflex. This may be elicited both by rib cage distortion[65] and respiratory loading,[66] and is known to inhibit respiratory effort in infants. Also, frequency spectrum analysis in diaphragmatic EMG recordings in preterm infants showed that, in 7 of 15 infants studied, EMG segments indicating diaphragmatic fatigue were followed by periods of apnea.[50] Thus, it is conceivable that similar to the obstructive sleep apnea syndrome in adults, where an increased work of breathing can lead to more central apneas, it may also play a role in the pathophysiology of AOP.

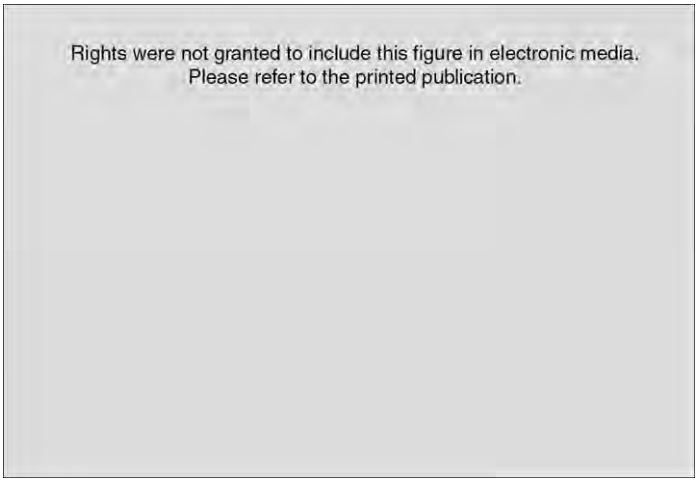

Figure 30-3 Data on the proportion of 12-hour recordings containing prolonged episodes of desaturation (SpO_2 < 80% for >4 seconds) and on the 95th centiles for desaturation rate per 12 hours in various groups of term (*right half*) and preterm (*left half*) infants. Note that intermittent hypoxia in both term and preterm infants is less frequent shortly after birth than at 2 to 3 weeks of age and decreases again thereafter. Median age at study for each group is given both as postconceptional (week) and postnatal (day) age. (Redrawn with permission from Poets CF: Pathophysiology of apnea of prematurity: implications from observational studies. In Mathew OP: Respiratory Control and Its Disorders in the Newborn. Dekker, New York, 2003, pp 295-316.

Upper Airway Obstruction

Traditionally, apnea has been divided into central, obstructive, and mixed. However, analyses of artefacts on the nasal thermistor signal, produced by the transmission of cardiac impulses on the patent airway, revealed that airway obstruction may also occur during apparently central apneas.[67] By amplifying these cardiac oscillations, Rigatto's group found indications for airway narrowing during 13% of apparently central apneas, starting after only 1 second. They speculated that their finding reflects a loss of upper airway muscle tone during apnea.[68] The same group also reported that diaphragmatic action is not needed to occlude the airway in mixed apneas, and speculated that airway closure during these apneas most likely reflects a lack of upper airway muscle tone that is not reinstated at the time the diaphragm starts to contract again.

An alternative explanation for the airway occlusion potentially occurring during apparently purely central apneas originated from continuous EMG recordings of the laryngeal adductor muscle in lambs, which found continuous EMG activity throughout 88.4% of all apneas and 98.4% of those occurring during periodic breathing, independent of sleep state.[69] EMG activity, however, was less likely to be continuous during apneas that were triggered by a sigh or a swallow. The authors concluded that active glottic closure, similar to that preventing outflow of lung water during the prolonged apneas that occur in utero,[70] would prevent gas from flowing out from the lungs, thereby preserving lung volume during apnea. Although evidence for active glottic closure has also been reported during obstructive apneas in human preterm infants and in a case report on a term infant during periodic breathing,[71,72] it is not yet known whether active glottic

closure generally occurs during central apneas also in the human preterm infant.

Not only can apparently central apnea result in upper airway obstruction, but also vice versa. Upton and colleagues studied the response to airway obstruction in 23 preterm infants born at less than 33 weeks' gestation.[73] Of 398 obstructions recorded, apnea occurred *during* the obstruction in 19%, and *upon relief* of the obstruction in 32%. This happened independently of where in the respiratory cycle the obstruction occurred. They speculated that their observation on the response to airway occlusion may be important in the prolongation of initially short respiratory pauses during which airway closure may occur.[74]

Waggener and coworkers[75] analyzed oscillations in breath-by-breath ventilation of preterm infants, and observed that central, mixed, and obstructive apneas all occurred at the minimum phase of spontaneous ventilatory oscillations, suggesting that all three patterns had one common underlying mechanism. Hence, it appears that all three apnea types form a continuum (i.e., that obstructive components are also involved in apparently purely central apneas and vice versa). This is probably related to the fact that the narrow upper airways of preterm infants are actively maintained open via a respiratory center input, and that it depends on which component stops being activated first (diaphragm or upper airway) whether an apnea will appear as central or obstructive. At autopsy the upper airway of young infants is closed, again suggesting that a neuromuscular mechanism is necessary to maintain airway patency during life.[76] The mechanism(s) through which airway closure occurs during apnea, however, is largely unclear. One factor may be flow- or pressure-sensitive airway receptors. In animal experiments, flow up and down the upper airway resulted in the maintenance of pharyngeal patency via increased genioglossus activity.[75] Thus, when flow ceases genioglossus activity falls and the airway collapses. Alternatively, cessation of respiratory drive may cause an immediate loss of lower (and probably also upper) airway tone,[77] or airway closure occurs as an active reflex as suggested from the preterm lamb data mentioned earlier.[69] Whatever the precise mechanism for both apnea types, the strict separation into apparently purely central or purely obstructive apneas cannot be maintained in the light of these data.

Hypoxic Ventilatory Depression (HVD)

It has been known for nearly 70 years that respiration in the fetus is diminished if oxygen supply via the placenta is reduced.[78] This is in contrast to adults, who show a sustained increase in ventilation in the presence of hypoxia. Although this is probably beneficial in fetal life, where respiratory movements are a waste of energy that the fetus cannot afford if oxygen supply via the placenta is reduced, this pattern is counterproductive ex utero. The switch-over from the fetal to the adult hypoxic ventilatory response only occurs some time after birth,[79] probably not before 35 weeks postconceptional age. This correlates well with the age at which AOP usually resolves.[80] When investigating the role of hypoxic ventilatory depression in AOP, however, infants with more apnea were found to have *less* ventilatory depression during a hypoxic challenge.[81] This issue requires further study.

Below what Pa_{O_2} level does HVD occur? This has not been studied systematically in infants. An early study suggested, however, that breathing already becomes irregular, and apnea starts to occur, if Pa_{O_2} falls below 75 to 97 mm Hg, levels close to or even above those associated with an increased risk of retinopathy of prematurity.[82] Weintraub and colleagues measured minute ventilation in 15 preterm infants (mean GA 29 weeks, age 20 days) at 21%, 25%, 30%, 35%, and 40% oxygen. With the increase in F_{IO_2}, breathing became more regular, apneas decreased, but minute ventilation did not change significantly; only breath-to-breath variability in expiratory times and tidal volume decreased. They concluded that oxygen facilitates the appearance of regular breathing independently of an increase in minute ventilation.[83] Interestingly, their study subjects had a relatively low Sp_{O_2} in room air (mean, 90.8%), which increased to 92.5% in 25% O_2. Even this relatively small increase in F_{IO_2} was associated with a decrease in apnea rate (>3 seconds) from 128 to 63 per hour ($P < 0.05$). Thus, although not necessarily resulting in a fall in minute ventilation, breathing irregularities and an increased propensity for short apneas may already develop at a Pa_{O_2} below 60 to 90 mm Hg. Whether this response to changes in Pa_{O_2} is mediated via the same mechanisms that elicit the HVD, however, is not yet known.

The molecular mechanisms responsible for HVD and the switch-over to the adult pattern are also unknown. One potential mechanism involves the creatine-phosphocreatine (Cr-PCR) system. In the absence of oxidative phosphorylation, provision of phosphate for generation of adenosine-triphosphate (ATP) relies predominantly on the PCR pool, before anaerobic glycolysis, with increased production of lactate and H^+, is activated.[84] This may also be relevant to the adaptation of ventilation during hypoxia. Investigations of the cytosolic levels of PCR during moderate hypoxia in adult rats by 31P nuclear magnetic resonance spectroscopy of the brain stem showed that the occurrence of HVD was preceded, by 30 seconds, by a significant decrease in PCR levels. This reached its minimum level 30 seconds after maximal respiratory depression and occurred without a significant change in ATP levels.[85] In the neonatal rat brain, total creatine kinase activity increases two to three times over the first month of life, reflecting a doubling of PCR content during this time span.[86] Thus, the neonatal brain is relatively deficient in creatine, and it is tempting to speculate that the much earlier onset of the HVD in this age group is related to a decreased availability of PCR in the neonatal brain stem. PCR is also important in muscle metabolism, where it serves as an energy buffer to guarantee provision of sufficient substrate for the phosphorylation of ADP to ATP.[87] In adults, creatine supplementation resulted in an increased exercise performance[88] and less muscular fatigue.[89] Wilken and coworkers recently showed that brain stem slices from pups of creatine-fed mice (2 g/kg/day) showed higher phosphocreatine contents and significantly less HVD (–14% versus –41%), than those from nonsupplemented control animals. This corresponded to nearly constant cerebral ATP levels in the former versus a 54% decrease in the latter animals after 30 minutes of anoxia.[90] Also, measurements of the maximal respiratory amplitudes in such pups during hypoxia showed an increase by 51%, compared to 22% in control animals.[91] Although the newborn apparently is creatine deficient, it

remains unclear whether creatine supplementation can ameliorate the characteristic HVD seen in this age group (see later).

Relevance of the CO_2 Apneic Threshold

Respiratory drive depends not only on O_2, but also on CO_2. A baseline concentration of CO_2 is essential for breathing to occur; conversely, if P_{CO_2} falls considerably below eupneic baseline, apnea occurs. The P_{CO_2} value at which this occurs is called the apnea-hypopnea threshold; it is approximately 3.5 mm Hg below eupneic P_{CO_2} in healthy adults.[92] It has been suggested that the closer this eupneic P_{CO_2} is to threshold P_{CO_2}, the more unstable breathing becomes, as minor behavioral changes in ventilation would be sufficient to propel the P_{CO_2} to below threshold, thereby inducing apnea.[92] Recently, Khan and associates measured the apneic P_{CO_2} threshold before and after an epoch of periodic breathing in term and preterm neonates. They found that the spontaneous pre-apneic threshold in both groups was only 1 to 1.3 mm Hg below eupneic values and speculated that this closeness between eupneic and apneic thresholds destabilizes respiration in neonates compared to older subjects, as minor oscillations in breathing may already lead to apnea.[93] Whether the logical clinical consequence of these findings, namely CO_2 inhalation as an apnea treatment, has any long-term effect on apnea rates remains to be seen.[93]

Therapeutic Implications

Based on the pathophysiology just discussed, interventions can be grouped according to three underlying mechanisms of action: those aimed at (1) reducing work of breathing, (2) increasing respiratory drive, and (3) improving diaphragmatic contractility. When considering the pros and cons of the interventions currently applied, the reader should keep in mind that the long-term benefit (or harm) of any intervention for AOP currently applied has never been proved, nor has the role of AOP in affecting long-term outcome ever been identified.[94]

Interventions Aimed at Reducing Work of Breathing

PRONE HEAD-ELEVATED POSITIONING

In the prone position, the chest wall is stabilized and thoracoabdominal asynchrony is reduced.[95] Several studies have demonstrated that the prone position reduces apnea rate in preterm infants, with some also reporting a decrease in desaturation rate.[95-98] An extension of the prone position is the head-elevated prone tilt position, which in a cross-over study on 12 neonates was associated with a 49% reduction in desaturations to less than 85% compared to the horizontal prone position.[99] Recently, however, two studies reinvestigated the issue, driven by the observation that infants appear more comfortable when only the chest rather than the entire body is being tilted. Whereas one found a slight (–13%) but statistically significant reduction in desaturation rate compared to the horizontal position,[100] the other did not find an advantage for either position (own unpublished data). Thus, the effect of head-up positioning on bradycardia and intermittent hypoxia may be less pronounced than previously thought. As it does not appear to have any deleterious effect, we continue to consider it a first-line intervention for infants with AOP. Infants, however, should be placed in supine position approximately 1 week prior to discharge to set an example for the sleep position that should be adopted at home (see primary prevention).

REMOVAL OF NASOGASTRIC TUBES

A nasogastric tube increases nasal resistance by 50%.[101] In line with these data, less apnea and a higher P_{O_2} were reported after removal of a feeding tube,[102] but this observation was based on only seven infants. Further study is required, which should also clarify whether an orogastric tube, or a nasal tube placed in the *smaller* of the two nares,[101] has a similar effect.

CONTINUOUS POSITIVE AIRWAY PRESSURE AND NASAL VENTILATION

CPAP has been shown to reduce extubation failure in preterm infants,[103] despite the fact that most systems currently available do *not* reduce work of breathing.[104] It has been suggested that CPAP reduces only the frequency of obstructive, not central apneas,[105] but it may also act via a stabilization of lung volume and thereby oxygenation (see earlier). CPAP can be applied via a nasopharyngel tube or binasal prongs. A Cochrane meta-analysis showed that reintubation rates were 40% lower with the binasal prongs (relative risk [RR] 0.59 [0.41;0.85]; number needed to treat [NNT] 5),[106] which is why this mode should be preferred when applying CPAP. An extension of CPAP treatment is nasal positive pressure ventilation (N-IPPV), which compared to CPAP has an extremely high effectiveness in preventing extubation failure (RR 0.21 [0.10;0.45]; NNT 3).[107] Typically, an inspiratory pressure of 15 to 20 cm H_2O, applied at a rate of 10 to 20 per minute, is combined with an expiratory pressure level of 5 to 6 cm H_2O.[108] There is theoretical concern that this might result in gastric distention because the peak pressure applied to the larynx exceeds the opening pressure of the upper esophageal sphincter. In clinical practice, however, gastric distention is not a relevant side effect.[107]

Interventions Aimed at Increasing Respiratory Drive

OXYGEN ADMINISTRATION

That oxygen stabilizes neonatal respiration was first observed in 1923[37]; its uncritical use following this discovery led to the first epidemic of retrolental fibroplasias, now known as retinopathy of prematurity, 20 years later. Nonetheless, several cross-over trials in infants with and without BPD have shown that the application of low-flow oxygen results in a reduced rate of intermittent hypoxia and both isolated and periodic apnea,[62,83,109,110] but application of this therapy has to be weighed against side effects potentially resulting from oxygen toxicity.[111] These issues must be addressed in a large, randomized controlled trial (RCT) before recommending this therapy for routine use in preterm infants.

RED BLOOD CELL TRANSFUSIONS (RBC)

An increase in respiratory drive resulting from an increased tissue oxygenation is also one of the proposed mechanisms for red cell transfusion to potentially ameliorate AOP, and

anemia has indeed been implicated in the pathophysiology of AOP and also of cyanotic episodes in infants.[112,113] It would seem logical to hypothesize that blood transfusion is an effective treatment modality in infants with AOP who are anemic. Data on the effect of blood transfusion on the frequency of these episodes, however, are conflicting. Some authors found less apnea and/or bradycardia following transfusion,[114-118] others did not.[119-121] Two cross-over studies including data on SpO_2 also found no improvement in intermittent hypoxia and bradycardia following transfusion.[122,123] Recently, however, Bell and colleagues published the results of an RCT comparing a liberal with a more restrictive transfusion policy in 100 very low birth weight (VLBW) infants.[124] Hematocrit was kept at >45% versus >35% if intubated; >38% versus >28% if on CPAP, and >30% versus >22% if no respiratory support was required. Mean rate of apneas requiring stimulation was 0.23/hour in the liberal versus 0.46/hour in the restricted transfusion group. A potential explanation for this apparent effect of red cell transfusion, however, could be that significantly more infants in the restrictive transfusion group happened to have brain lesions and were more likely to develop AOP. Nonetheless, a subanalysis only in the restrictive group also showed a 55% reduction in apnea rate following transfusion ($P < 0.01$). Based on these conflicting findings, no clear recommendation on the role of RBC in anemic VLBW infants with AOP can be given.

METHYLXANTHINES

Methylxanthines increase chemoreceptor sensitivity as well as respiratory drive and can also improve diaphragmatic contractility. Of the substances available, caffeine has a wider therapeutic range, fewer side effects, and better effect on bradycardias than theophylline.[125,126] Methylxanthines, however, are adenosine antagonists. Because adenosine increases tolerance to hypoxia, they may also be harmful in the VLBW infants who need them most (i.e., those with recurrent hypoxia resulting from severe apnea).[1] In addition, the only RCT investigating the effect of caffeine on recurrent hypoxia did not show an effect.[127] Also, a follow-up study reinvestigating 130 of 154 consecutive VLBW survivors at 14 years of age found that 13% of 69 infants exposed to theophylline had cerebral palsy versus 1.6% of those not exposed; this association remained after controlling for confounders.[9] The concerns surrounding the use of methylxanthines could only be addressed by performing an RCT, and first results from such a trial, enrolling more than 2000 infants, were recently reported.[128] Caffeine or placebo was started during the first 10 days of life in infants of 500 to 1250 g birth weight and was given at a dose of 5 to 10 mg/kg caffeine citrate until no longer needed for AOP treatment. Mechanical ventilation, CPAP, and oxygen could all be discontinued approximately 1 week earlier in infants treated with caffeine. Somewhat unexpectedly, and not a primary end point, was the finding of a 40% lower risk of BPD (36% versus 47%; odds ratio [OR] 0.6; 95% CI 0.5;0.8) and a 30% lower risk of developing a symptomatic patent ductus arteriosus (OR 0.7; [0.5;0.8]) in the caffeine group.[128] Results from the 18-month follow-up have been published in abstract form. They show a reduced rate of cerebral palsy and less cognitive delay in infants in the caffeine group.[129]

DOXAPRAM

Doxapram stimulates peripheral chemoreceptors at low, and central chemoreceptors at high, doses.[130-132] It shows a dose-response curve with a 50% reduction in apnea rate occurring in 47%, 65%, 82%, and 89% of infants at a dose of 0.5, 1.5, 2.0, and 2.5 mg/kg/hour, respectively. Most studies used a continuous intravenous infusion, although some suggest that the intravenous solution may also be given orally at twice the dose[133-135] (enteral absorption is approximately 50%).[136] Short-term side effects become quite common at doses above 1.5 mg/kg/hour and include irritability, myoclonus, elevated blood pressure, and gastric residuals.[131] Of most concern, however, is the fact that nothing is known about the long-term neurologic outcome after doxapram treatment. This is particularly unsatisfying given that doxapram is a centrally acting drug. A study on factors associated with poor motor development in extremely low birthweight infants used a case-control design to match variables such as GA, sex, intraventricular hemorrhage, and socioeconomic status for 40 patients with a mental development index (MDI) less than 70 and an equal number of controls. The only difference found was that subjects had received a mean cumulative doxapram dose of 2233 mg, compared to 615 mg in controls ($P < 0.01$).[10] Although such a retrospective analysis cannot distinguish whether this reflects the severity of apnea for which doxapram had been given or a direct drug effect, it clearly raises concern about long-term side effects of this drug. Without such data, doxapram cannot be recommended to treat AOP.

CREATINE

As mentioned earlier, creatine is likely involved in HVD. An RCT on creatine supplementation (200 mg/kg/day) or placebo in 38 infants, however, showed no effect on the combined rate of bradycardia and desaturation, but it remains unclear whether the dose, duration, and timing of treatment were sufficient for an effect to be achieved.[137]

Interventions Aimed at Improving Diaphragmatic Strength

If muscle fatigue is involved in AOP, then improvements in diaphragmatic strength should be beneficial. This consideration, however, remains speculative. Our own results on creatine supplementation, which should improve muscular exercise performance (see earlier), were disappointing. Another study enriched total parenteral nutrition (TPN) solutions with branched-chain amino acids, which improve diaphragmatic function in vitro, and found a decrease in the average number of episodes of apnea from 58 during standard TPN to 11 with the enriched solution infusion during matched 12-hour periods ($P < 0.01$) in an unblinded cross-over study design.[138] This somewhat original approach to the treatment of AOP should be investigated further.

Others

OSCILLATING WATERBED

The theory behind this intervention is that entrainment can be achieved between an infant's own breathing rhythm and an external rhythm generator (e.g., an inflatable mattress

connected to a respirator). A meta-analysis of 3 RCTs testing this intervention, involving a total of 165 infants, showed no effect on apnea or bradycardia (RR 1.06; 95% CI 0.82;1.36).[139] This may be explained by the observation that synchronization with an external rhythm generator is significantly better beyond 35 weeks GA than before that,[140] but at that age AOP is no longer a major issue. As a result, this intervention has largely been abandoned in recent years.

OLFACTORY STIMULATION

A French group made the chance observation that odors modulated an infant's respiratory pattern, particularly during active sleep, when apnea is more common.[141] This led them to study the effect of exposure to vanillin, a stimulus known selectively to affect the olfactory nerve, on apnea and bradycardia. In a group of 14 infants born at 24 to 28 weeks GA (mean age at study 22 days) and unresponsive to both caffeine and doxapram, they found that exposure to 15 drops of saturated vanillin solution applied on the periphery of an infant's pillow led to a 45% reduction in the frequency of apnea associated with bradycardia to less than 70 per minute.[142] They hypothesized that the presence of a pleasant odor helped the infants better to regulate their psychological and physiologic states. Although many questions remain, this is another approach that is worth more investigation.

Summary of Data on Apnea of Prematurity

Despite some evidence of brain stem immaturity in infants with AOP,[143] there is nothing to suggest that these infants have gross deficits in respiratory control.[144] As suggested by the data summarized earlier, it appears that the early (and frequent) occurrence of hypoxemia during apnea in preterm infants is related to their low expiratory lung volume, which falls even further during apnea, while the accompanying bradycardia results from this combination of apnea and hypoxemia. Feeding is an important trigger for AOP. While hypoxemia *during* feeding is most likely related to an immature coordination between sucking, swallowing, and breathing, that *after* feeding may be caused by diaphragmatic fatigue; GER does not appear to play a major role. The time course of AOP (i.e., its increased occurrence during the second and third rather than the first week of life, together with data from physiologic studies), also suggests a role for diaphragmatic fatigue in AOP. Additional factors include upper airway obstruction and the unique response of the preterm to hypoxia. Treatment may follow an incremental treatment plan, starting with infant care procedures such as prone positioning, followed by methylxanthines and CPAP/N-IPPV (Table 30-1). What is urgently needed are data on how much intermittent hypoxia/bradycardia can be tolerated in an individual infant without putting her/him at risk, and whether pharmacologic treatments such as caffeine or doxapram are safe, although this has now been demonstrated for caffeine.[129]

Table 30-1
Incremental Treatment Plan for Apnea of Prematurity (AOP)

Step 1: Changes in neonatal care procedures
15-degree head tilt—prone position
Gavage feeding via orogastric tube
SpO_2 at upper limit of range used in the unit
Step 2: Caffeine
Step 3: Nasal continuous positive airway pressure (CPAP)
Step 4: Nasal intermittent positive pressure ventilation (N-IPPV)
Step 5: Intubation and mechanical ventilation*

*Doxapram may be considered as an alternative to intubation in infants who have been found to exhibit recurrent hypoxia and bradycardia during mechanical ventilation, e.g., those with chronic lung disease.

SUDDEN INFANT DEATH SYNDOME (SIDS)

History

Sudden and unexpected infant deaths have been recognized since biblical times (I Kings 3:19: "And this woman's child died in the night; because she overlaid it"). As in the Bible, these deaths were believed to be caused by the parents accidentally or intentionally overlaying their children. For example, a law issued in medieval Germany in 1291 forbade parents to take children younger than 3 years of age into their bed[145]; a very similar law still existed in Prussia in 1791.[146] In 1834, Fearn was the first who argued against overlaying as the cause of death. He used the term "sudden and unexplained death" in his description of two infants "who, without having been previously indisposed, were found dead in bed" and in whom he could not discover any "lesions . . . sufficient to produce death."[147]

One of the first scientific attempts to explain sudden and unexpected infant deaths was made by Paltauf, an Austrian pathologist, in 1889. He observed an enlarged thymus, a narrowing of the aorta and an over-development of the lymphatic system in infants who had died suddenly and unexpectedly and introduced the concept of "status thymicolymphaticus."[148] Despite good evidence against it, this concept persisted into the first half of the 20th century, leading to the prophylactic irradiation of the thymus, with subsequent malignancy of the thyroid, in the 1920s. With the decline of this theory in the 1930s, voices accusing the parents of having killed or neglected their babies grew again, and it was only in the 1950s and 1960s that doctors became aware that these deaths might form a distinct entity of unexplained natural deaths. From today's perspective, the concept of "status thymico-lymphaticus" may be regarded as one of the first "modern" attempts to explain these deaths, and its uncritical adoption, resulting in potentially harmful preventive measures, bears similarities to the apnea theory developed some 80 years later.[149]

In 1970, Bergman and colleagues[150] coined the term *sudden infant death syndrome* (SIDS), which they defined as the "sudden death of an infant or young child, which is unexpected by history, and in which a thorough postmortem examination fails to demonstrate an adequate cause for death." This definition clearly has its weaknesses, which predominantly relate to the fact that it defines a syndrome by exclusion.[151] Nevertheless, it helped with transmitting to the public that the vast majority of sudden unexpected deaths in infants have a natural cause.

Terminology

The term SIDS was recently redefined by an expert panel as "the sudden unexpected death of an infant less than 1 year

of age, with onset of the fatal episode apparently occurring during sleep, that remains unexplained after a thorough investigation, including performance of a complete autopsy and review of the circumstances of death and the clinical history." To facilitate research, this definition was stratified into cases with the "classic" features of SIDS present and completely documented (so-called Category IA SIDS), those with these features present, but incompletely documented (IB), and those meeting Category I criteria except for any of the following: age less than 3 weeks or more than 270 days; similar deaths in siblings; close relatives or infants in the custody of the same caregiver; perinatal conditions such as a history of premature birth; suspected mechanical suffocation; or marked inflammatory changes not sufficient to be assigned a cause of death (Category II SIDS).[152] According to this definition, all cases not meeting criteria for category I or II SIDS, including those for which an autopsy has not been performed, are now called "unclassified sudden infant death."[152] The practicality of this new definition, and its subclasses, remains to be seen.

An apparent life-threatening event has been defined as "an episode that is frightening to the observer and that is characterized by some combination of apnea (central or occasionally obstructive), color change (usually cyanotic or pallid but occasionally erythematous or plethoric), marked change in muscle tone (usually marked limpness), choking, or gagging."[153] In clinical practice, the acronym "ALTE" has been restricted to events that fulfill the above criteria and involve vigorous stimulation or resuscitation. This somewhat narrower definition will also be used in this chapter.

There is no consistent definition for apneas. In this chapter, the term "apneic pause" will be used to describe spontaneous interruptions in breathing movements and nasal airflow, lasting for 4 to 20 seconds, and "prolonged apneic pause" for those apneic pauses that last for more than 20 seconds. The term "periodic apnea" will describe a pattern during which three or more apneic pauses, each followed by less than 20 breaths, occur in sequence. An "obstructive apnea" is characterized as an episode of continuous breathing movements, but absent airflow, presumably caused by intermittent upper airway closure, and a "mixed apnea" is a combination of an obstructive event and an apneic pause of any length.

Epidemiology

INCIDENCE

In contrast to previous centuries, when sudden unexpected deaths accounted for only a small fraction of total infant mortality, SIDS is now the leading cause of post-perinatal mortality in developed countries, accounting for approximately 2600 deaths per year in the United States alone.[154] In the early 1970s, an alarming trend toward an increase in SIDS rates occurred, which at that time was related to the recent introduction of SIDS as a cause of death (i.e., to changes in diagnostic fashion). Only in the late 1980s was the discovery made that SIDS rates had begun to increase shortly after general advice had been given that babies should be put to sleep in the prone position.[155,156] SIDS rates then decreased again after this advice was reversed[157] (Fig. 30-4; Table 30-2). Although the initial increase and subsequent decrease reflected a true change in incidence, as they were paralleled by similar changes in postneonatal mortality, there is now a trend to classify many deaths previously diagnosed as SIDS into other categories such as (positional) asphyxia. In fact, a

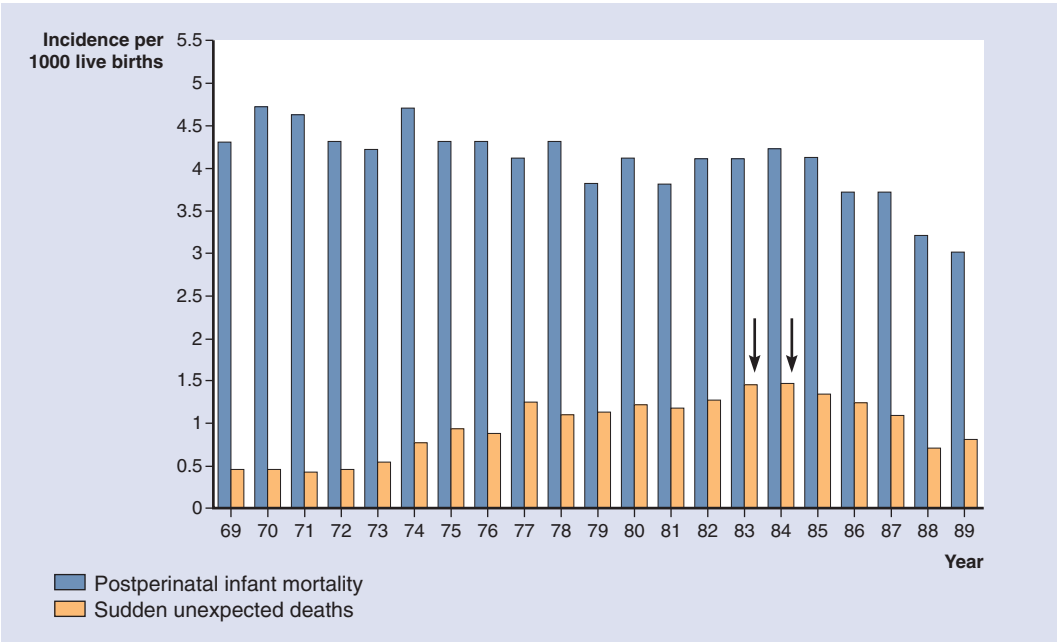

Figure 30-4 Changing trends in post-perinatal infant mortality (*blue bars*) and sudden unexpected deaths (*yellow bars*) in The Netherlands, 1969 to 1989. *Arrows* indicate years when sudden death incidence was not corrected for autopsy data—the given incidences during these 2 years are, therefore, estimated as being 10% too high. The prone sleeping position was publicly recommended in 1972. A campaign aimed at avoiding the prone sleeping position was started in October, 1987. (Redrawn with permission from Engelberts AC, de Jonge GA, Kostense PJ: An analysis of trends in the incidence of sudden infant death in The Netherlands 1969-89. J Paediatr Child Health 27:329-333, 1991.)

Table 30-2
Sudden Infant Death Syndrome (SIDS) Incidence in Different Countries, 1987 Versus 1997*

Country	Rate (deaths/1000 live births) 1987	Rate 1997
Australia	2.18	0.60
Austria	1.63	0.58
Canada	1.06	0.47
England/Wales	2.40	0.60
Germany	1.64	0.88
Hong Kong	0.30	0.16*
Netherlands	0.91	0.17
New Zealand	4.30	1.50
Sweden	0.90	0.41†
United States	1.37	0.77

*Data for 1999-2002.
†Data for 1995 derived from Ponsonby AL, Dwyer T, Cochrane J: Population trends in sudden infant death syndrome. Semin Perinatol 26:296-305, 2002; Nelson T, To KF, Wong YY, et al: Hong Kong case-control study of sudden unexpected infant death. N Z Med J 118:1788, 2005.

recent analysis of U.S. mortality data showed that concurrent increases in postneonatal mortality rates for unknown and unspecified causes and suffocation accounted for 90% of the decrease in SIDS rates in 1999 to 2001.[158] Agreement on a more standardized approach to certifying sudden infant death may help to avoid this worrying development, as was attempted with the introduction of the new SIDS definition (see earlier).

In addition to differences between countries, SIDS rates also differ between ethnic groups within a country.[159-161] These differences may be related to both socioeconomic and genetic factors.[162,163] For example, Mitchell and coworkers, in a nationwide study in New Zealand, found a decrease in OR from 3.8 to 1.4, the latter being no longer significant, when they controlled their results on SIDS rates in Maori versus non-Maori infants for socioeconomic confounders.[161] In recent years, differences in the efficiency with which the Reduce-The-Risk campaigns reached the different groups also contributed to this ethnic variation in SIDS rates.[164,165]

AGE AND TIME OF DEATH

One of the most striking epidemiological features in SIDS is its characteristic age distribution (Fig. 30-5). There is a relative sparing of the neonatal period, then a sharp increase in the second month of life, a peak at around 3 months of age, and a gradual decrease thereafter. Hence, 75% of deaths occur between 2 and 4 months of age, and 95% before 9 months of age.[154,166] This age distribution is related to gestational, not postnatal age: in VLBW infants (≤1500 g), the peak incidence occurs about 6 weeks later.[166] Early beliefs that SIDS is extremely rare in the neonatal period cannot be maintained: 6% to 7% of SIDS victims are younger than 1 month of age,[154,166] and 11% of neonatal deaths in term infants are due to SIDS.[167]

Throughout the year there used to be a clear preponderance of the cold season. In the northern hemisphere, up to 95% of deaths occurred between October and April.[168] This seasonal distribution has been related to respiratory tract infections, which show a similar distribution and are frequently reported to precede death.[169] Infections may also be the explanation for observations of a clustering of deaths,

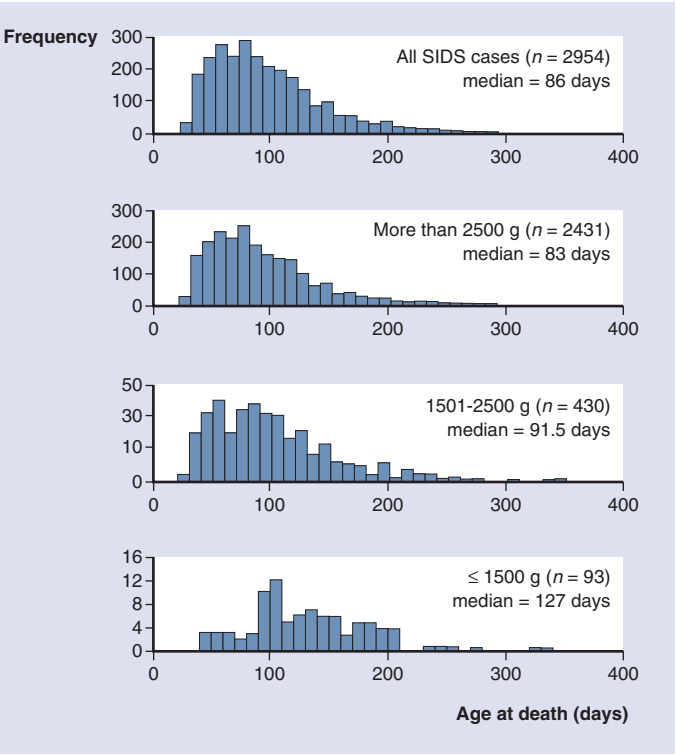

Figure 30-5 Histograms for age at death for three birth weight groups of SIDS cases in California from 1978-1982. (Reprinted with permission from Grether JK, Schulman J: Sudden infant death syndrome and birth weight. J Pediatr 114:561-567, 1989.)

with multiple cases on one day and long "silent" periods on others.[170] This clustering of deaths may coincide with the outbreak of viral or pertussis epidemics in the same region.[171,172] Indirect evidence for the role of respiratory tract infections in SIDS has been given by several reports that infants immunized against pertussis are less likely to die of SIDS.[173-175] The winter peak, however, has almost disappeared following the campaigns to place infants to sleep on their back.[154] In a recent study from the United Kingdom, only 27% of deaths occurred between December and February.[176] The reason(s) for this remains unclear.

There appears to be a tendency for SIDS to occur more frequently on weekends and public holidays.[154,159,177,178] This has been related to the fact that the infant's daily routine and environment are more likely to be disturbed or changed on these days.[177,178] In a nationwide study from New Zealand, however, visits to and by friends or relatives, which would certainly disturb the infant's daily routine, appeared to have a *protective* effect on SIDS.[179] Hence, the mechanisms responsible for the increased occurrence of SIDS on weekends and public holidays remain poorly understood.

SIDS apparently occurs predominantly during the night, a time when both parents and infants are most likely to be asleep. For example, in a study from Hannover, Germany, 61% of 270 SIDS victims were found in the morning (6 AM to noon).[180] This does not prove, however, that SIDS occurs during sleep.

RISK FACTORS

A large number of factors associated with an increased risk of SIDS have been identified from epidemiologic

Table 30-3
Risk Factors for Sudden Infant Death Syndrome

Maternal Factors	Infantile Factors
Young age	Male gender
Multiparity	Low birth weight
Smoking during pregnancy	Low birth length
Maternal drug abuse	Premature birth
Previous fetal deaths	Blood type B
Anemia during pregnancy	Low Apgar scores
Placenta previa	Low hematocrit at 48 hours
Premature rupture of membranes	Not using a pacifier
Low social class	Prone or side sleeping position
Low family income	Bed-sharing
Short inter-pregnancy interval	Overheating
Unmarried mother	Not breastfed
Partner unemployed	Siblings in family
Late attendance of antenatal clinic	Sleeping in own room
Postnatal depression	Previous SIDS in family
Attendance to psychiatrist	Previous cyanotic episode
Urinary tract infection in pregnancy	

SIDS, sudden infant death syndrome.
From references 163, 181-186.

studies[163,181-186] (Table 30-3). Many of these risk factors underline the importance of social factors in the pathogenesis of SIDS (although the mechanisms through which these social factors affect the risk of SIDS are poorly understood); others, like maternal smoking or anemia during pregnancy, suggest that there must already be a disturbance during intrauterine life that puts an infant at risk. In the following, we will concentrate on risk factors that are potentially amenable to modification, namely maternal smoking, not breast feeding, not using a pacifier, overheating, bed sharing, and a nonsupine sleeping position.

Maternal smoking has long been recognized as a risk factor for SIDS. The increase in SIDS risk is dose dependent.[187] With the decline in other SIDS risk factors in several countries, smoking is now considered the single most important preventable risk factor for SIDS.[181,187] There is a further increase in SIDS risk if both parents smoke[188] or if the mother not only smokes but is also anemic.[189] Smoking may be related to SIDS via a number of mechanisms, including fetal hypoxia,[189] an inhibition of airway growth and development,[190] a decreased ability to arouse to noxious stimuli,[191] and an increased susceptibility to respiratory tract infections.[192]

Not breast feeding was only recently confirmed as a risk factor for SIDS.[193,194] The beneficial effect of breast feeding may be related to its protective effect on the infants' susceptibility to respiratory tract infections. In some studies, however, the protective effect was lost after controlling for socioeconomic factors.[195]

Not using a pacifier was reported as a risk factor for SIDS in several studies and was confirmed in a recent meta-analysis, where the pooled OR for pacifier use during the last sleep was 0.39 (0.31 to 0.50).[196] In an even more recent population-based study from California, the adjusted OR for SIDS associated with using a pacifier was 0.08 (0.03 to 0.21).[197] Although pacifiers become dislodged from the mouth of more than 80% of infants within the first hour of sleep, they have been shown to reduce the arousal threshold (i.e., facilitate arousal from sleep).[198] Reluctance to promote pacifier use results from the belief that it interferes with breastfeeding, although data on this issue are sparse. One randomized controlled trial found infants who started using a pacifier at 2 to 5 days of age were slightly less likely to be exclusively breast fed at 1 month compared to non-users.[199] After 1 month, no detrimental effect has been shown.[196] Taken together, current evidence suggests that it is no longer justified to *discourage* parents from using a pacifier, but data are not yet sufficient to *recommend* pacifier use.[200]

Evidence that overheating (arising from overwrapping and/or high room temperatures) may be a risk factor for SIDS was initially largely circumstantial.[201,202] Several case-control studies found that the level of bedding and clothing was significantly higher among SIDS cases.[203,204] Heavy wrapping may become particularly important if occurring in combination with other risk factors for SIDS (e.g., the prone sleeping position[205] or a respiratory tract infection).[206] Gilbert and colleagues found an OR for SIDS of 51.6 for the combined presence of heavy wrapping (more than 10 togs) and a viral infection.[206] There is also physiologic evidence supporting the concept that hyperthermia may be a risk factor for SIDS: it has deleterious effects on respiratory control[207,208] and may also impair lung mechanics.[201]

Bed-sharing as a risk factor for SIDS was first observed in 1972,[209] but has not received much attention until it was confirmed by Mitchell and coworkers,[181] who found that 24% of the SIDS victims but only 10.5% of the controls had shared the bed with their parents. These data apparently reconfirm the concept already mentioned in the Bible that accidental suffocation through overlaying may be a mechanism for SIDS, but they can also be interpreted as supporting the hypothesis that hyperthermia, resulting from the infant sleeping close to his parents, may play a role as a trigger for SIDS (see earlier). Although it is now widely accepted that bed-sharing is unsafe for infants of smoking mothers, there is controversy for infants of nonsmoking mothers because bed-sharing purportedly promotes breast feeding.[210] The magnitude of its effect as a risk factor for SIDS, however, has frequently been underestimated because bed-sharing is often compared with not bed-sharing as reference. The latter includes sleeping in a separate room, a previously described risk factor for SIDS.[211] In a recent study from Scotland, sharing a bed when less than 11 weeks of age was associated with a 10-fold increase in SIDS risk (OR 10.2; 3.0 to 34.8) when compared to room-sharing, which remained statistically significant if analysis was restricted to infants of nonsmoking mothers (OR 8.0; 1.2 to 53).[212] Thus, bed-sharing should not be promoted regardless of smoking status, at least not in the first 3 months of life.

The prone sleeping position was first reported as a risk factor for SIDS in 1944,[213] but was not widely noticed until 1989, when a Dutch group, based on results from their own retrospective study, started a campaign in their country advising parents to avoid the prone sleeping position.[156] This is particularly tragic because a recent cumulative meta-analysis of 40 comparative studies on infant sleep position found that the association between death and the prone compared to the supine position had become statistically significant by 1970, 20 years before the Dutch group started their campaign.[214] Uptake of the advice to place infants on their backs

was hampered by physiologic studies suggesting that the prone position may be advantageous, although these data were not from healthy infants, but from hospitalized preterm neonates or infants with respiratory tract infections.[96,97,215-218] Mechanisms through which the prone position can become dangerous to some infants include a higher risk to develop hypercapnia (due to rebreathing of expired air,[219] hypoxemia,[220] upper airway closure,[221] or an arousal deficit[222] while sleeping in the prone position.

Whatever the pathophysiological mechanism, propagation of the "back-to-sleep" message has been one of the most successful public health campaigns ever launched, resulting in a 50% to 70% decline in SIDS rates around the world (see Table 30-2). With an increasing number of infants sleeping non-prone, one could better differentiate between supine and side sleeping. This showed a two- to sixfold increased risk of SIDS in the side position.[223-225] The most likely explanation for this is that the side position is inherently unstable,[225] and that the risk of SIDS is particularly high for infants not accustomed to the prone sleeping position.[226,227]

Pathology

INTRATHORACIC PETECHIAL HEMORRHAGES

As implied by its definition, there is no morphologic finding in SIDS that sufficiently explains the occurrence of death. There are, however, a number of characteristic findings in these infants, some of which are so consistent that they appear to support the concept that SIDS may indeed form a specific disease entity. The most consistent among these findings, first described by Fearn in 1834,[147] are intrathoracic serosal petechiae, which are found on the surfaces of lungs, pericardium, and intrathoracic portion of the thymus. In a study involving 1144 sudden unexpected deaths, serosal petechiae were found in 99% of infants who did not have any morphologic finding that could possibly explain death (true SIDS).[228] The distribution of these hemorrhages has led some researchers to suggest that large intrathoracic pressure swings are involved in their production.[229] These large pressure swings may result from breathing efforts against a closed (upper) airway.[230,231] Petechial hemorrhages were also observed following repetitive airway obstruction with intermittent recovery.[232,233] Guntheroth, however, found no petechiae in rats if these were killed by unremitting airway occlusion (i.e., total occlusion until death). Only if death was induced by *intermittent* tracheal occlusions, or by the administration of 100% N_2, did petechiae occur.[234] He later reported that lung volume in rats killed by unremitting airway occlusion was 24% smaller than that of rats killed with nitrogen asphyxiation, suggesting that a fully expanded lung might be required to produce petechial hemorrhages.[235]

Risse and Weiler confirmed these findings from animal experiments in observing that infants who had been intentionally suffocated and had thus died very rapidly exhibited much less petechiae than those who had died from prolonged asphyxia or SIDS, and concluded from their findings that an episode of prolonged asphyxia is required to produce these bleedings.[236] Others supported these findings in reporting that abrupt death due to sudden airway occlusion, unresolving until death, did not produce pulmonary hemorrhages, whereas slower forms of hypoxic death did.[237,238]

An alternative explanation why petechiae do not always occur in lethal airway obstruction had already been offered in 1897. Brouardel, a French pathologist, occluded the nose and mouth of dogs in whom a window had been placed in the parietal wall of the thorax and saw that petechiae appeared only during the second stage of asphyxia (i.e., with the onset of gasping, but not initially, when the animals made vigorous inspiratory efforts against the closed upper airway).[239] These observations were confirmed by Winn, who found that young rats exposed to an oxygen-free gas developed petechiae (and frothy pink fluid in their nares, see later) only if there had been gasping, regardless of whether they subsequently recovered or died.[240] It is thus possible that the petechiae so frequently observed in SIDS are indicative of a period of prolonged asphyxia (during which gasping occurred) rather than of a specific disease mechanism (e.g., upper airway obstruction) that has led to death.

BLOOD-STAINED FROTHY SECRETIONS IN THE AIRWAYS AND LUNGS

Another characteristic finding in SIDS is the occurrence of froth around the nose and mouth (occasionally blood-stained), which is found in approximately 60% of SIDS victims.[241] This latter phenomenon again may be caused by a combination of pulmonary edema and high transpulmonary pressures (e.g., due to vigorous breathing movements) immediately prior to death.[240,242] *Frank* nasal or oral bleeding, however, was originally *not* considered a typical feature of SIDS and was instead related to intentional suffocation. This view was supported by Meadow[243] who reported that 39% of infants from parents who had been legally convicted of causing their death had frank blood in the mouth, nose, or on their face. In a recent analysis of data from the nationwide New Zealand study, however, nasal hemorrhage was reported in 15% of 385 cases whose parents were interviewed.[244] It was associated with younger infant age, bed-sharing and non-prone sleeping position. According to these and other recent data, nasal hemorrhage is more common in SIDS than previously thought and is not necessarily indicative of smothering.[244,245]

INFECTION

The majority of SIDS victims (56% to 79%) show histologic evidence of an upper respiratory tract infection,[246,247] and infectious agents, mostly viruses, have been isolated in 40% to 80% of SIDS.[171,248,249] Similarly, grossly increased lung immunoglobulin concentrations have been found in SIDS victims.[250] The histologic changes caused by these agents are apparently not severe enough to explain death as being directly caused by respiratory infection, but the latter may function as a trigger for SIDS. This is still an area of ongoing research, particularly given the recent finding of impaired immunologic function in some SIDS infants (see later).

HYPOXIC TISSUE MARKERS

Following the concept that SIDS may be related to the repeated occurence of apneic pauses (see later), a search for morphologic changes indicative of chronic tissue hypoxia began. As a result, a number of so-called hypoxic tissue markers was found. These include, among others, the retention of periadrenal brown fat, gliosis of the brain stem, hyperplasia of pulmonary neuroendocrine cells, and an increased

wall thickness of both pulmonary arteries and airways.[251-254] Although there has been some debate about the specificity of these hypoxic tissue markers for SIDS,[252] the fact that they are present in SIDS suggests that these deaths may not be a sudden event without antecedent illness. This is also supported by the observation of elevated hypoxanthine levels in the vitreous humor[255] or of upregulated vascular endothelial growth factor (VEGF) expression in SIDS,[256] indicating that death must have been preceded by an episode of prolonged (4 to 5 hours) tissue hypoxia.

ABNORMALITIES IN BRAIN STEM SEROTONINERGIC SYSTEM

Serotonin is a neurotransmitter involved in regulating various processes potentially related to SIDS (e.g., sleep and arousal, control of breathing, airway reflexes, and autonomic function).[257] Endogenously released serotonin is also required for gasping.[258] Comparative studies on the binding properties of neurotransmitter receptors in SIDS infants found the most marked differences to controls in serotonin receptors located in the arcuate nucleus and caudal raphe.[257] SIDS infants also have different serotonin transporter genotypes compared to controls.[259,260] Finally, there is evidence that serotonin binding in the arcuate nucleus is influenced by toxic exposures to nicotine and alcohol, substances associated with an increased risk of SIDS.[257] This suggests that a disturbance in serotonin metabolism may not only be genetically determined, but may also be influenced by the environment in a way compatible with the epidemiology of SIDS.

GENETIC STUDIES IN SIDS

For many years, it has been known that some infants who die suddenly and unexpectedly do so because they have an inherited disease such as the A984G mutation in the medium-chain acyl-CoA dehydrogenase (*MCAD*) gene.[261] More recently, mutations in genes encoding cardiac ion channels have been identified (see later). These well-defined diseases, however, contribute only a few percent to all cases of sudden infant death (and, by definition, prohibit defining SIDS as the cause of death). More relevant to SIDS are recent data on gene polymorphisms that may predispose infants to SIDS under certain circumstances, such as those found in the serotonin transporter gene (see earlier). Specific polymorphisms in the gene coding for interleukin-10 have also been found in SIDS (and also in infectious deaths).[262] More recently, mutations in genes pertinent to the embryologic origin of the autonomic nervous system were found in 14 of 92 SIDS cases investigated; only 1 mutation was identified in 2 of 92 controls.[263] This exciting new field of research has just begun to evolve. Future genomic studies will enhance our understanding of the polygenic risk factors associated with SIDS, but have to be carefully related to phenotype (i.e., require particularly careful history taking and postmortem examination).

SUMMARY OF PATHOLOGIC FINDINGS IN SIDS

The following conclusions can be drawn from the studies summarized above: (1) respiratory tract infections appear to play an important role as a trigger for SIDS; (2) most SIDS victims have either suffered tissue hypoxia for some time prior to death, or have an increased reactivity of their pulmonary airways and vessels, or both; (3) the final pathway leading to death apparently involves large intrapulmonary pressure swings, but whether these are caused by upper airway obstruction, lower airway occlusion, or asphyxic gasping, is unknown; and (4) recent data on gene polymorphisms or mutations in SIDS are intriguing but incompletely understood.

Pathophysiology

Investigations into the pathophysiology of SIDS have been hampered by the fact that the occurrence of death is unpredictable. They have, therefore, predominantly been confined to prospective studies in large numbers of infants, aiming to obtain data in future SIDS victims, and to studies on infants who are known to be at increased risk of SIDS, particularly those who survived a near-death event (i.e., an ALTE). Although both approaches have provided invaluable data about the development of respiratory control in infancy, they are unlikely to ever provide conclusive evidence about the pathogenesis of SIDS. This would be possible if data were collected only *during* deaths or near-death events. With the introduction of memory monitors, which record physiologic signals during alarms on home monitors, such data are now available.

DATA RECORDED IN FUTURE SIDS VICTIMS

The first large population-based study that prospectively collected physiologic data in future SIDS victims was carried out by Southall and colleagues, who performed 24-hour tape recordings of ECG and breathing movements on 9856 infants, 29 of whom subsequently died of SIDS.[264] None of the recordings in the SIDS infants showed a prolonged apneic pause (≥20 seconds), cardiac arrhythmia, pre-excitation, or a prolonged QT-interval. Compared to surviving matched controls, the SIDS cases did not show significantly increased numbers of short apneic pauses or quantities of periodic breathing.[265] In fact, SIDS victims studied after 1 month of age showed significantly *fewer* apneic pauses (≥4 seconds) than control infants.[266] However, the infants who died exhibited, as a group, higher mean heart rates[267] and higher levels of sinus tachycardia than the controls.[268] Since then, this unique data set has been used for more refined analyses—only to confirm that recordings of breathing movements and ECG cannot serve as predictors for SIDS.[269]

Studies of the autonomic cardiovascular control in the SIDS victims produced mixed results. Analysis of overall heart rate variability by power-spectral techniques showed no differences between SIDS cases and controls.[270] More detailed analysis, however, revealed that the extent of respiratory sinus arrhythmia was lower in the SIDS victims across all sleep-waking states,[271] and that heart rate variability was diminished in the SIDS cases during waking and rapid eye movement (REM) sleep, but not during quiet sleep.[272] A dynamic analysis of beat-to-beat heart rate variability showed a reduced dispersion of interbeat intervals across all sleep-waking states.[273] These findings indicate a disturbance in autonomic control mechanisms, namely either an increased sympathetic or a reduced vagal tone, or some interaction of the two, in infants who succumb to SIDS.

A study on sleep state organization in 22 recordings from 16 term future SIDS victims in the above data set and 66 recordings from age-matched controls showed less waking and more sleep during the early morning hours.[274] Interestingly, the future SIDS victims also showed fewer body movements during REM sleep compared to controls. Unfortunately, sleeping position was not recorded; it is, therefore, not clear whether these findings indicate a disturbance in sleep organization and/or arousal responsiveness, or are merely related to a higher proportion of future SIDS victims sleeping prone. The latter position is associated with less motility and longer sleep times.[275,276]

André Kahn's group analyzed polygraphic sleep studies in 40 future SIDS victims and 607 healthy infants matched for sex and age, taken from a data set of 27,000 infants who had been studied polygraphically in 10 Belgian sleep laboratories between 1977 and 2000.[277] The only group difference between SIDS cases and controls was an increase in the number of obstructive apneas, defined as a pause in airflow for more than 2 seconds and observed in 75% of future SIDS victims, but in only 42% of controls. Also, the decrease in frequency of apneic pauses with age was smaller in the SIDS infants than in the control group. All other polygraphic parameters (duration of different sleep states, number and duration of apneic pauses, heart and respiratory rates) were not significantly different in the two groups. However, the group of future SIDS victims included 6 siblings of SIDS victims and 9 infants who had experienced an ALTE.

A number of investigators prospectively recorded electrocardiograms in future SIDS victims to define the incidence of a prolonged QT interval because the latter is associated with an increased susceptibility to potentially fatal ventricular arrhythmias.[278] The results of those studies are controversial. Schwartz[279] found a "markedly prolonged" QT interval in 6 of 9 SIDS victims, identified in a population of 8000 infants. In contrast, Southall and colleagues in the prospective study mentioned earlier,[264] and in a second prospective study involving standard ECGs on 7254 infants—15 of whom suffered SIDS—found no abnormal prolongation of the QT interval.[280] Weinstein and Steinschneider[281] were also unable to identify a prolonged QT interval in any of their eight prospectively studied SIDS victims. By 1998, however, Schwartz and coworkers had increased their original data set to more than 34,000 infants, including 24 who subsequently died of SIDS.[282] Twelve of these infants (50%) had a corrected interval (QTc) above 440 ms, the 97.5th centile in the underlying population, giving an OR of 41 (17; 98). These impressive data, however, were widely criticized (e.g., for insufficient blinding and unclear criteria for the selection of QRS complexes or SIDS cases).[283] Moreover, it remains puzzling that torsades-de-pointes tachycardia, the proposed death mechanism related to a prolonged QT interval, has never been observed in the more than 35 ECG recordings obtained during sudden infant death on a monitor (see later). Recent genetic studies suggest that a molecular diagnosis of SIDS related to long-QT-syndrome (LQTS) genes is rare and only valid if corroborated by a electrophysiologic characterization of the mutated ion channel.[284,285] A general screening for LQTS, therefore, cannot be recommended.[286]

The results from these prospective studies can be summarized as follows: (1) no marker has yet been identified from physiologic recordings obtained some weeks prior to death that would identify future SIDS victims with a sensitivity and specificity high enough to justify a specific intervention; (2) short or prolonged cessations of breathing movements, if analyzed some weeks prior to death, bear no unequivocal relation to SIDS; (3) the same applies to cardiac arrhythmias; (4) episodes with an intermittent absence of airflow, but continued breathing movements ("obstructive apnea") may be found significantly more frequently in future SIDS victims than in controls; and (5) there are indicators to suggest a disturbance in autonomic control and/or in sleep state organization in some future victims of SIDS, but the exact mechanism(s) through which these disturbances can lead to sudden death has not yet been determined.

It should be made clear that the differences identified between SIDS victims and controls were only group differences and could not be used to identify individuals at risk. Some of the studies involved multiple analyses for which statistical corrections were made. Such corrections may have over- or underestimated statistical significance.

DATA RECORDED DURING DEATHS ON A HOME MONITOR

There are now a number of recordings from cardiorespiratory monitors that were obtained during SIDS.[287-291] Despite some limitations, these recordings have for the first time provided us with objective data on the pathophysiologic mechanisms immediately preceding SIDS. In an analysis of nine recordings of chest wall impedance and heart rate from infants who had an autopsy diagnosis of SIDS or mild BPD, gasping was the predominant pattern, being already present at the time of the monitor alarm in three infants and occurring within 3 minutes after the alarm in a further four infants (Fig. 30-6).[290] One infant began to gasp only 13 minutes after the first monitor alarm. The duration of gasping ranged from 3 seconds to 11 minutes in those five

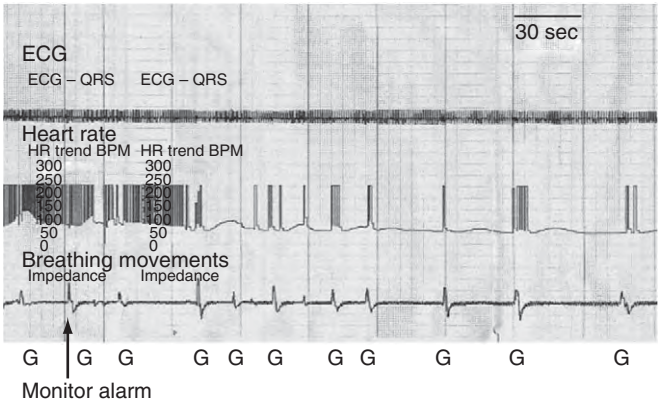

Figure 30-6 Section from a memory monitor printout of a 1-month old infant born at 34 weeks' gestation and with an autopsy diagnosis of SIDS. There are 11 gasps (G) which progressively decrease in amplitude. There is an increase in heart rate from 72 to 140 beats per minute (bpm) during the first 20 seconds of recording, followed by several smaller increases in heart rate that appear to occur in response to the gasps and are also decreasing in amplitude over time. (Reprinted with permission from Poets CF, Meny RG, Chobanian MR, Bonofiglo RE: Gasping and other cardiorespiratory patterns during sudden infant death. Pediatr Res 45:350-354, 1999.)

infants in whom it was not interrupted by resuscitation. Primary trigger for the monitor alarm had been bradycardia in all but two infants, but there was no indication of heart block or ventricular tachycardia. Prolonged apnea (>20 seconds) began up to 13.7 minutes (median 2.7) after this alarm in five infants and 7 to 20 seconds before the alarm in three infants; in the remaining infant, stimulation occurred prior to any apnea.

These observations should be interpreted with caution because all infants had been born at less than 37 weeks' gestation. This, however, reflects only the population monitored in the centers providing these recordings. Nonetheless, prolonged apnea seems unlikely to be a primary mechanism in the sequence of events leading to most cases of SIDS. Also, bradycardia is unlikely to be a primary mechanism, and there was little evidence for an arousal reaction (e.g., body movements). Finally, gasping occurred in the majority of these SIDS victims, but was obviously not successful as an autoresuscitative mechanism. The latter data were confirmed in a similar study observing gasping in 23 of 24 infants immediately preceding death.[291] In animal studies, gasping occurs only if PaO_2 has fallen to below 5 to 10 mm Hg (i.e., once the animal is severely hypoxemic).[292] Thus, many SIDS infants who die on a monitor may have already been severely hypoxemic at the time of their first monitor alarm, with the progressive decrease in heart rate being due to hypoxic cardiac depression.

Hence, it appears from these recordings that the sequence of events finally resulting in these deaths was initiated by a slowing of the heart, which in turn was most likely caused by hypoxemia. In addition, there seems to be some failure or depression of the two most important mechanisms involved in autoresuscitation, namely arousal and gasping. The underlying causes of both the hypoxemia and the failure of these infants to resuscitate themselves from this hypoxemia remain to be determined.

Prevention

PRIMARY PREVENTION

As stated earlier, dissemination of advice on a safe sleeping environment has been one of the most effective health interventions ever performed. These information campaigns on safe child care practices, based on epidemiologic data on modifiable risk factors, have to be reviewed in regular intervals to incorporate new data. The current advice given by the American Academy of Pediatrics includes the following (abbreviated):[293]

- Infants should be placed in a supine position for every sleep.
- Use a firm sleep surface. Pillows or sheepskins should not be placed under a sleeping infant.
- Keep soft objects and loose bedding out of the crib.
- Let your baby share your room for sleep, but not your bed.
- Do not smoke during pregnancy, and keep infant in smoke-free environment after birth.
- Consider offering a pacifier at nap time and bed time.
- Avoid overheating. Bedroom temperature should be comfortable for a lightly clothed adult.

Similar advice is given in countries around the world, although differences exist (e.g., the Dutch campaign recommends use of a sleeping bag; the English campaign does not discourage bed sharing, whereas the Scottish campaign does). In general, however, there is broad agreement, and it is this kind of information, not any secondary prevention, that is primarily responsible for the impressive reduction in SIDS rates seen around the world in recent years (see Table 30-2).

One group of infants still commonly placed to sleep on their side is preterm infants. Recent data from the United Kingdom, however, suggest that the risk of SIDS for infants who are "small at birth" (<37 weeks or <2500 g) and placed to sleep on their side is 15 times higher (multivariate OR 14.93 [5.1; 54.9]) than for normal birth weight infants placed on their backs. An even higher risk was found in this group for bed sharing with parents who smoke (OR 37.4 [5.5; 239.9]).[294] Because preterm infants initially benefit from prone sleeping, but observed nursery staff behavior has a strong influence on parental behavior after discharge,[295] it is our practice to start placing preterm infants on their back and in a sleeping bag, and to provide advice on safe sleeping to parents, approximately 1 week prior to discharge. In the delivery hospital, infants should be placed on their backs starting on their first day of life.

SECONDARY PREVENTION

For many years, the use of home monitors in specific risk groups (i.e., secondary prevention) has been the only method to prevent SIDS. Its effectiveness in reducing the incidence of SIDS, however, has never been proved. This is largely for methodologic reasons: with the current incidence of SIDS, more than 110,000 infants would have to be randomized in a controlled population-based trial to gain sufficient power to demonstrate (or exclude) a reduction in SIDS rate from 1 to 0.5/1000 as a result of home monitoring. This seems impractical. Despite its unproven effect, however, there are still specific patient groups in whom home monitoring appears indicated. Thus, home monitoring may be prescribed as a diagnostic tool or as an early warning of potentially dangerous pathophysiology. The first group comprises infants after an ALTE (see later) and infants from families who had two or more sudden unexpected infant deaths. The second group involves technology-dependent infants (e.g., with a tracheostomy), infants with respiratory control disorders (e.g., Pierre-Robin sequence), and preterm infants with persistent AOP. The latter is not associated with an increased risk of SIDS,[296] but monitoring may be indicated to prevent potential sequelae (e.g., cerebral palsy).[297] Whether monitoring at home (or in hospital) can prevent such sequelae, however, has never been proved, and this indication remains controversial. For all of these infants, we recommend a pulse oximeter with motion-resistant technology to reduce the frequency of false alarms.[298] Although there are no controlled trials on this issue, there is evidence to suggest that apnea and hypoxemia may occur too late during the events leading to death to allow for intervention in time for successful resuscitation.[290] Monitoring should continue for 4 weeks after the last (true) monitor alarm except for siblings from families with multiple deaths who should be monitored until the age of the oldest infant who died.[298]

Summary of Data on Sudden Infant Death Syndrome

The mechanisms responsible for SIDS remain a mystery. However, there is a growing body of evidence to suggest that approaches to investigate its possible pathophysiology should focus on the regulation of auto-resuscitative mechanisms (arousal and gasping). Although we do not understand the exact mechanisms leading to these deaths, a large proportion can be effectively prevented. The success of primary prevention programs based on epidemiologic data has been rather impressive. Only if the links between the epidemiologic, pathologic, and physiologic characteristics observed in SIDS can be elucidated, however, will we be able to better understand and possibly finally prevent these tragedies.

APPARENT LIFE-THREATENING EVENTS

There is no disease that invariably results in death, and SIDS is no exception to this rule. Hence, there are events during which an infant was about to die, but was found early enough for successful resuscitation. Although there is controversy about the epidemiologic similarities between ALTE and SIDS,[299,300] they are often regarded as a living model for SIDS. However, there are some problems with this approach. First, as is probably the case with SIDS, a large number of treatable disease entities can cause ALTE. These cannot always be identified from investigations performed after an event has occurred (see later). A proportion of apparently idiopathic ALTE will be caused by an identifiable mechanism, which is temporary and, if identified, can be treated and does, therefore, not bear any relation to SIDS (e.g., pneumonia, meningitis, etc.). Second, it will always be impossible to say whether an infant that was resuscitated by his parents would indeed have died without this intervention. Third, certain "abnormalities" identified between ALTE may be coincidental and irrelevant to the ALTE themselves (e.g., gastroesophageal reflux, see later). Hence, there are some inherent ambiguities in the relationship between SIDS and ALTE, and this must be kept in mind if one draws conclusions from studies performed in infants with ALTE to the pathophysiology of SIDS.

Apnea in Infants with Apparent Life-Threatening Events

Alfred Steinschneider was the first to infer a potential pathomechanism for SIDS from observations made in infants who had experienced an ALTE. He reported prolonged (≥15 seconds) cessations in breathing efforts in three infants who had experienced an ALTE and two of their siblings. Two of these five infants (one with ALTE and her brother) subsequently died, and Steinschneider concluded that prolonged apnea is part of the final pathway resulting in SIDS.[301] This paper soon formed the scientific basis for the so-called *apnea hypothesis*, which was enthusiastically received by the scientific community at its time and resulted in the prescription of thousands of apnea monitors around the world.[302] Twenty-five years later, however, legal evidence emerged suggesting that the two SIDS infants on whom the apnea hypothesis was predominantly based had not died of SIDS but had instead been killed by their mother.[303] This does not only highlight the complexity and heterogeneity of the phenomena currently called SIDS and ALTE, but does also raise doubts about the true relevance of the apnea hypothesis to the pathophysiology of these two phenomena.[304] Whatever its validity, the apnea hypothesis clearly stimulated many researchers to look for apneas in infants considered to be at risk of SIDS. Some investigators found larger quantities of periodic breathing and higher numbers of apneic pauses in infants with ALTE; others did not.[305,306]

Apneas that were associated with an intermittent closure of the upper airway at the level of the larynx, documented by means of an ultrafine fiberoptic endoscope during spontaneous sleep, were observed in three previously preterm infants with ALTE.[71] These infants were selected from a group of 25 term and preterm infants with a history of ALTE because they had demonstrated some obstructive apneas during an initial routine sleep study. Interestingly, the laryngeal closure occurring in these infants did not appear to happen as a passive collapse of the airway structures, but as a much more abrupt action, suggestive of an active process. The authors speculated that this abrupt closure might have been caused by stimulation of the laryngeal chemoreflex. Although this observation corresponds to prospective data showing an increased number of obstructive apneas in future SIDS victims,[277] it should be noted that this mechanism was found in only 3 of the 25 infants with ALTE enrolled in the study; all 3 had been born at less than 32 weeks' gestation. It is interesting to note that (passive) upper airway collapse was more likely to occur in the prone compared to the supine position in term infants under general anesthesia,[221] again suggesting that airway closure may be related to SIDS.

Impaired Arousal from Sleep

Based on the hypothesis that SIDS may be related to an impaired arousal responsiveness to hypoxic and/or hypercapnic stimuli, a number of investigators studied the response to hypoxic or hypercapnic gas mixtures in infants with ALTE. Results, however, were inconclusive, and it was concluded that hypoxic or hypercapnic challenge tests do not appear to have any value as a screening tool for SIDS risk.[307]

Nevertheless, a disturbed arousal response has been reported in several well-defined SIDS risk groups or behaviors (e.g., infants with ALTE[308] or nicotine exposure,[191,309] or healthy infants studied in the prone position or without a pacifier[310,311]). These observations point toward a common pathophysiologic mechanism for SIDS, namely an impaired ability of SIDS infants to arouse to noxious stimuli such as hypoxia or hypercapnia (e.g., during re-breathing of expired air), which may, therefore, progress in some of these infants until they are becoming potentially life-threatening.

Ventilation/Perfusion Mismatch and Small Airway Function

Most studies on the pathogenesis of SIDS and/or ALTE have concentrated on the neurologic control of breathing. However, investigations performed during apneic/cyanotic episodes in infants revealed a number of physiologic phenomena that could not be sufficiently explained on the basis of primary disturbances in the central control of the respiratory genera-

tors or of upper airway patency. These include (1) the extremely rapid development of hypoxemia during some episodes; (2) the occurrence of sudden hypoxemic episodes despite continuous ventilation (Fig. 30-7); (3) differences in the speed of desaturation between different forms of apneic episodes (Fig. 30-8); (4) the presence of continued breathing efforts and yet absent airflow despite bypass of the upper airway; and (5) evidence that apnea and hypoxemia may begin simultaneously.[312] These observations become explicable only if one assumes that a right-to-left shunt may cause or contribute to hypoxemic episodes in infants and young children. Such a shunt has, in fact, been demonstrated in patients with severe cyanotic episodes clinically resembling cyanotic breath-holding spells.[313]

Intrapulmonary right-to-left shunting may result from the flow of blood through unventilated areas of lung caused by atelectasis and/or distal airway closure, or from the flow of blood through discrete anatomic pathways that allow direct passage of deoxygenated blood from the pulmonary arteries to the pulmonary veins. The latter possibility has been suggested from postmortem data in SIDS victims,[314] but could not be demonstrated when injecting radioactively labeled microspheres (20 to 50 μm in diameter) during cyanotic breath-holding spells in infants.[315]

Distal airway closure may occur, for example, if small airway size is reduced. The potential role of small airway closure in SIDS was reviewed in an elegantly written hypothesis.[242] This concept is supported by reports of a reduced specific airway conductance and/or $\dot{V}max_{FRC}$ in ALTE infants.[316,317] These data confirm the hypothesis that a proportion of infants with ALTE may have abnormally small airways, and that this may predispose these infants to potentially life-threatening episodes of progressive peripheral bronchial occlusion.

Gastroesophageal Reflux

In 1978, Herbst and colleagues[318] reported on 14 infants with a history of cyanotic and apneic spells, all of whom had "severe GER" on a barium esophagogram. Five of these infants had a clinically apparent episode of apnea and cyanosis during and immediately following a decrease in esophageal pH. One infant died of SIDS 1 week after the parents had discontinued positional antireflux therapy. Although these data clearly showed that GER may be associated with apneic/cyanotic episodes or even sudden death, it remains questionable how relevant this potential pathomechanism is for the majority of infants with ALTE. For example, in the study by

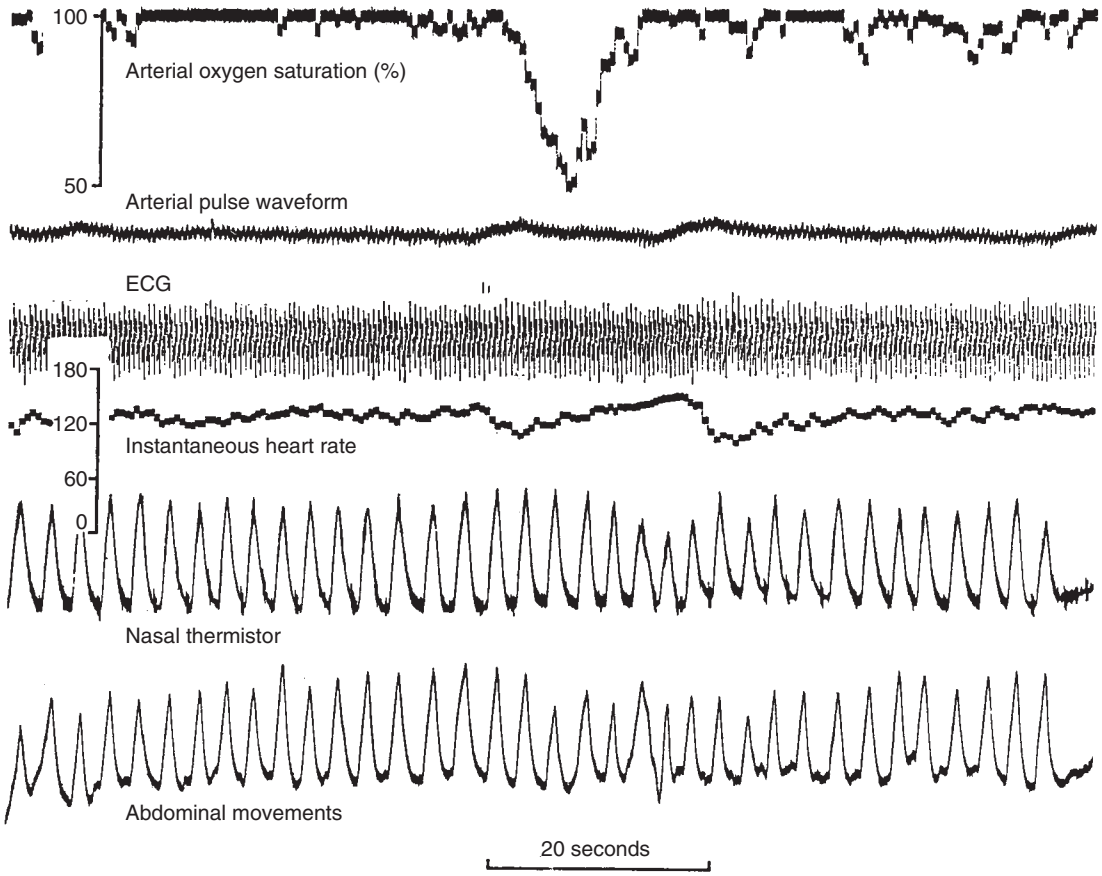

Figure 30-7 Section from a multichannel recording in a 6-month-old infant who had experienced an apparent life-threatening event. There is a fall in SaO_2 to 50%, lasting 12 seconds, which occurs without any significant change in either breathing movements or nasal airflow and can, hence, be best explained by a sudden mismatch between ventilation and perfusion in the lung. (Reprinted with permission from Poets CF, Samuels MP, Southall DP: The potential role of intrapulmonary shunting in the pathogenesis of hypoxemic episodes in infants and young children. Pediatrics 90:385-392, 1992.)

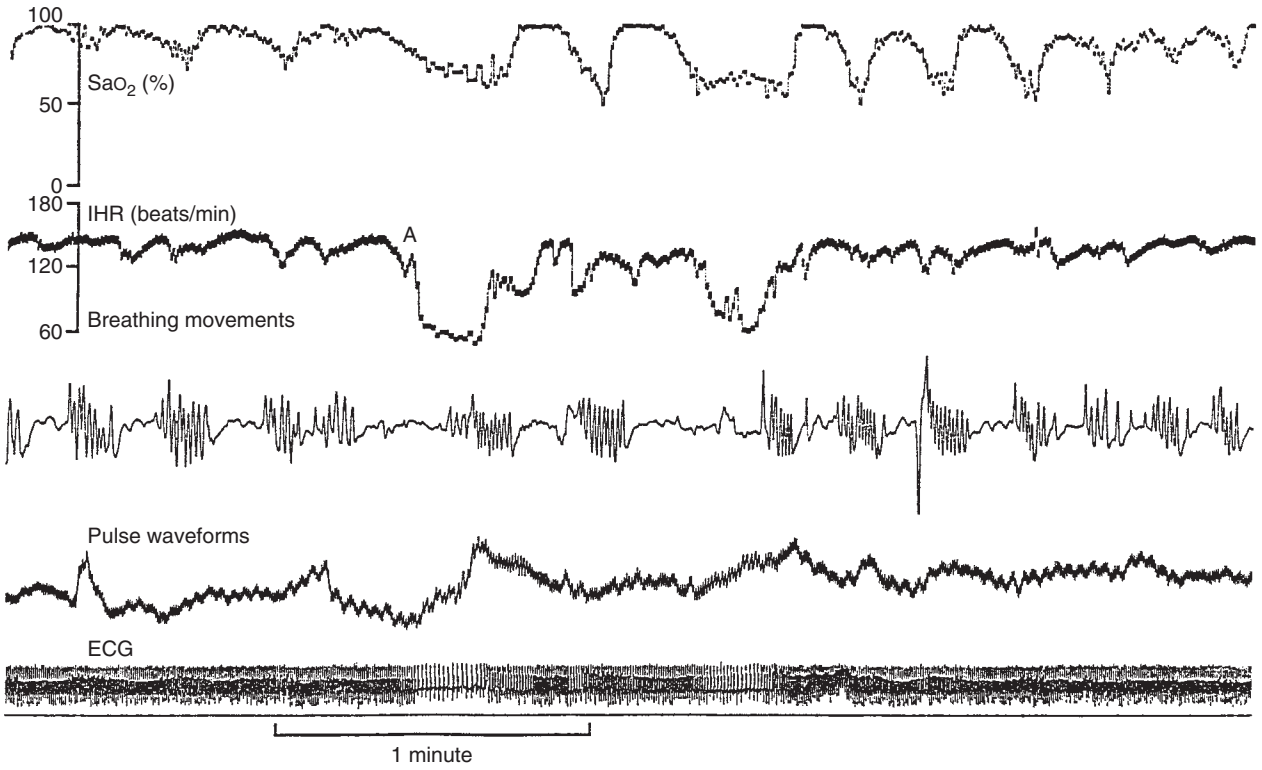

Figure 30-8 Section from a multichannel recording in a preterm infant, studied at 40 weeks' gestational age and showing periodic apnea. Note the much faster decrease in SaO_2 during the desaturations that follow a relatively severe desaturation that is also associated with a bradycardia (A).

Herbst and colleagues no mention was made about the size of the total group of infants with ALTE seen during the study period, and most of their 14 patients also appeared to have extremely frequent events (up to 10 per day), which is not a characteristic feature in the majority of infants with ALTE.[318]

Nevertheless, the possibility that ALTE or even SIDS is caused by GER remains intriguing, particularly because there are several potential pathways through which GER may cause apnea and/or cyanosis (e.g., via stimulation of the laryngeal chemoreflex[319] or via a vagally induced disturbance in pulmonary gas exchange).[320] Unfortunately, there is no study that has investigated the temporal relation between clinical events (i.e., ALTE) and GER, except for the above study by Herbst and colleagues[318] In addition, all but one study investigating the temporal relation between polygraphically recorded short *apnea* (not associated with clinical events such as cyanosis) and GER did *not* demonstrate that such a relation exists.[54,321-327] In the one study which did observe such a relation, all infants had been specifically selected because of a history of apneic spells and frequent regurgitations.[54] However, the majority of prolonged apneic spells even in these infants was not associated with regurgitation. Only one study investigated the temporal relation between hypoxemia and GER in infants with ALTE, but did not control their pulse oximetry data for motion artifact.[328]

In summary, it remains questionable whether GER accounts for a significant proportion of ALTE. This does not imply that GER should not be suspected and possibly treated if there are additional features (e.g., a history of vomiting immediately prior to an ALTE) suggesting GER. Further studies on the temporal relation between GER and ALTE are needed.

Data Recorded during Apparent Life-Threatening Events

Few studies analyzed recordings of breathing movements and ECG obtained with memory monitors at home. In a study using a device that recorded breathing movements, ECG, heart rate, SpO_2 and the pulse waveforms from the oximeter for approximately 20 minutes around an alarm in 94 infants with a history of at least two ALTEs, a total of 52 events was reported in 34 patients.[329] In 23 of the 45 further events in 19 of these infants, one of four characteristic patterns suggesting specific underlying mechanisms for events could be identified. These four patterns were as follows:

1. A sudden fall in $P_{Tc}O_2$ (to <20 mm Hg) but without a fall in SpO_2 (Fig. 30-9). This pattern was considered to represent changes in skin perfusion, not arterial hypoxemia, and was found during six events in five patients
2. A fall in both $P_{Tc}O_2$ and SpO_2 associated with an attenuation, irregularity, or absence of breathing movements and an increase in heart rate by at least 20% from baseline (Fig. 30-10). This pattern was seen in five patients (six events) and was considered to be suggestive of an epileptic seizure. This tentative diagnosis was subsequently proved during further events using continuous EEG recordings.[330]
3. A fall in $P_{Tc}O_2$ and SpO_2 preceded by the sudden onset and continued presence (for at least 40 seconds) of a clear increase in amplitude and irregularity of the breathing movement signal, and associated with an initial sinus

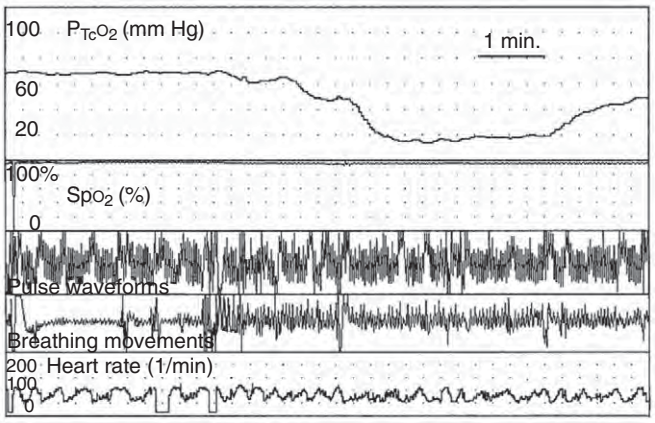

Figure 30-9 Section from a documented monitor recording in a 4-month-old infant with recurrent cyanotic episodes perceived by his parents as life-threatening. There is a fall in $P_{Tc}O_2$ to 15 mm Hg lasting 3 minutes, matching the parental report of cyanosis. The SpO_2 signal, however, remains unchanged, and there is also no change in breathing movements or heart rate. Thus, this episode most likely reflects a sudden change in skin perfusion that was not accompanied by any change in arterial oxygenation. (Reprinted with permission from Poets CF: Apparent life-threatening events and sudden infant death on a monitor. Pediatr Resp Rev 4 [Suppl 1], S397-S400, 2003.)

tachycardia and artifact on the ECG and plethysmographic signal—suggesting massive body movements. This pattern, when accompanied by false or varying descriptions of the time or sleep state of the infant, was considered suggestive of suffocation and was found during four events in four patients. This suspicion was subsequently proved with covert video surveillance.[331,332]

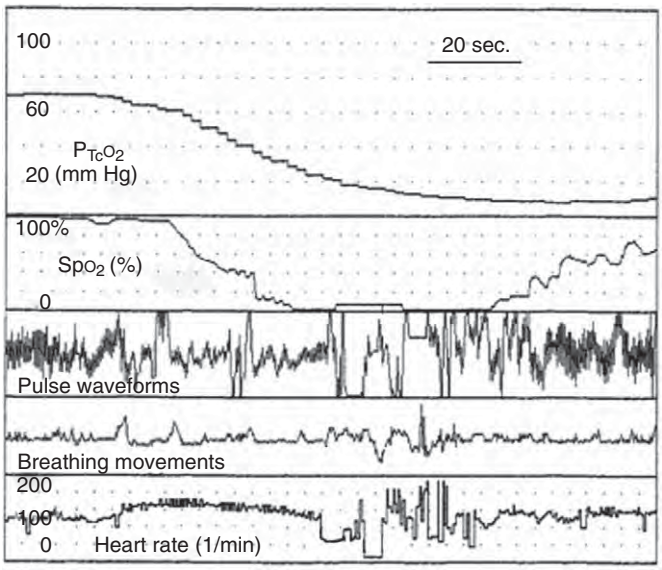

Figure 30-10 Section from a documented monitor recording in an 8-month-old infant with a history of recurrent apparent life-threatening events (ALTE) of unknown cause. A standard EEG had been normal. There is a fall in $P_{Tc}O_2$ and SpO_2 that is accompanied by shallow, irregular breathing movements and an increase in heart rate from 110 to 160 beats per minute (bpm). The child was subsequently shown to have seizure-induced cyanotic episodes. (Reprinted with permission from Poets CF: Apparent life-threatening events and sudden infant death on a monitor. Pediatr Resp Rev 4 [Suppl 1], S397-S400, 2003.)

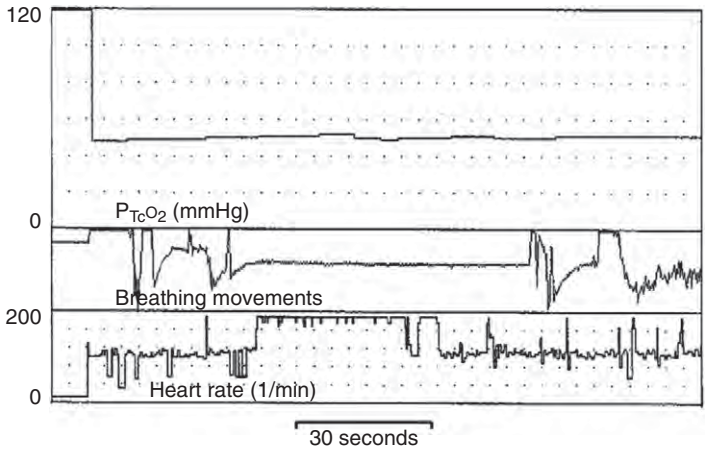

Figure 30-11 Home event recording of $P_{Tc}O_2$, breathing movements, and heart rate in a 7-month-old boy with a history of recurrent ALTE of unknown cause. There is a sharp deflection in the breathing movement signal, which then becomes electronically straight (for 28 seconds), before it abruptly starts to show breathing movements again. During this apparent prolonged apneic pause there continues to be sinus arrhythmia on the instantaneous heart rate signal (visible shortly before the end of the apnea). The events in this infant were subsequently found to be factitious (Münchausen syndrome by proxy); the prolonged apneic pause in this recording being caused by the mother temporarily disconnecting the breathing movement sensor (Graseby pressure capsule).

4. Data entries in the user log and changes in signals that were inconsistent with the parental history of the date, time, and clinical status of the infant and were also incompatible with natural pathophysiology. This would include, for example, the occurrence of an extremely prolonged pause in breathing movements without any accompanying change in heart rate or heart rate variability, reported to have occurred at night, but being in fact recorded during the day. Such inconsistencies suggested that the symptoms reported were fabricated (Münchausen syndrome by proxy; Fig. 30-11).

In all of these patients, specific measures were introduced to prevent or reduce the occurrence of further events, or parents could be reassured that the events they had considered life threatening were, in fact, of no clinical significance. Twenty-two events in 12 patients that could not be attributed to one of the above patterns[329] were regarded as idiopathic ALTE. All showed definite hypoxemia, but apneic pauses were found in only nine events (six infants) and only five of these lasted for more than 20 seconds. Bradycardia developed during only four events.

This study showed that documented monitoring can help to identify potentially preventable mechanisms for ALTE in a considerable proportion of patients who may otherwise be considered to have suffered idiopathic ALTE. However, there was certainly some referral bias, particularly with regard to infants with parentally induced or fabricated events. Nevertheless, these data clearly show that the majority (64%) of idiopathic ALTE involved severe prolonged hypoxemia that occurred without prolonged apneic pauses and without bradycardia and would not (or only much later) have been identified by a cardiorespiratory monitor. It could not, however, determine the mechanism(s) (e.g., rebreathing, hypoventilation) by which this non-apneic hypoxemia developed.

Table 30-4
Some Possible Underlying Diagnoses in Patients Presenting with ALTE

Respiratory Tract Disorders	***Neurologic Disorders***
Bronchiolitis	Intracranial infection
Pneumonia	Epileptic seizures
Pertussis	Congenital central hypoventilation syndrome
Tracheoesophageal fistula	Spinal muscular atrophy (Werdnig Hoffmann)
Aspiration	Hyperexplexia (startle disease)
Laryngomalacia; tracheomalacia	Joubert syndrome
Pierre Robin sequence	Arnold Chiari malformation
Laryngeal cyst or angioma	Myopathy
Cardiovascular Disorders	***Gastrointestinal Disorders***
Long QT syndrome	Gastroesophageal reflux
Cardiac arrhythmias	Volvulus; intussusception
Aortic stenosis	Aspiration and choking
Vascular ring	Toxic shock syndrome caused by gastroenteritis
Metabolic Disorders	***Others***
Medium chain acyl-CoA deficiency	Cyanotic breath-holding spells
Biotinidase deficiency	Anemia
Ornithine transcarbamylase deficiency	Intentional suffocation (smothering)
Glutaric aciduria type II	Münchausen syndrome by proxy
Systemic carnitine deficiency	
Reye syndrome	

ALTE, apparent life-threatening event.

Summary of Physiologic Data in Apparent Life-Threatening Events

Most idiopathic ALTEs appear to be caused by the progressive development of hypoxemia, which may progress until it becomes life-threatening or even fatal because of a failure of these infants to resuscitate themselves by arousal and/or gasping. This hypoxemia apparently does not, in most instances, result from a primary cessation of respiratory efforts, but is more likely to be caused by some form of upper or lower airway closure (e.g., obstructive apnea). The trigger(s) eliciting this airway closure remain unknown.

Management of Infants with Apparent Life-Threatening Events

The list of diagnoses possibly manifesting with an ALTE is long (Table 30-4), and an extensive diagnostic work-up is often required in these infants to exclude treatable causes of ALTE.[333] Some suggestions regarding issues that should be covered when obtaining the medical history and organizing the subsequent diagnostic work-up in these patients have been summarized in Table 30-5.

Because of the importance of obtaining objective data during an ALTE, and because the likelihood of further events

Table 30-5
The Medical Interview and Diagnostic Work-up in Patients with ALTE*

Question/Investigation	Reason for Question/Investigation
Medical History	
During/after event	
Skin color (pale/blue/gray)	Estimation of severity of event and of necessity for further action
Duration of event (seconds/minutes)	
State of consciousness (awake/asleep/unconscious)	
Mode of termination (spontaneous/following mild or vigorous stimulation/following CPR)	
Time to full recovery (seconds/minutes/hours)	
Immediately prior to event	
Shock, fear, anger	? Breath-holding spell
Sudden noise followed by startle reaction	? Hyperekplexia (startle disease)
Coughing, choking, vomiting	? Aspiration, tracheoesophageal fistula
	? Laryngeal chemoreflex-induced apnea
Feeding	? Gastroesophageal reflux
Turning of eyes, jerky movements, abnormal tongue or mouth movements	? Epileptic seizure–induced event
Tremor, profuse sweating	? Hypoglycemia, hypocalcemia
Face covered by bedding/in mattress	? Positional asphyxia
Hours/days prior to event	
Fever, cold, diarrhea	? Infection
Abnormal sleepiness and/or irritability	? Meningitis, Reye syndrome
Snoring	? Obstructive sleep apnea
Stridor	? Laryngo- or tracheomalacia
Wheezing	? Bronchiolitis
Seizures, turning of eyes, "staring"	? Epileptic seizure–induced events
Fasting for several hours (± infection)	? Medium chain acyl-CoA deficiency
Cyanosis during crying/feeding	? BPD, bronchiolitis, cardiac anomaly
Weeks/months prior to event	
Previous events with onset *always* in presence of the same person	? Münchausen syndrome by proxy, deliberate suffocation
Gradual reduction in spontaneous motor activity	? Spinal muscular atrophy, myopathy
Profuse sweating	? Disorder in autonomic regulation
Pertussis or RSV epidemic in area?	? Pertussis, bronchiolitis
Prematurity, bronchopulmonary dysplasia	? "BPD-spells"
SIDS/ALTE in sibling	Inheritable disease (metabolic disorder, long QT syndrome, startle disease) or parentally induced event more likely

Table 30-5
The Medical Interview and Diagnostic Work-up in Patients with ALTE*—Cont'd

Question/Investigation	Reason for Question/Investigation
Specific Features During Physical Examination	
Pallor	? Anemia
Stridor	? Laryngo- or tracheomalacia, vascular ring
Micrognathia	? Pierre Robin sequence
"TOF-cough"	? Tracheoesophageal fistula
Wheezing, dyspnea	? Bronchiolitis, pneumonia
Pronounced second heart tone	? Increased PVR, subclinical hypoxemia
Heart murmur	? Aortic stenosis or other heart defect
Muscular hypotonia, no spinal reflexes	? Spinal muscular atrophy
Chest wall recession	? Increased upper airway resistance; BPD
Specific Laboratory Tests	
Arterial or capillary blood gas analysis (as soon as possible after event)	Estimation of severity of event ? Metabolic disorder, hypoxic/ischemic insult
Complete blood count including differential	? Anemia, infection (e.g., pertussis)
C-reactive protein	? Infection
Serum glucose (preferably after fasting period)	? Hypoglycemia, metabolic disorder
Serum calcium and magnesium	? Hypocalcemia, hypomagnesemia
Nasal swab, including immunofluorescence	? Pertussis, RSV, adenovirus
Organic acids in urine	? Medium chain acyl-CoA deficiency
Serum ammonia	? OTCD carrier, glutaric aciduria, carnitine deficiency
Further Investigations	
Electrocardiogram	? Long QT syndrome
Chest radiograph	? Aspiration, pneumonia, cardiovascular anomaly, bronchopulmonary dysplasia
Electroencephalogram	? Epileptic seizure–induced events
Cranial ultrasound/NMR	? Intracerebral hemorrhage, brain stem abnormalities
Sleep study (only if treatable causes for ALTE have been ruled out)	? Baseline hypoxemia, hypoventilation, epileptic seizure–induced hypoxemia
Home event recording (only if above measures have not helped to identify mechanism)	Documentation of further events at home

*Note that this list is not complete; in particular, further investigations (e.g., barium swallow, esophageal pH monitoring, echocardiography) may be necessary depending on the results of the initial work-up.
ALTE, apparent life-threatening event; BPD, bronchopulmonary dysplasia; CPR, cardiopulmonary resuscitation; OTCD, ornithine transcarbamylase deficiency; PVR, pulmonary vascular resistance; RSV, respiratory syncytial virus; SIDS, sudden infant death syndrome; TOF, tracheoesophageal fistula.

is highest during the first 48 hours after the initial event,[334] all infants with a history of an ALTE should be admitted to hospital and immediately connected to a memory monitor. If a further event occurs, important clues to the underlying diagnosis may be gained. For example, if an increase in heart rate in association with a severe hypoxemic episode is observed on such an event recording, this may indicate the presence of epileptic seizure–induced hypoxemia as the underlying mechanism.[330]

If the diagnostic work-up summarized in Table 30-5 has failed to identify a treatable cause for the ALTE, a polysomnogram should be performed. This includes a continuous (>6 hours) recording of breathing movements, nasal airflow, ECG, SpO_2, transcutaneous partial pressures of oxygen and carbon dioxide, electro-oculogram and electroencephalogram. These recordings occasionally have been valuable in identifying respiratory control disorders such as sleep-related upper airway obstruction or epileptic seizure–induced hypoxemic episodes. As discussed earlier, however, they do not have any predictive value with regard to SIDS.

SUGGESTED READINGS

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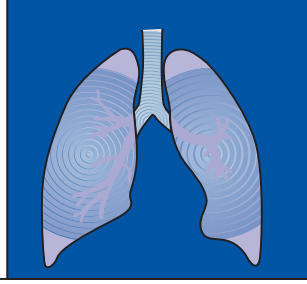

CHAPTER 31 Epidemiology of Respiratory Infections

Philip Keith Pattemore and Lance C. Jennings

TEACHING POINTS

- Technological developments in molecular biology are showing that known respiratory viruses are more prevalent than previously thought across the childhood age range. New viruses continue to be discovered in association with acute respiratory tract infections.
- The study of morbidity and mortality that is due to acute lower respiratory tract infection is hampered by lack of precise definitions and specific, practical diagnostic methods.
- Children in developing countries account for at least 70% of the global burden and mortality from acute lower respiratory tract infection.
- Malnutrition, poverty, indoor smoke, and comorbid conditions, including malaria, tuberculosis, and human immunodeficiency virus infection, greatly increase the risks of children acquiring and dying from acute lower respiratory tract infection.
- Emerging respiratory diseases present an ongoing risk for children in an era of globalization.

This chapter deals with three aspects of the epidemiology of respiratory infections in children: common respiratory viruses, acute lower respiratory tract infection (ARI), and emerging/reemerging organisms.

COMMON RESPIRATORY VIRUSES

Respiratory tract infections are among the most frequent diseases in early life. Many viruses are known to be associated with symptomatic respiratory tract infections, the most common being respiratory syncytial virus (RSV), influenza viruses types A and B, parainfluenza viruses, adenoviruses, and rhinoviruses. Viral infections are consistently more commonly found in younger children,[1,2] among whom viruses are the cause of as many as 90% of all lower respiratory tract infections (LRIs).[3] Increasingly, these viruses are also being associated with a substantial burden of respiratory disease in adults, including elderly persons, and in immunocompromised persons. The advent of molecular technologies has improved laboratory detection of virus in clinical samples and extended the ability to characterize the epidemiology of respiratory virus infections, but it has also led to the identification of subtypes and genotypes of known respiratory viruses and to the discovery of novel respiratory viruses.

Laboratory Detection

CONVENTIONAL DIAGNOSTIC METHODS

Conventional virologic methods, including antigen detection, serology, and culture, have clearly identified the viruses most frequently causing respiratory illnesses in children and associated with both upper respiratory tract (URI) and LRI infections. Table 31-1 shows the relative frequency of viruses identified within the Tecumseh, Michigan, community study, from 1976 to 1981.[4]

MOLECULAR DIAGNOSTIC METHODS

The inclusion of nucleic acid technologies (e.g., polymerase chain reaction [PCR]) for the detection of respiratory virus infections in children has substantially increased the diagnostic sensitivity for most respiratory viruses.[5-7] This technology has allowed the recovery of viruses that have been difficult to detect by conventional methods.[8] For example, PCR is three to five times as sensitive as cell culture for detecting rhinoviruses.[9,10] Figure 31-1 shows the viral identification breakdown in three recent studies of children[5,11,12] in different countries over the winter viral season using PCR techniques. This figure illustrates the differences between studies in patient sampling and methods and the consequent differences in results. However, in all three studies, rhinovirus and RSV are the dominant viruses, with the relative proportions of each differing even between the two studies in infants (studies A and B). Mixed viral infections, particularly with rhinovirus, are common. Finally, studies find only the organisms they look for—only study C tested for bocavirus.

Molecular methods have also allowed the rapid identification and characterization of previously unknown viruses causing respiratory illness. The human metapneumovirus (hMPV) was first identified in the Netherlands in 2000[13] and shows a wide geographic distribution.[14,15] Five new human coronaviruses have been discovered,[16] including severe acute respiratory syndrome (SARS) coronavirus (SARS-CoV),[17,18] human coronavirus NL63 (hCoV-NL63),[19] and human coronavirus HKU1 (hCo-HKU1).[20] Another virus, the human bocavirus (hBoV), has also been identified in association with respiratory illness in hospitalized patients.[21]

MULTIPLE INFECTIONS

Studies using conventional virology have detected multiple respiratory viruses in 1.8% to 15.8% of acute LRIs.[22] While more recent studies using nucleic acid technologies have identified multiple viruses in up to 27% of hospitalized

Table 31-1
Annual Isolation Rates of Respiratory Viruses, Tecumseh, Michigan, 1976-1981

Numerator	Annual Isolation Rate, Adjusted by Proportion of Illnesses Sampled. By age group		Percentage Isolated	Annual Number of Attributable Illnesses	Percentage of Illnesses Resulting in Consultation
Denominator	**100 Person-years**		**All Respiratory Illnesses**	**10,000 Population**	**Illnesses Attributable to Specific Agent**
				All ages: children and adults	
Age group	**0-4 yr**	**5-19 yr**	**%**	***n***	**%**
Rhinoviruses	59.6	13.2	54	8325	17.6
Coronaviruses			14	3428	17.6
Influenza viruses	14.6	30.4	9	2204	37.9
Parainfluenza viruses	28.3	7.5	4	979	26.2
Respiratory syncytial viruses	29.3	3.7	4	979	55.6
Adenoviruses	16.6	3.4	2	490	43.2
Other viruses	4.8	2.7	2	490	27.8
Bacterial			8	1959	48.6
Unknown and/or noninfectious			23	5650	21.5
Total or average	154.3	61.1	100	24,484	25.4

Adapted from Monto AS: Epidemiology of viral respiratory infections. Am J Med, 2002 Apr 22;112 Suppl 6A:4S-12S.

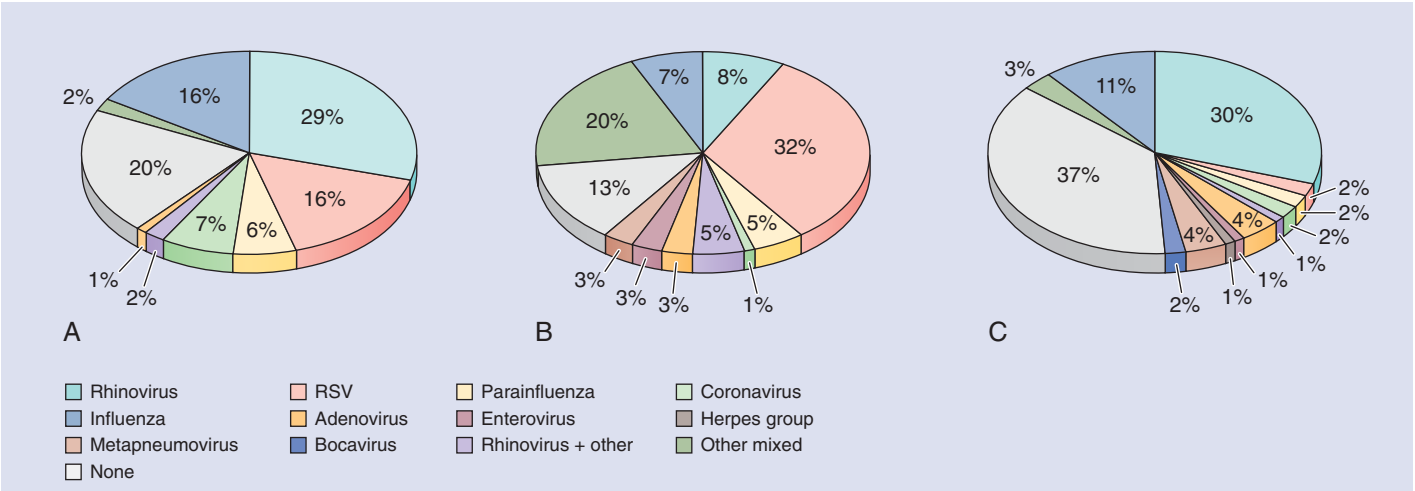

Figure 31-1 Three studies of virus isolation in childhood respiratory tract infection (RTI) over winter using molecular virology. Data sources and details are as follows: **A,** Legg et al.[11] *Denominator:* 123 RTIs in a cohort of 88 infants with at least one atopic parent, followed in Southampton, UK. *Specimens:* nasal lavage. *Virology methods:* individual RT-PCR for six virus groups including picornavirus (not specifically identified as rhinovirus), *M. pneumoniae*, and *C. pneumoniae*. **B,** Jennings et al.[5] *Denominator:* 75 children (65 under 12 months old) presenting to hospital in Christchurch, New Zealand, with acute respiratory illness suggesting lower RTI. *Specimens:* nasopharyngeal swabs. *Virology methods:* PCR/RT-PCR for 11 viruses as well as immunofluorescence and viral culture. **C,** Arden et al.[12] and personal communication, Ian Mackay. *Denominator:* 315 respiratory specimens obtained from people (1 day to 80 years old, 79% under 5 years old) presenting with RTIs to Brisbane hospitals, selected from all four seasons in 2003-2004. *Specimens:* not described. *Virology:* immunoassay, culture, and 17 PCR/RT-PCR assays.

children with LRI.[5] All of the common respiratory viruses have been identified as contributing to multiple infections. They have been recognized more frequently in younger children (≤4 years) and in hospitalized children. The presence of more than one virus may result in more severe or prolonged infection.[15,23,24] Alternately, because young children are immunologically naïve and experience a median of 4.4[25] to 5.5[26] respiratory illnesses per year and because viral shedding is commonly prolonged in young children, a continuum of residual virus or viral nucleic acid may be being detected.

Epidemiology

PERIODICITY AND SEASONALITY

Both the periodicity and the seasonality of viruses that cause respiratory tract infections are well established in temperate climates[3,11,26] (Fig. 31-2; also Fig. 31-1). Most viruses circu-

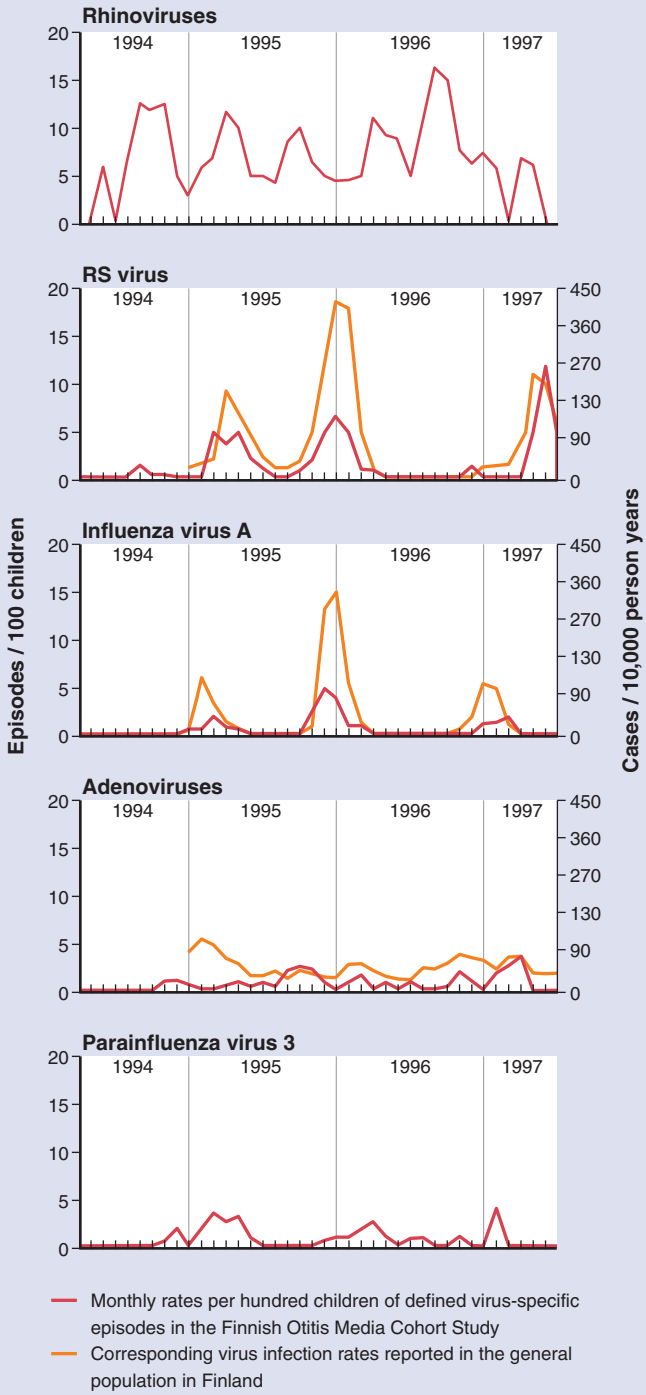

Figure 31-2 Monthly rates per 100 children of defined virus-specific episodes in the Finnish Otitis Media Cohort Study (*red lines*). This was a population cohort study. Corresponding virus infection rates (cases per 10,000 person-years) that were reported in the general population in Finland are also shown (*yellow lines*), although data for rhinoviruses and parainfluenza viruses were not available. (From Vesa S, Kleemola M, Blomqvist S, et al: Epidemiology of documented viral respiratory infections and acute otitis media in a cohort of children followed from two to twenty-four months of age. Pediatr Infect Dis J 20:574-581, 2001. Used with permission of Lippincott Williams & Wilkins.)

late in a community every year; however, some, especially influenza type B and the parainfluenza viruses, may cause epidemics at biennial or longer intervals.[3] Different viruses also predominate in a community during different seasons of the year; overlap invariably occurs and the actual timing and severity of each outbreak or epidemic can vary from year to year. In tropical climates, seasonality also exists. In these regions, RSV occurs predominantly in the rainy season, whereas influenza activity occurs throughout the year with a marked peak in activity during the dry season and a lesser peak during the rainy season.[27,28] Seasons of both higher and lower temperature have been associated with these viruses in different countries.[27] The reasons for the seasonality of respiratory virus infections and their variation by latitude are not clear. More important than the environmental conditions themselves may be their effect on behavior. Seasons when people spend more time indoors, in closer contact with other people (colloquially called "closed-in season" in some regions), will favor more rapid person-to-person transmission.

AGE

Respiratory viruses cause infections in children at specific ages. RSV causes the most severe LRI in children less than 1 year of age, with a peak occurring at a mean age of 3 months.[29] The peak age for hMPV infection is later than that for RSV,[30] but the majority of children have had clinical or subclinical infection by 2 years of age. Similarly, hPIV infections occur at an older peak age than RSV. Human parainfluenza virus-1 causes LRIs predominantly in infants aged 7 to 36 months, with peak infection occurring in the second and third years of life. The peak infection of hPIV-2 occurs in the second year of life, but hPIV-3 differs in that it infects infants younger than 6 months and most children experience infection in the first year of life. All age groups are at risk of infection from influenza type A and B viruses, but preschool-age children in day care and school-age children have the highest infection rates.[31] The very young, the elderly, and those with chronic conditions experience more severe disease. Rhinoviruses and coronaviruses commonly cause URI and infect individuals many times throughout their lives. Rhinoviruses are also clearly associated with LRI in children, but their role remains to be elucidated.[32]

Signs and Symptoms

The common respiratory viruses are often associated with specific clinical syndromes, although most can cause infection at any level in the human respiratory tract.

RSV is clearly the most important pathogen associated with bronchiolitis and pneumonia in infancy,[33] but it can infect all age groups, causing influenza-like illness.[34]

Infection of young children with *hMPV*, a newly described virus, causes illness that resembles hRSV bronchiolitis but also upper respiratory tract disease and diarrhea with fever.[13,35-38] Metapneumovirus now surpasses the parainfluenza viruses as the second most common cause of bronchiolitis and pneumonia among young children.

The *parainfluenza viruses* (hPIV 1-4) are also an important cause of LRIs and regularly cause pneumonia, bronchiolitis, and croup among infants and young children. The most frequent are hPIV-1 and hPIV-2 infections. hPIV-1 is most

commonly associated with croup, whereas hPIV-3 is an important cause of bronchiolitis and pneumonia in young infants. hPIV-2 is most commonly associated with croup, but all respiratory syndromes have been described. Studies rarely identify hPIV-4, although this virus has also been associated with all respiratory syndromes.[39]

Influenza viruses can cause any of the typical respiratory syndromes. Very young infants often present with fever only and no specific lower respiratory tract symptoms. School-age children and adolescents most often present with symptoms of classic influenza (i.e., febrile tracheobronchitis with myalgia and cough).[1]

The most common lower respiratory syndrome caused by *adenoviruses* is pneumonia, but all syndromes can occur.[40] Damage to bronchial architecture can occur with certain adenovirus strains, leading to life-threatening infections, and to bronchiolitis obliterans and bronchiectasis.

Rhinoviruses are the most ubiquitous respiratory pathogens. They cause the majority of cases of the common cold and may also commonly be associated with LRIs in children and adults.[32]

The *coronaviruses* (hCoV-229E and hCoV-OC43) are a frequent cause of URIs in children and adults.[41] Human *bocavirus*[42] and the newer coronaviruses (hCoV-NL63 and hCo-HKU1)[16,19,43] have been associated with respiratory tract infection in children, but their epidemiology remains to be fully elucidated.

ACUTE LOWER RESPIRATORY TRACT INFECTION

Scope and Limitations of Epidemiologic Study of Acute Lower Respiratory Tract Infection

DEFINITIONS AS USED IN THIS SECTION

Pneumonia: Inflammation of the lung with consolidation.[44] The term is usually used to indicate infection (most commonly bacterial or viral) of the lung parenchyma resulting in obliteration of alveolar air space by purulent exudate.

ARI or clinical pneumonia: These terms are commonly used in studies in developing countries for a clinical diagnosis of infection of the lower respiratory tract (below the larynx) based on the three signs of fever, cough, and rapid breathing. Other signs, such as grunting, indrawing, bronchial breathing, auscultatory crackles, etc., may or may not be present.

Community-acquired pneumonia (CAP): This term is most commonly used in studies in developed countries and usually includes a radiological finding of pneumonia. Used in distinction to hospital-acquired pneumonia, which follows injury, surgery, immobility, or immunosuppression or is due to unusual hospital pathogens.

To prove a diagnosis of "pneumonia" according to the first, pathologic definition requires proof that there is infection of the lung parenchyma and proof that there is airspace consolidation. The definition of ARI or clinical pneumonia, on the other hand, relies on clinical signs only and requires no such proof. The chief difficulty in studying cases of pneumonia, especially for epidemiologists, is that of reconciling these two definitions. Why is this important? When we describe the epidemiology of clinical pneumonia we need to know:

- What is the relationship between the condition we are describing and the more objective pathologic entity of pneumonia? *(Validity)*
- How confident are we that the studies we collect in our description are identifying the same condition? *(Reliability)*

The difficulties inherent in answering these two questions include the following.

1. *Limitations of identifying the organism:* Clinical signs and symptoms provide only a limited guide to the many possible organisms causing a respiratory infection. Different organisms require different types of sample and different specialized laboratory identification methods, few of which are in routine use, even in developed countries. For example, sensitive detection of RSV, *Streptococcus pneumoniae*, and *Mycobacterium tuberculosis* requires, respectively, immunofluorescent antigen detection on nasopharyngeal swab or aspirate, bacterial culture of lung biopsy tissue, and inoculation of bronchoalveolar lavage or gastric aspirate specimens into liquid broth with subsequent confirmation by PCR speciation.
2. *Limitations of identifying consolidation:* Chest radiography accurately identifies established pathologic consolidation but may miss early infection. However, as with microbial diagnosis, radiology is not routinely necessary for clinical management and is not consistently performed during respiratory infections.
3. *Limitations of availability of facilities and expertise:* Clinical, laboratory, and radiology facilities and diagnostic expertise are distributed in a very patchy fashion throughout the world. In many parts of the developing world, diagnosis and case management rely on poorly resourced village health workers with the support of a central clinic. Often, these are the regions with the highest incidence, morbidity, and mortality from childhood respiratory infection.

THE WORLD HEALTH ORGANIZATION CASE MANAGEMENT GUIDELINE

The difficulties and limitations of identifying ARI by microbial cause and radiologic consolidation, particularly in developing countries, have forced epidemiologists to develop tools using clinical pattern recognition to estimate the burden of respiratory disease. The World Health Organization (WHO) guideline for the management of ARIs and pneumonia (Fig. 31-3) was developed by Shann and others[45,46] in Papua, New Guinea, from 1980 onward. The aim was a simple step-by-step instruction in recognizing and treating respiratory infection, requiring minimal training, and usable by health workers in developing countries. By 1994, 130 developing countries were using the protocol with or without modification.[47] The guideline has been incorporated into the global Integrated Management of Childhood Illness (IMCI) program,[48] which had been adopted by 81 developing countries by 2000. For these reasons, the WHO guideline has become an important tool for measuring the incidence and mortality due to ARI.

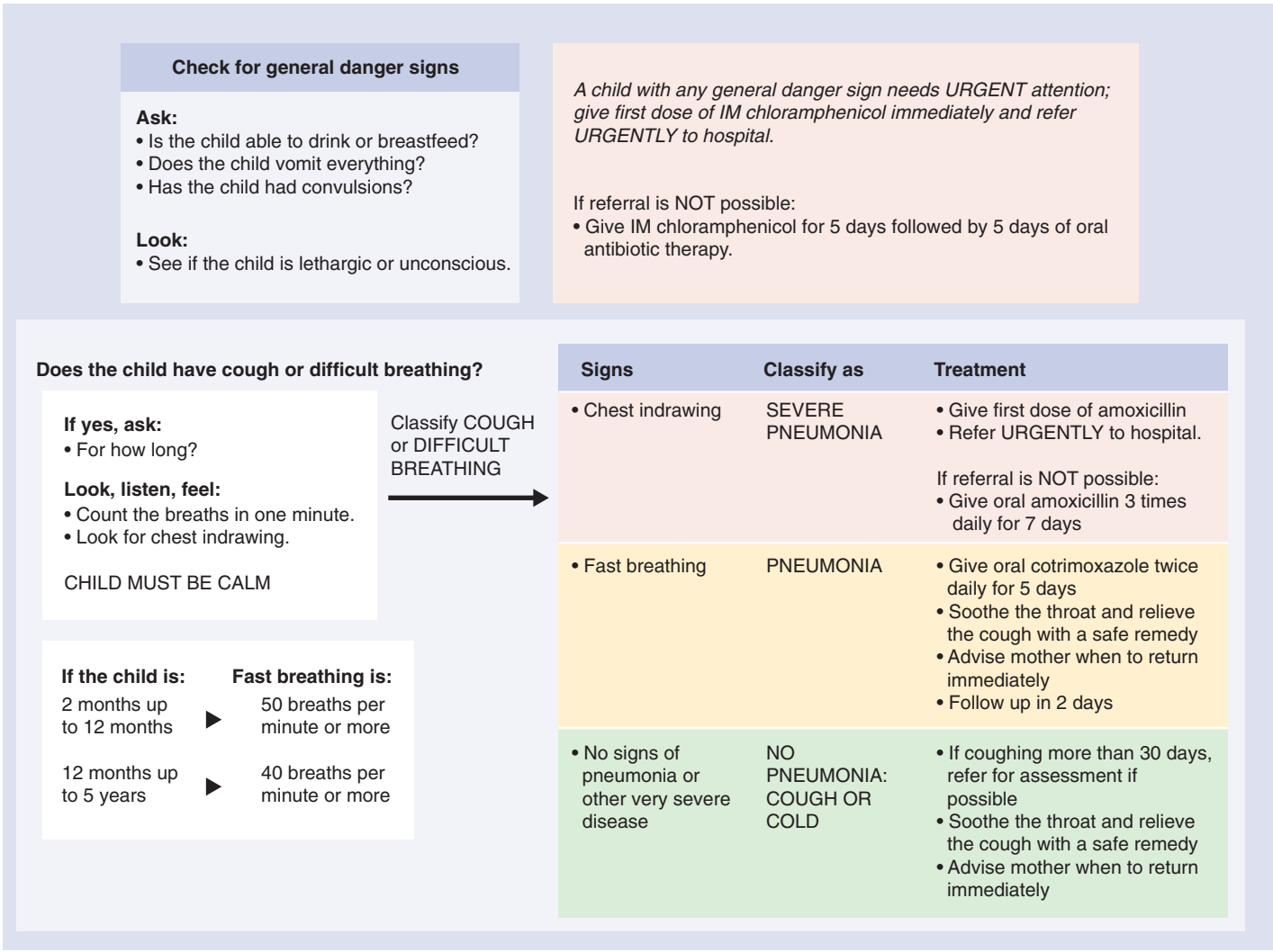

Figure 31-3 The modified WHO case management guideline for acute respiratory illness. (Used with permission. This chart and its explanation can be found at http://www.who.int/child-adolescent-health/Emergencies/ARI_chart.pdf.)

STRENGTHS AND LIMITATIONS FOR EPIDEMIOLOGY STUDIES IN THE WHO GUIDELINES

The strengths of the WHO case management guideline for epidemiological study of ARI are as follows:

- Minimal training required, needing no specialized facilities; therefore, low cost and wide applicability across geopolitical and socioeconomic boundaries
- Proved effective as a basis for management and reducing mortality

A meta-analysis of nine community-based trials[49,50] has shown that application of the WHO case management system reduced pneumonia mortality by 36% and total mortality by 24% in the 0- to 4-year-old age group (Fig. 31-4). The impact is most likely due to improved recognition of antibiotic treatable pneumonia due to *S. pneumoniae* and *H. influenzae*, but identification of malnutrition and other health factors may also contribute.

Compared to a radiologic definition of pneumonia, the WHO guideline lacks specificity due to:

1. Lack of distinction between viral bronchiolitis, virus-associated asthma, and viral or bacterial pneumonia
2. Possible inclusion of the following:
   - Measles and malaria in high prevalence areas, because they can also cause rapid breathing or may be comorbid with pneumonia[51-53]
   - Bacteremia due to nontyphoidal salmonella,[54,55] despite lack of evidence of lung tissue infection due to these organisms[56]
   - Any other cause of rapid breathing such as cardiac failure[57]
3. Respiratory rate, a key element of the WHO criteria, may be raised by increased body temperature[53,58] and high altitude[59] and lowered by malnutrition.[47,60]

In two studies in The Gambia[61] and Peru,[62] radiographs confirmed pneumonia in 24% and 36% of cases, respectively, identified by WHO criteria.

THE "VERBAL AUTOPSY": USE AND LIMITATIONS IN MORTALITY ESTIMATES

The "verbal autopsy," commonly used for gathering mortality data in developed countries, consists of a questionnaire (including the WHO criteria for ARI) administered to families about the final illness. This is a simple method of obtain-

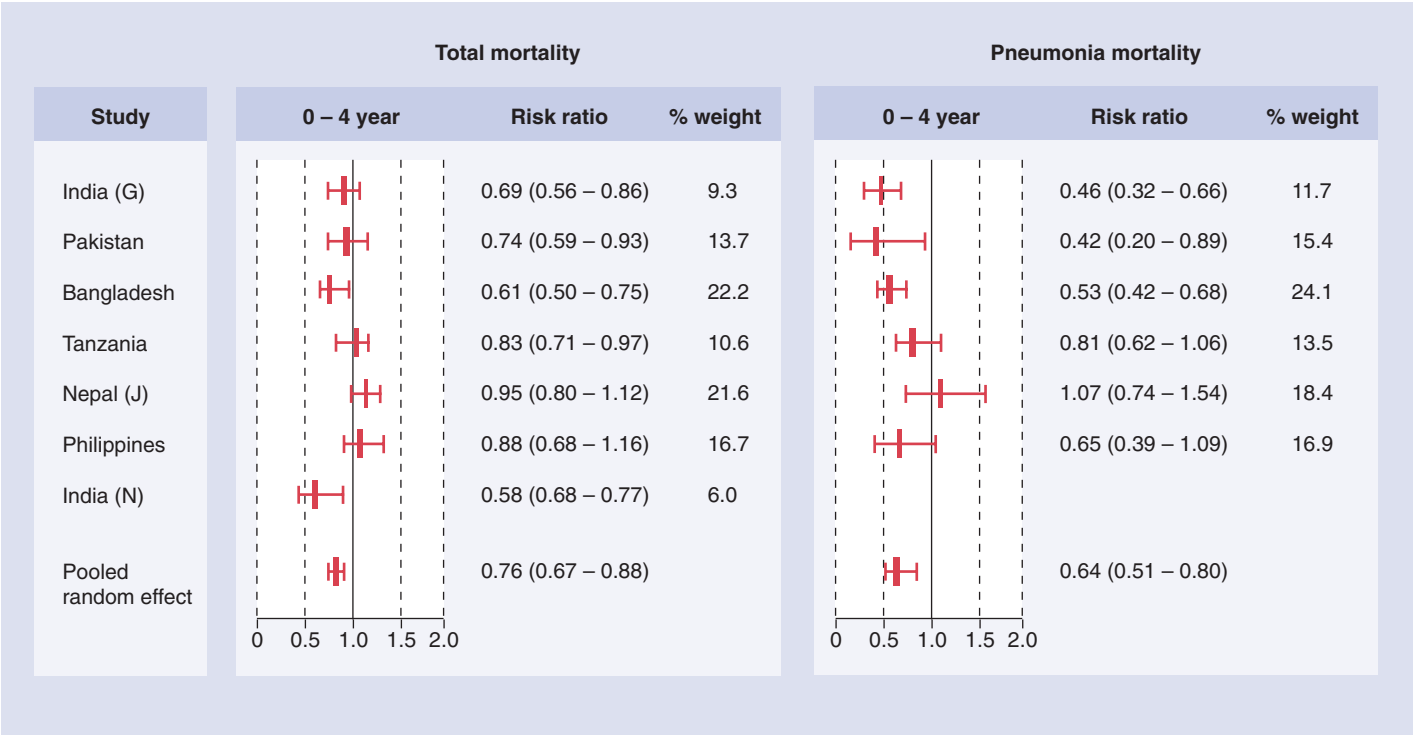

Figure 31-4 Risk ratio and 95% confidence interval for reduction in total and pneumonia mortality in children 0 to 4 years old, showing estimates in individual studies and random effects, pooled estimates, and weights for each study. Letters in study column refer to study locations (G, Gadchiroli, India; J, Jumla, Nepal; N; Navangwal, India). See source article for complete study references. (From Sazawal S, Black RE: Effect of pneumonia case management on mortality in neonates, infants, and preschool children: A meta-analysis of community-based trials. Lancet Infect Dis 3:547-556, 2003.)

ing circumstantial data regarding causes of death without the cultural problems often associated with medical autopsy. Verbal autopsies have a range of reported sensitivity for pneumonia of 28% to 72% and specificity of 60% to 90%.[49] Limitations of the verbal autopsy are similar to those listed for the WHO guideline; such as possible inclusion of deaths from malaria (where prevalent) among deaths from ARI[63] and frequent confounding of cause of death by comorbidities such as malnutrition, measles, or human immunodeficiency virus (HIV) infection in poor countries.[49] ARI is an associated cause or final mode of death even more often than it is a direct cause of death.[64]

LIMITATIONS IN COMPARING EPIDEMIOLOGY IN THE DEVELOPING VERSUS THE DEVELOPED WORLD

We should bear in mind the sensitivity and specificity of the tool used when comparing data. Compared with children in developed countries, children in developing countries have high exposure to risk factors, high rates of bacterial infection, low access to medical care, and high incidence of and mortality from pneumonia. The WHO criteria for ARI have been deliberately chosen to have high sensitivity, accepting the cost of lower specificity. This may have the effect of exaggerating differences in estimates of ARI between developed and developing countries. On the other hand, many researchers state that their best estimates of ARI in developing countries remain conservative and are likely to underestimate the rates. These differences in method should be kept in mind when discussing the estimates below.

OTHER LIMITATIONS OF METHODS

Global estimates and national estimates of ARI incidence and mortality usually depend on data derived indirectly by curve fitting, extrapolation, and applying one proportion to another. Studies at different time points and using different methods may be included. Many of the incidence studies go back to the 1980s,[65] whereas mortality estimates are based on more recent total and cause-specific mortality data.

LIMITATIONS OF AGE GROUPS STUDIED

The majority of international studies of the epidemiology of ARIs deal with children under the age of 5 years. There are fewer data for older age groups; nonetheless, several studies[66,67] have shown a decreasing incidence with age. For the remainder of this section, we confine our discussion to the child less than 5 years of age.

Incidence of Acute Lower Respiratory Tract Infection

Rudan and associates[65] recently estimated worldwide incidence for ARI in children under 5 years of age. They performed a meta-analysis of 28 studies completed mostly in the late 1980s in developing countries. They sought to confirm the directly reported rates in these studies with indirectly calculated rates using case-fatality, rates of severe pneumonia, and case-fatality of severe pneumonia. Their best estimate for the incidence of ARI in the developing world was 0.29 events per child-year, or 150.7 million new cases of ARI per

year, of which 11 to 20 million are severe enough to require hospital admission.

Rudan and associates were unable to find studies for the developed world that used active surveillance and WHO criteria for ARI. They based their estimate of 0.026 event per child-year (or 2.1 million cases of pneumonia per year) on four large population-based studies of community-acquired pneumonia in the United States and Europe.

The recent UNICEF/WHO report on pneumonia[68] indicates that in 2004, 15 countries accounted for three quarters of childhood pneumonia cases worldwide, amounting to approximately 113 million cases. These countries, and the estimated number of cases in 2004, were India (44 million), China (18 million), Nigeria and Pakistan (7 million each), Bangladesh and Indonesia (6 million each), Brazil and Ethiopia (4 million each), Democratic Republic of the Congo and Philippines (3 million each), followed by Afghanistan, Egypt, Mexico, Sudan, and Vietnam (2 million each).

Mortality Due to Acute Lower Respiratory Tract Infection

By country, the percentage of annual deaths of children under 5 years that are due to ARI is related in a logarithmic fashion to the total under 5-year mortality (Fig. 31-5).[49] Figure 31-6 shows the estimated percentage range of deaths from lower ARI among children of each country in 2000.[49] These data were estimated by extrapolating to the year 2000 the 1999 WHO total under-5 mortality data by country, and using the blue fitted curve in Figure 31-5 to estimate the percentage of deaths due to ARI. The authors estimated that between 1.6 and 2.2 million children died of ARI in 2000 and that 40% of these deaths occurred in Africa and 30% occurred in Southeast Asia. Mortality from ARI in excess of 25% of total under-5 deaths was estimated for Afghanistan, Sierra Leone, and Niger. The regions with the lowest proportions of deaths due to ARI were in Western Europe, North America, and Australasia. Other respiratory deaths in young children, estimated for 1998, fell into the following categories: upper respiratory infection and otitis media—37,000, neonatal pneumonia—215,500, pertussis—287,000, measles—594,700, and AIDS-associated ARI—87,500.[69]

Table 31-2 gives an updated summary of mortality due to ARI from the WHO 2005 report[70] by region averaged for the years 2000 to 2003. The numbers have slightly increased but are otherwise similar to those of Williams and associates.[49] Table 31-3 gives a summary of global statistics for ARI in children under 5 years of age, divided into those for the developing and those for the developed world. These figures are based on Rudan and colleagues[65] and the recent UNICEF/WHO report.[68]

If for the moment we ignore the potential errors due to the limitations mentioned above, it would seem that 90% of the child deaths from ARI occur in the developing world, with 75% of them in Africa and Southeast Asia. ARIs constitute about 20% of total mortality in the developing world but only 2% of total mortality in the developed areas of Europe, the Western Pacific, and the Americas. The differences in estimation and comparison are unlikely to have caused such large discrepancies.

Risk Factors for Acute Lower Respiratory Tract Infection

Table 31-4 shows well-established risk factors for developing ARI or pneumonia. Risk factors such as malnutrition are prevalent in developing countries, whereas vehicle emissions may be higher in developed countries.

Risk factors for dying from ARI (almost all from pneumonia) include most of the same factors, but comorbid diseases (especially diarrhea, malaria, measles, tuberculosis, and HIV infection) further increase the mortality risk.[49,71] Lack of adequate health care is also an important associated factor in

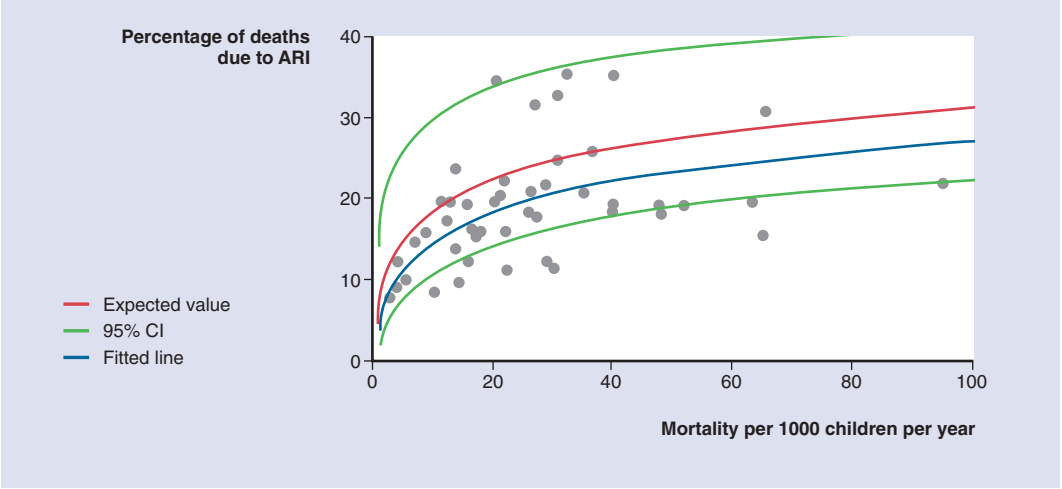

Figure 31-5 Percentage of deaths due to acute lower respiratory tract infection, adjusting for bias in verbal autopsies. The *blue curve* is a weighted log-linear fit to the data points, which are assembled from a number of studies. The *red* and *green curves* are (respectively) expected values and their 95% confidence intervals after correcting for the calculated underestimation and variability of reporting deaths from acute lower respiratory tract infection because of the use of verbal autopsies in many of the studies. (From Williams BG, Gouws E, Boschi-Pinto C, et al: Estimates of world wide distribution of child deaths from acute respiratory infections. Lancet Infect Dis 2:25-32, 2002.)

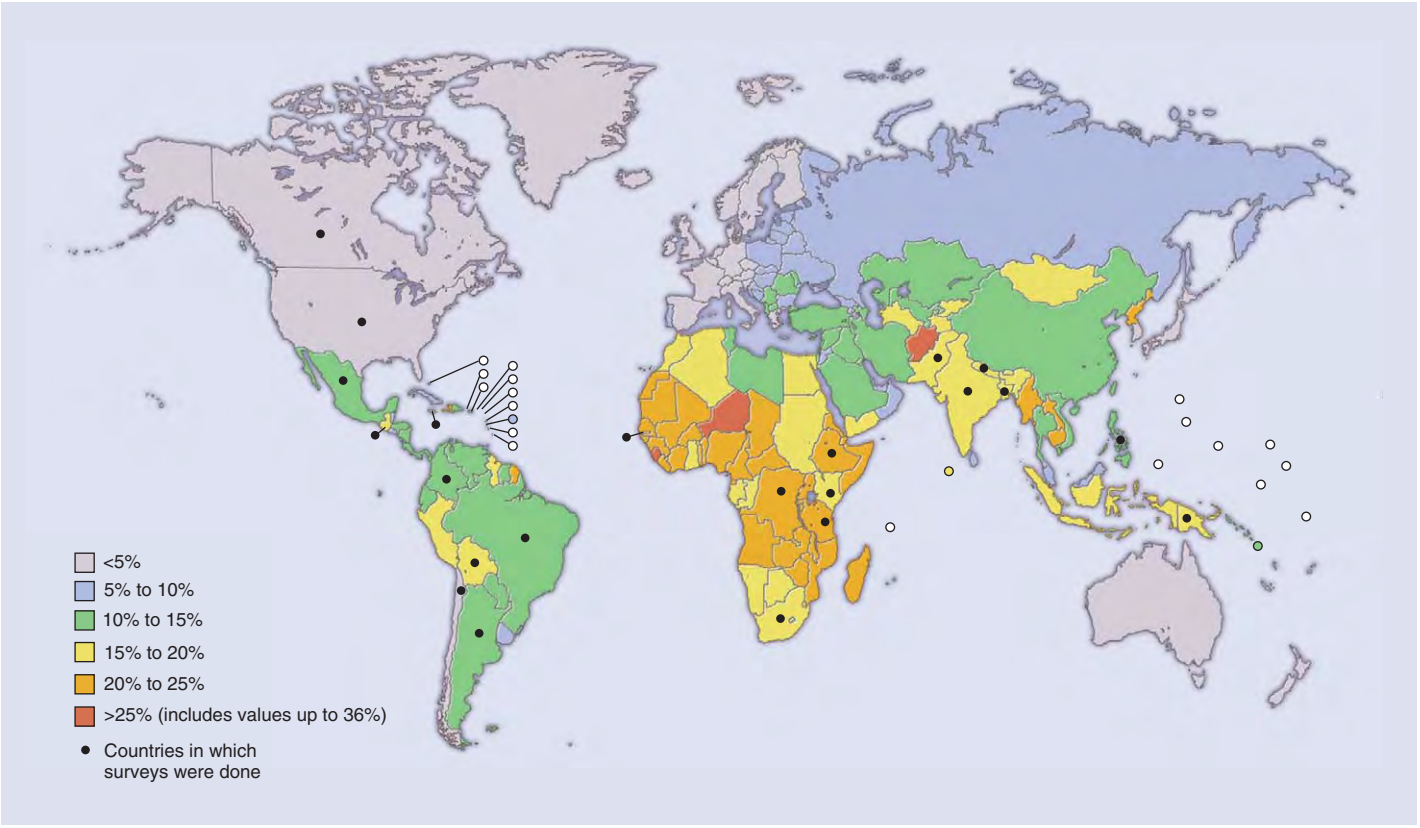

Figure 31-6 Estimates of the percentage of childhood deaths that are attributable to acute lower respiratory tract infection by country in 2000. The last category includes values up to 36%. (From Williams BG, Gouws E, Boschi-Pinto C, et al: Estimates of world wide distribution of child deaths from acute respiratory infections. Lancet Infect Dis 2:25-32, 2002.)

deaths from pneumonia. Geography, education, access, and accessibility are all factors in the adequacy of health care. Where there is access to health care, the cost of life-saving treatment for pneumonia is relatively small.

According to a *Lancet* editorial in 2003,[72] 26% of the world's children under the age of 2 do not receive basic diphtheria, tetanus, and pertussis vaccination, 58% do not receive exclusive breastfeeding for the first 4 months of life, 25% have malnutrition, and 40% do not receive appropriate antibiotic treatment for pneumonia. These risk factors are of course bound together by many strands within communities. As Bawaskar[73] has pointed out, illiteracy is a major factor in infant malnutrition, and low income and illiteracy are enmeshed with impoverished, unsanitary and crowded living conditions, high rates of HIV infection, and lack of access to health care.

Table 31-2
WHO Report 2005: Data for 2000-2003 on Deaths Due to Acute Respiratory Infection (ARI) under 5 Years of Age

	ARI Deaths by Region	ARI as Proportion of All Deaths in Each Region	Distribution of Global ARI Deaths by Region
World	2,027,000	19%	100%
Africa	924,000	21%	45%
The Americas	54,000	12%	3%
Canada, United States	1000	2%	
Rest of the Americas	53,000	14%	
Southeast Asia	590,000	19%	29%
Europe	32,000	12%	1.6%
Low-mortality countries*	<1000	2%	
Rest of Europe	31,000	13%	
Eastern Mediterranean	292,000	21%	14%
Western Pacific	137,000	13%	7%
Australia, Japan, New Zealand	<1000	4%	
Rest of Western Pacific	137,000	13%	

*Andorra, Austria, Belgium, Croatia, Cyprus, Czech Republic, Denmark, Finland, France, Germany, Greece, Iceland, Ireland, Israel, Italy, Luxembourg, Malta, Monaco, the Netherlands, Norway, Portugal, San Marino, Slovenia, Spain, Sweden, Switzerland, and the United Kingdom.
Adapted from van Lerberghe W, World Health Organization: Make Every Mother and Child Count. Geneva, World Health Organization, 2005.

Table 31-3
Acute Respiratory Infection (ARI) under 5 Years of Age: Epidemiology at a Glance

		Incidence 2004: Millions of Cases per Year	Incidence: Events per Child-Year	Case-Fatality Rate: Median	Mortality 2004: Deaths per Year
Developing countries	All ARI	154.5	0.29	2%	2,039,000
	Severe ARI*	11-20	0.03	10%	
Developed countries		1.6	0.026	—	1,000
World		158.5	0.26	—	2,044,000

*Severe ARI is ARI severe enough to require hospital admission.
From UNICEF/WHO: Pneumonia: The Forgotten Killer of Children. New York, UNICEF/WHO, 2006; and Rudan I, Tomaskovic L, Boschi-Pinto C, et al: Global estimate of the incidence of clinical pneumonia among children under five years of age. Bull World Health Org 82:895-903, 2004.

Table 31-4
Risk Factors for Getting Acute Respiratory Infection

Personal Health Factors	Local Environmental Factors
Small Child	***Poverty***
Low birth weight/prematurity	Low family income / parent education level
<5 years old, and especially <1 year old	↓ Access to clean water, sanitation, clothing, housing, health care, immunizations
Lack of Breastfeeding	***Crowding***
Malnutrition	Large families, late–birth order children, early child care groups, peri-urban slums
Kwashiorkor/marasmus	***Indoor Air Pollution***
Micronutrient deficiency (zinc, vitamin A)	Use of biomass fuel (wood products, refuse, dung)
Underlying Heart or Lung Disease	Tobacco smoke exposure
Left-to-right shunt/heart failure	***Outdoor Air Pollution***
Bronchiectasis/cystic fibrosis	Vehicle emissions/CO
Asthma/ciliary dyskinesia	***Geographic Factors***
Immunodeficiency	High rainfall?
HIV infection	High altitude?
Immunosuppression	Wet or cold season
Congenital immunodeficiency	

Data from references 65, 71, 75, 78, 79, and 82.

MALNUTRITION AND ACUTE LOWER RESPIRATORY TRACT INFECTION

Black and colleagues[71] have estimated that as many as 50% of the deaths from ARI/pneumonia in children are attributable to being underweight (Fig. 31-7). A study in Costa Rica in the early 1970s documented a 12-fold increased risk (71% versus 6%, respectively) of pneumonia among malnourished compared with normally nourished children.[74]

Rice and coworkers[75] presented a comprehensive review of the recent literature regarding the effects of malnutrition on death from diarrhea, ARI, malaria, and measles. They summarized three community studies and 12 facility-based studies. The results were consistent across all studies showing a major association between death from ARI and low weight-for-age (W/A) Z-scores or median W/A less than 80% of median. The odds ratios, risk ratios, or relative risks of dying from respiratory infection compared with that for normally nourished children ranged very widely from single figures up to an odds ratio of 26 for W/A Z-score = –2.0 (compared with >0) in a Brazilian study and an adjusted relative risk of 27 for children whose W/A was less than 60% of the local reference median (compared to ≥90%) in a Philippines study. All studies that analyzed risks by degree of malnutrition found a dose-response effect.

Figure 31-8, taken from Victora and colleagues[76] and based on Kirkwood and colleagues,[77] shows that 84% of deaths from pneumonia occur in the first 18 months of life and indicates the potential impacts of nutritional problems at different ages. Victora and colleagues' estimated reduction in pneumonia mortality by region and by intervention is shown in Table 31-5.

HUMAN IMMUNODEFICIENCY VIRUS INFECTION AND ACUTE LOWER RESPIRATORY TRACT INFECTION

Graham and coworkers[78] have summarized recent data for the respiratory effects of HIV infection in African children. Approximately 90% of the HIV-infected children in the world come from sub-Saharan Africa. HIV infection greatly increases the incidence of and mortality from pulmonary disease, mostly in children under 5 years. Conversely respiratory disorders are the most common cause of death in HIV-infected African children. For children hospitalized for severe pneumonia, HIV-infected children in Malawi were three times as likely to die, and in South Africa six times as likely to die, as were non–HIV-infected children.

The high incidence of opportunistic infections (such as *Pneumocystis jirovecii*—formerly known as *Pneumocystis carinii*) of the respiratory tract in HIV infection is well

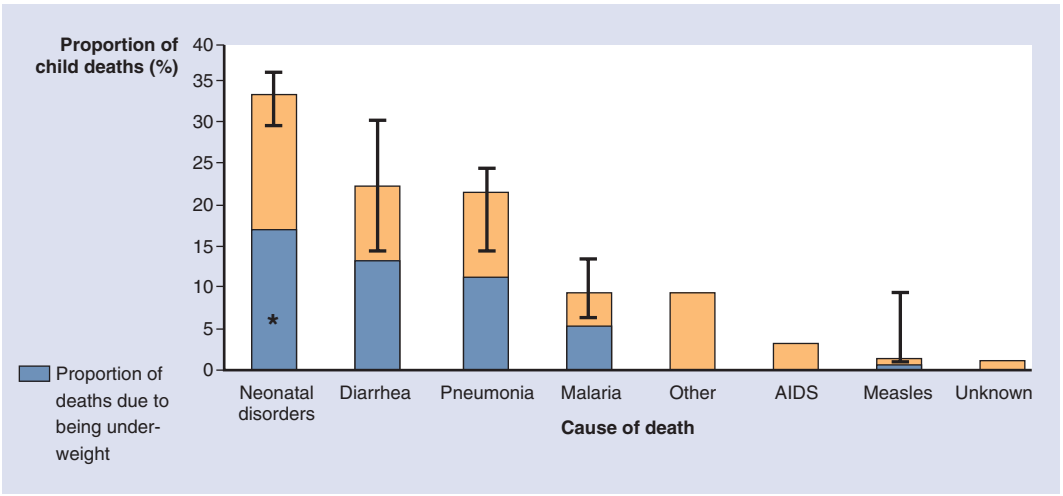

Figure 31-7 Distribution of global deaths by cause. *Bars* indicate uncertainty bounds. *Work in progress to establish the cause-specific contribution of being underweight to neonatal deaths. (From Black RE, Morris SS, Bryce J: Where and why are 10 million children dying every year? Lancet 361:2226-2234, 2003.)

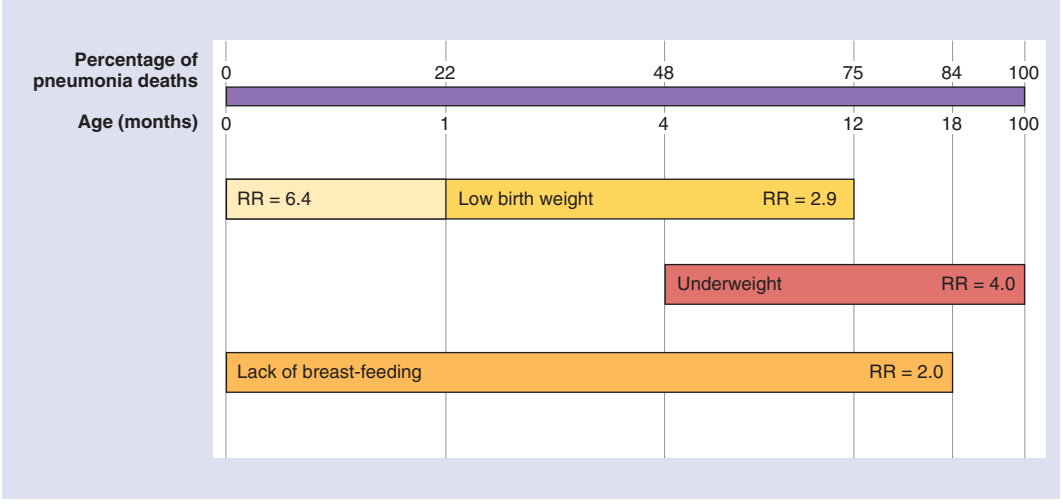

Figure 31-8 Relations between nutritional risk factors for pneumonia mortality and distribution of pneumonia deaths by age. RR, relative risk. (Redrawn from Victora CG, Kirkwood BR, Ashworth, A, et al: Potential interventions for the prevention of childhood pneumonia in developing countries: Improving nutrition. Am J Clin Nutr 70:309-320, 1999.)

Table 31-5
Hypothetical Reductions in Pneumonia Mortality According to Different Nutritional Interventions, Assuming a 40% Reduction in Prevalence of the Risk Factor

	Risk Factor to Be Reduced*		
Region	**Low Birth Weight**	**Malnutrition**	**Non–breastfeeding**
Sub-Saharan Africa	9.0	10.0	0.5
Middle East and North Africa	6.5	7.0	4.3
South Asia	14.0	13.3	—
East Asia and the Pacific	6.9	9.1	2.2
Latin America and the Caribbean	6.9	5.1	7.0
All developing countries	10.1	10.7	3.3

*Values given in percent reduction in pneumonia mortality rates.
Adapted with permission from the *American Journal of Clinical Nutrition* from Victora CG, Kirkwood BR, Ashworth A, et al: Potential interventions for the prevention of childhood pneumonia in developing countries: Improving nutrition. Am J Clin Nutr 70:309-320, 1999.[76]

known. The common pathogens found in HIV-infected children with pneumonia are, in the United States, *S. pneumoniae* and *Salmonella* spp., and in Africa, *S. pneumoniae*, *H. influenzae*, *Staphylococcus aureus*, *Escherichia coli*, *Klebsiella* spp., and nontyphoidal *Salmonella* spp.[78]

HIV infection is commonly associated with other risk factors for pneumonia including poverty and malnutrition, such as children with marasmus.[78] As a result, it can be difficult to determine the relative importance of the HIV infection compared with other risk factors in determining the nature and outcome of pneumonia in regions with high HIV prevalence.

Epidemiology and Prevention of Pneumonia Due to *Streptococcus pneumoniae* and *Haemophilus influenzae*

Among causes of ARIs in young children, the two organisms responsible for the largest number of cases (and 70% of the deaths)[57] are *S. pneumoniae* and *H. influenzae*, the latter including nontypable strains, type B (Hib), and sometimes other typable strains.[79] We now have the means to prevent pneumonia due to Hib and to many strains of *S. pneumoniae*. Madhi and colleagues[80] demonstrated that Soweto children (both HIV positive and negative) immunized with pneumococcal conjugate vaccine had 31% fewer episodes of virus-associated pneumonia compared with placebo controls. This seems to imply that virus-associated pneumonia commonly involves mixed infections with bacteria.

STREPTOCOCCUS PNEUMONIAE

Isolation rates of *S. pneumoniae* in pneumonia are very dependent on sample and identification method and are highly variable in studies in developing and developed countries.[79,81] Berman[82] reported an overall isolation rate of 27% in 14 studies, and 60% of the studies reported isolation rates greater than 30%. The estimated incidence of pneumonia due to *S. pneumoniae* also varies greatly. Incidence rates from 18.1 to almost 200 per 100,000 children per year have been described in developing countries.[79,83,84] Incidence rates estimated in Southern California were 17 per 100,000 per year in 1996.[67,85] Serotypes 1, 2, 5, 7, 9, 14, 15, 18, 19, and 23 are common in both developing and developed countries.[79] Despite the frequency of isolation of *S. pneumoniae*, there are few specific estimates of pneumonia mortality due to this organism.

The peak season for pneumococcal pneumonia in developed countries is winter[66,86] (Fig. 31-9), closely corresponding to peak isolation rates of RSV and influenza. In tropical countries, studies have reported either little seasonal variation[84] or small peaks in the hot season and the monsoon season[83] (Fig. 31-10). The peaks observed could be explained either by secondary infection on the heels of seasonal viral infections or (in parallel to virus infections) by increased interpersonal transmission of bacteria during seasons when people spend more time indoors.

Studies in developing countries have indicated that both total child mortality and mortality due to pneumonia could be lowered by the use of pneumococcal vaccines. Black and coworkers,[87] in a double-blind randomized controlled trial of heptavalent pneumococcal conjugate vaccine in California, reported a 32.2% reduction in pneumonia with positive radiographs in children under 1 year, 23.4% in children under 2 years, and 9.1% in children over 2 years old. Cutts and coworkers[88] have reported a randomized double-blind placebo controlled trial of nine-valent pneumococcal conju-

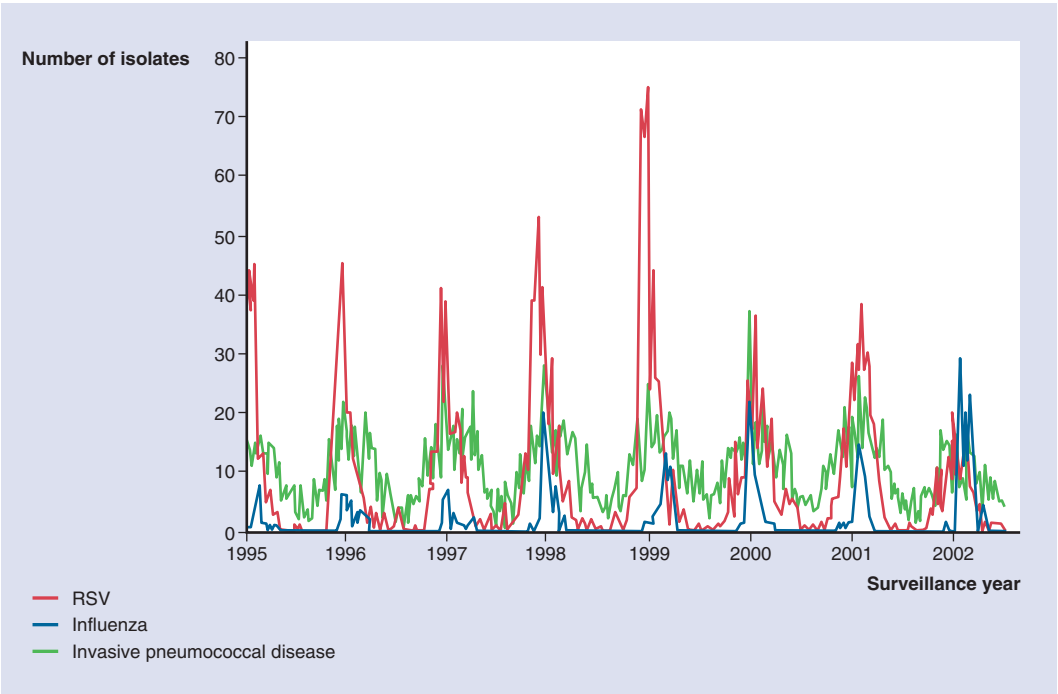

Figure 31-9 Weekly isolation of winter respiratory viruses RSV (*red line*) and influenza (*blue line*) and frequency of invasive pneumococcal disease (*green line*) from January 1, 1995, through June 30, 2002. (From Talbot TR, Poehling KA, Hartert TV, et al: Seasonality of invasive pneumococcal disease: temporal relation to documented influenza and respiratory syncytial viral circulation. Am J Med 118:285-291, 2005.)

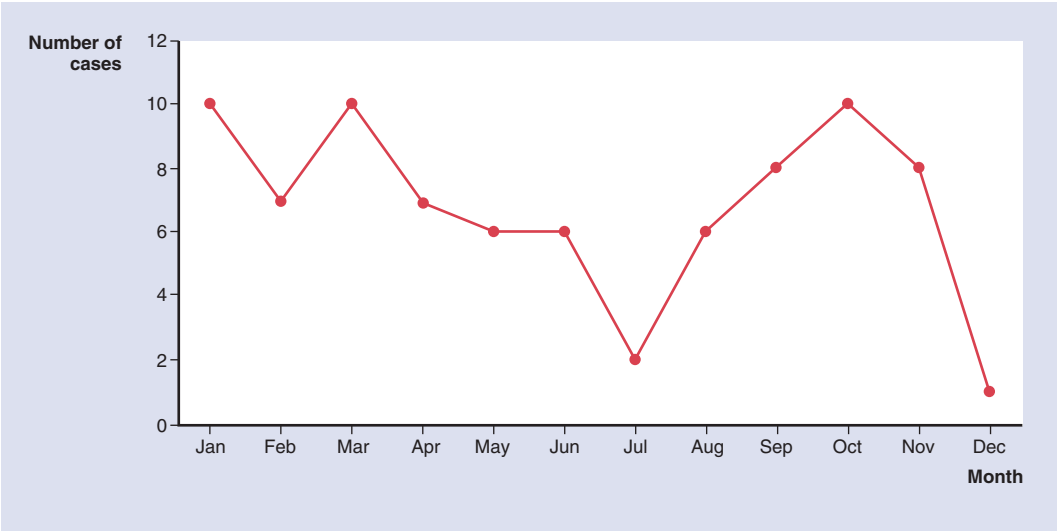

Figure 31-10 Seasonal distribution of pneumococcal pneumonia in 103 children in Upper River Division, The Gambia, 1989 to 1991. (Data from O'Dempsey TJ, McArdle TF, Lloyd-Evans N, et al: Pneumococcal disease among children in a rural area of west Africa. Pediatr Infect Dis J 15:431-437, 1996. Used with permission of Lippincott Williams & Wilkins.)

gate vaccine in Gambian infants less than 1 year old. They estimated (based on intention-to-treat analyses) a reduction in first episodes of pneumonia of 6%, reduction of admissions to hospital of 13%, reduction of admissions due to potentially invasive pneumococcal disease of 19%, and reduction in all-cause mortality of 14%. Vaccine efficacy was 77% against invasive pneumococcal disease due to vaccine-related serotypes and 50% against invasive disease due to all serotypes.

HAEMOPHILUS INFLUENZAE

Levine and coworkers,[89] in a 1998 review, estimated that *H. influenzae* (all strains) caused 16% of all pneumonia deaths not due to measles or pertussis or 482,000 deaths from pneumonia each year in children under 5 years in developing countries. Peltola[90] conservatively estimated the annual prevaccination incidence of Hib pneumonia in children under 5 years in developing countries at 300 per 100,000 based on Gambian studies in the 1990s.[90,91] This represents 1.7 million cases and 220,00 to 400,000 deaths with a case-fatality rate of 13% to 24%. In developed countries, Peltola estimated a prevaccination incidence of 6 per 100,000, representing 5000 cases, 250 deaths, and a case-fatality rate of 5%.

Nontypable strains have been found to be as commonly or more commonly associated with pneumonia in several studies,[79,90] but only in developing countries. Levine and colleagues[89] reported that Hib accounted for a mean of 35% of all *H. influenzae* pneumonia cases in three studies of all *H. influenzae* pneumonias but for a mean of 71% of bacteremic *H. influenzae* pneumonias in eight studies. If most deaths occur in bacteremic pneumonia, as is supposed, then Hib may be responsible for up to 70% of the deaths from *H. influenzae* pneumonia in under-5 children.

Vaccination for *H. influenzae* type B has dramatically reduced all causes of invasive Hib in the developed world[92] (Fig. 31-11).

Trials of Hib conjugate vaccine in developing countries have included prospective case-control studies in Chile[93] and Brazil[94] and a double-blind randomized placebo controlled trial in The Gambia.[95] Vaccine efficacy in young children ranges from 21% to 31% against radiology-confirmed pneumonia from all causes in these studies. The Gambian study showed reduction of oropharyngeal carriage of Hib.[96]

Levine and co-workers in 1998[89] estimated the potential impact of routine immunization of infants with 3 doses of Hib conjugate vaccine in developing countries (Table 31-6). The estimates include all Hib disease (the majority being pneumonia and meningitis). They suggested that 60% of deaths and 67% of cases would be prevented if no herd immunity were operative. In the presence of herd immunity over 300,000 deaths (83% of deaths) and 2.5 million cases (85% of cases) might be prevented. Miller[97] estimated that among Asian countries, about 136,000 (87%) Hib deaths could be prevented annually with incorporation of Hib vaccine into the immunization programs at a cost of between 0.1% and 3.0% of per capita gross national product per child younger than 5 years. However, a recent Hib vaccine probe trial among 55,073 children in Lombok, Indonesia,[98] found no protective effect against radiology-confirmed pneumonia despite a protective effect against clinically defined pneumonia and against meningitis. Various reasons are discussed in the paper and the accompanying editorial.[99]

Conclusion

ARI and pneumonia contribute a massive burden of death and morbidity to young children and much more so in developing countries than in developed countries. Vaccination strategies to prevent disease are well proved for single-agent diseases with obligate human hosts. However, vaccine implementation, acceptance, and coverage are always going to offer challenges when different political, economic, health, and cultural systems have to be engaged. Other major factors that will be required to decrease the morbidity and mortality due to ARI in children must include the reduction or eradication of poverty, malnutrition, and HIV infection and improve-

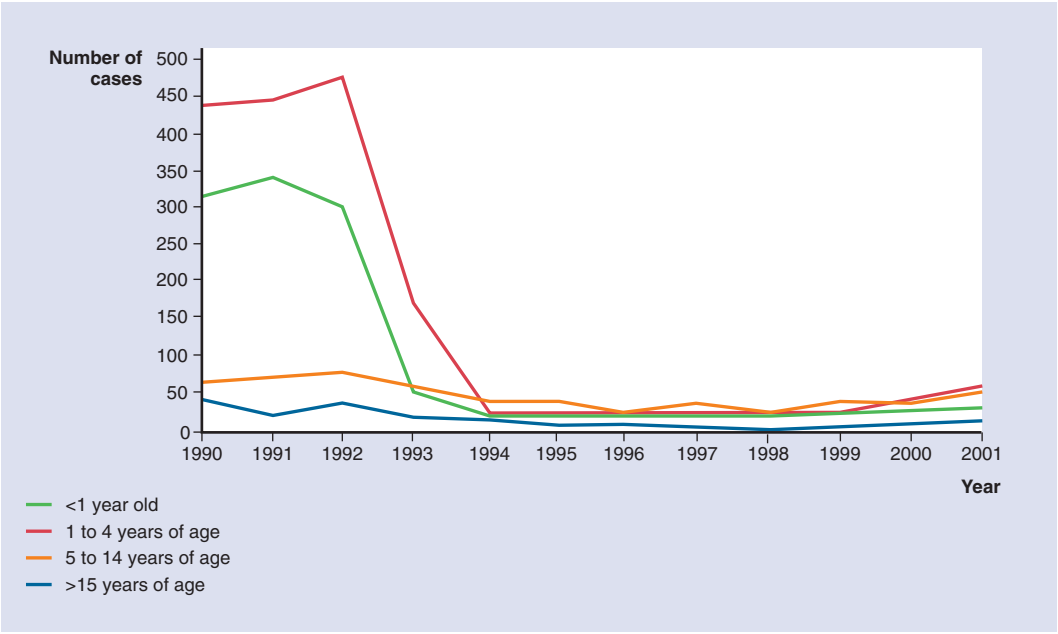

Figure 31-11 Invasive Hib infections by age, 1990 to 2001, England and Wales, combined PHLS HRU/CDSC data. (From McVernon J: Hib surveillance and remaining HIB disease in the UK. Paper presented at Global Reduction of Hib Disease Meeting, September 22-25, 2002, Scottsdale, Arizona.)

Table 31-6
Estimated Impact of Routine Immunization of Infants with Hib Conjugate Vaccine in Developing Countries

		Three-Dose Vaccine Regimen	
Outcome Measure	**No Immunization**	**Without Herd Immunity**	**With Herd Immunity**
No. of Hib deaths			
Expected	377,470	150,670	65,120
Prevented		226,800	312,350
Percent of deaths prevented		60%	83%
No. of Hib cases			
Expected	2,915,000	957,800	423,750
Prevented		1,957,200	2,491,250
Percent of cases prevented		67%	85%

Adapted from Levine OS, Schwartz B, Pierce N, Kane M: Development, evaluation and implementation of *Haemophilus influenzae* type b vaccines for young children in developing countries: Current status and priority actions. Pediatr Infect Dis J 17(9 suppl):S95-S113, 1998. Used with permission of Lippincott Williams & Wilkins.

ments in air quality through reduction of smoke exposure from cigarettes and biomass fuels.

EMERGING AND REEMERGING DISEASES

Infectious diseases are the leading cause of death among young people under the age of 50 years.[100] The complex matrix of these diseases from endemic diseases, which pose an ongoing threat, through to new emerging and reemerging diseases that present new challenges[101] is shown in Figure 31-12. Respiratory pathogens, including SARS, influenza, and tuberculosis, are some of the emerging and reemerging threats that have recently received or are receiving ongoing attention as global public health concerns. These infections, many of which are zoonotic in origin, are creating unprecedented challenges, and spurring the development of new approaches. The application of epidemiology simulation modeling to identify the best public health responses under a variety of conditions[102] and for specific interventions with pandemic influenza[103] are examples.

Influenza

GENERAL EPIDEMIOLOGY

Of all the viruses that infect the human respiratory tract, influenza viruses cause the predominant number of serious acute respiratory tract illnesses.[104] There are three types of influenza virus, A, B, and C, of which the influenza A and B

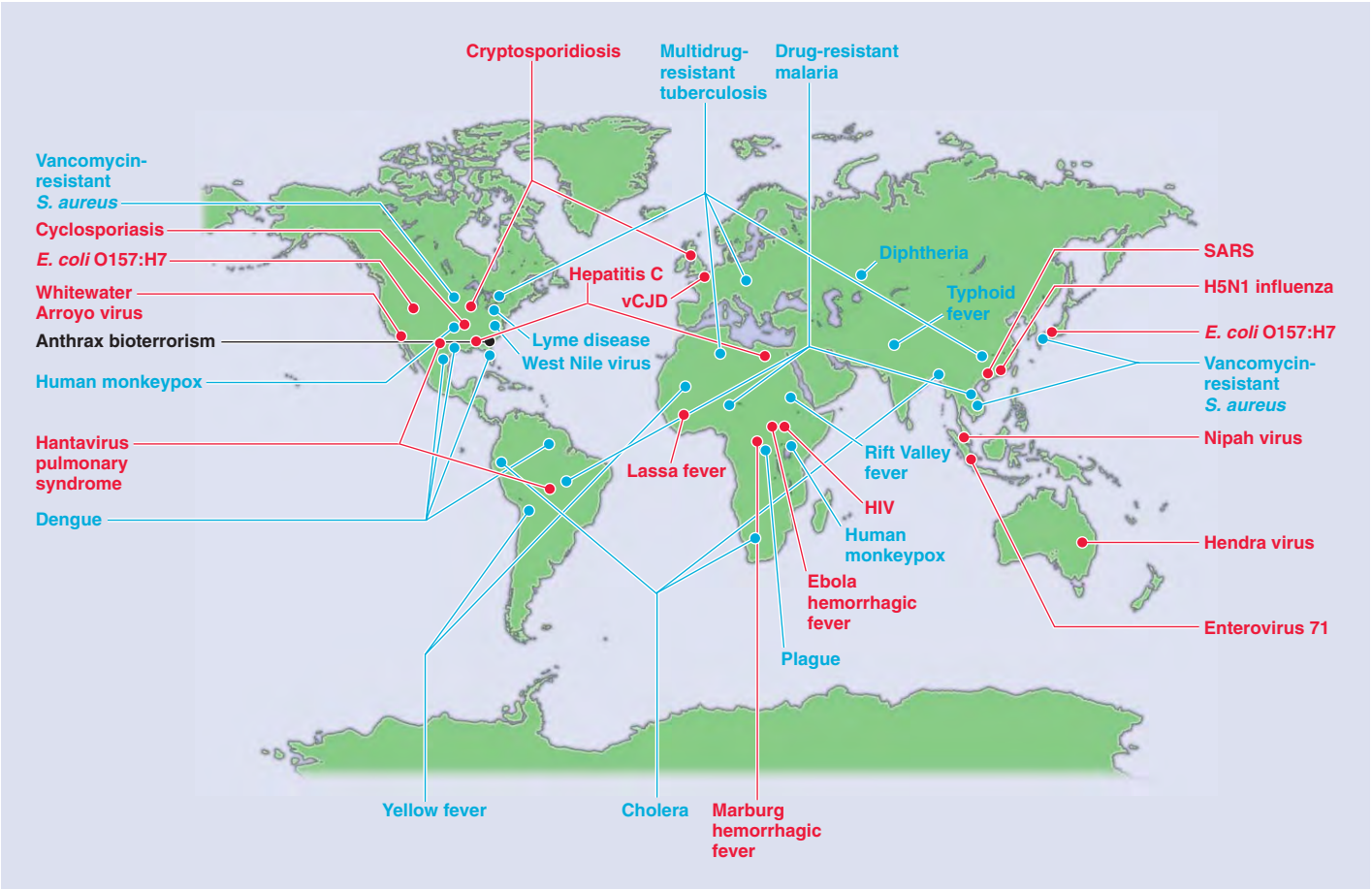

Figure 31-12 Global examples of emerging and reemerging infectious diseases. *Red* represents newly emerging diseases; *blue*, reemerging/resurging diseases; *black*, a "deliberately emerging" disease. (From Morens DM, Folkers SK, Fauci AS: The challenge of emerging and re-emerging infections diseases. Nature 430:242-249, 2004.)

viruses are clinically relevant in humans. Influenza B viruses have a human reservoir, whereas influenza A viruses have a reservoir in aquatic birds and are antigenically diverse. Influenza A viruses have two major antigenic surface proteins, the hemagglutinin (H) and neuraminidase (N). We recognize 16 different H antigens (named H1–16) and nine different N antigens (N1–9), and unique combinations of H and N antigens are called influenza A subtypes. All of these subtypes have been found circulating among wild aquatic birds, their primary natural reservoir. From time to time, these viruses cross the species barrier, with some becoming established in another avian or animal species. In the past century, the influenza A subtypes H1N1, H2N2, and H3N2 have been able to infect and establish sustained transmission among humans, whereas the H5N1 subtype has become established in domestic poultry (Fig. 31-13). The constant evolution of influenza A and B viruses occurs through the accumulation of mutational changes in the H and N antigens. This antigenic *drift* leads to the selection of new variants and regular epidemics of disease, while reassortment of the H and N genes of different influenza A subtypes (antigenic *shift*) leads to the emergence of a novel virus and pandemic influenza.[105] However, it is becoming clear that the emergence of human influenza virus lineages can occur through avenues other than drift and shift.[106]

EPIDEMIC INFLUENZA

Epidemics of influenza occur almost every year. They are caused by new variants of influenza A and B viruses that have evolved through antigenic drift, allowing them to evade the host's immune defenses. This requires regular updates of the composition in influenza vaccines. In countries with temperate climates influenza activity peaks during the winter months with influenza A epidemics occurring every 1 to 2 years and influenza B circulating every 2 to 4 years.

ATTACK RATES IN CHILDREN

Influenza incidence and illness are high in children. Attack rates can be 40% or more in preschool-aged children and 30% in school-age children, which is higher than the 10% to 20% rate commonly observed in young adults.[26,33,107-109]

DISSEMINATION

Children have an important role in spreading influenza. School provides an ideal environment for the spread of respiratory viruses, and school-age children serve as the main channels through which influenza A and B virus infections are introduced into households.[107,109,110] Exacerbations of COPD in adults were found to be correlated with epidemics of viral infections including influenza A and B in school children and to decline during school holidays.[111] In young children, influ-

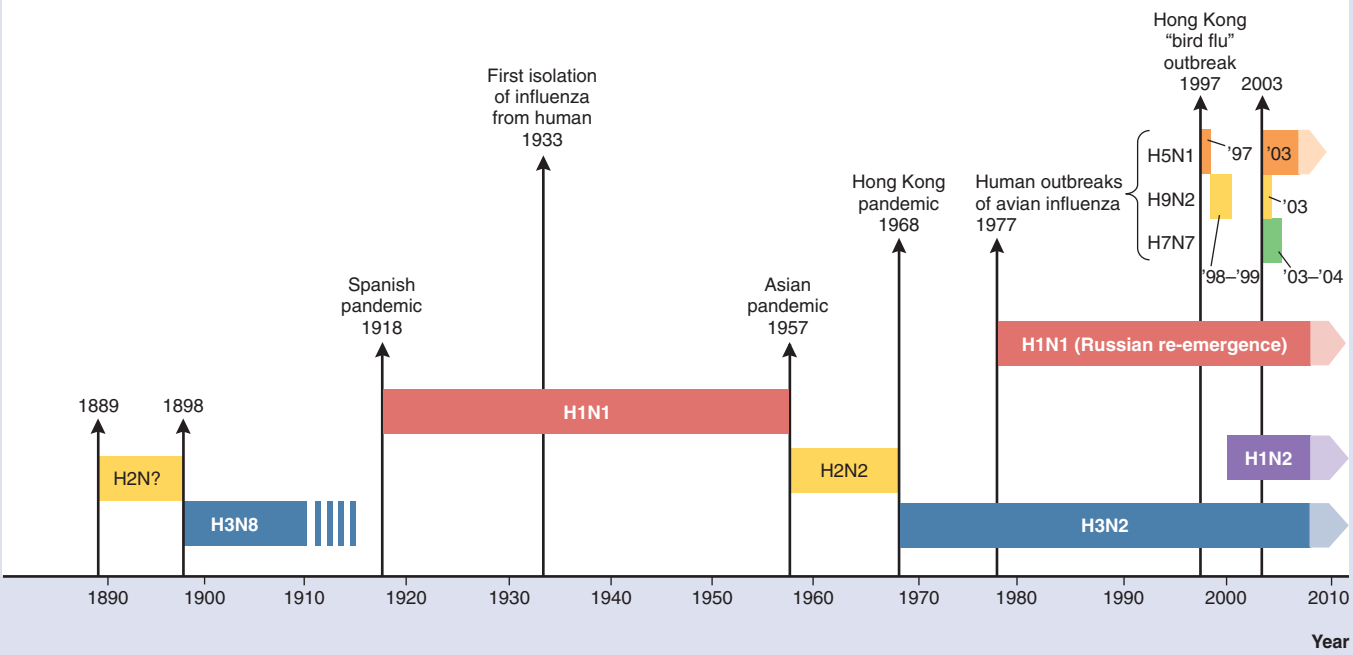

Figure 31-13 Time course of global spread of human influenza virus A subtypes and human outbreaks of avian influenza viruses. (Redrawn from Fauci AS: Emerging and reemerging infections diseases: The perpetual challenge. Acad Med 80:1079-1085, 2005.)

enza virus is detectable 1 to 3 days after infection and shedding often persists for 10 days to 3 weeks.[112]

HOSPITALIZATIONS

During childhood, influenza is the most significant cause of acute respiratory illness leading to hospitalization,[113] outpatient visits,[108] and courses of antibiotics in children of all ages.[114] Healthy children younger than 1 year are hospitalized at rates similar to those for adults at high risk for influenza.[115] The rate of hospitalization decreases with age. Similarly high hospitalization rates have been reported among children in the subtropics compared with those reported in temperate regions.[116]

PANDEMIC INFLUENZA

Human pandemics of influenza have been reliably described since the 16th century, with an average of three occurring every 100 years.[117] Over the 20th century, there have been the 1918-1919 "Spanish" H1N1 pandemic, which caused an estimated 20 to 50 million deaths, mainly in previously healthy persons aged 20 to 40 years old, and the 1957 "Asian" H2N2 and 1968 "Hong Kong" H3N2 pandemics, which caused large numbers of cases and a combined mortality estimated to be more than 3 million deaths, mostly in the very young, the elderly, and people with underlying chronic conditions (see Fig. 31-13).

Recovery of lung tissue from victims of the 1918 pandemic has allowed the isolation of viral RNA and the reconstruction of the complete 1918 pandemic virus in the laboratory.[118,119] These experiments support the hypothesis that the 1918 H1N1 virus was of avian origin and adapted to human infection and transmission. In contrast, the influenza viruses that caused the 1957 and 1968 pandemics are human-avian reassortant viruses, and this difference may be relevant to the severity of the 1918 pandemic.[120]

AVIAN INFLUENZA ASSOCIATED WITH HUMAN CASES

Human infections and outbreaks following interspecies transmission of highly pathogenic avian influenza viruses have rarely been reported before 1997.[121] Reports are increasing of human infections associated with direct or indirect contact with infected birds. In 1997, the infection of 18 humans, of whom 6 died, with an avian H5N1 virus raised the level of global concern of a possible human influenza pandemic. In 1999, H9N2 avian influenza infected two children in Hong Kong and there were other cases in mainland China. In 2003, H5N1 and H9N2 infections were confirmed in Hong Kong, while in the Netherlands, a large avian influenza outbreak involved an H7N7 virus. Up to 1000 cases among farmers and poultry workers occurred. Since late 2003, outbreaks of avian H5N1 have been reported among poultry in Southeast Asia.[122] Human infections and deaths were initially reported in Vietnam and Thailand. This virus has become endemic in domestic poultry in Asia and has spread globally after infecting migratory waterfowl.[123] Subsequently, there have been reports of human infections in an increasing number of countries. Clusters of human infection are small, suggesting that if human-to-human transmission is occurring, it is very inefficient.

As this H5N1 virus continues to circulate in and be spread by domestic and migratory avian species, there is an ongoing risk of human infection and a threat of the emergence of a human pandemic virus. Whether the H5N1 virus or one of the other potential pandemic subtypes (H2, H5, H7, or H9

viruses) will adapt to efficient human-to-human transmission remains unknown. Currently, no mechanism of prediction of the emergence of novel influenza A viruses exists, highlighting the importance of the ongoing global surveillance of animal and human influenza viruses by the WHO.

Severe Acute Respiratory Syndrome

GENERAL EPIDEMIOLOGY

SARS is an acute viral respiratory syndrome caused by a novel coronavirus, the SARS coronavirus (SARS-CoV), and recognized as a global threat in mid-March 2003. The virus is an animal virus that has crossed the species barrier to humans.[124,125] The first known cases are believed to have occurred in Guangdong Province, China, in November 2002.[126] Early cases were associated with occupational exposure to infected animals[127]; however, once the number of cases started to increase, health care workers and their close contacts were at greatest risk of infection. The epidemic was characterized by "superspreading events,"[128-130] which seeded outbreaks in Canada, China, Hong Kong, Taiwan, Singapore, and Vietnam (Fig. 31-14). By July 2003, the international spread of SARS-CoV presented a global public health threat resulting in 8098 SARS cases in 26 countries and 774 deaths.[131] The epidemic caused social and economic disruption in areas with sustained transmission of SARS, and on the travel industry internationally, in addition to the impact on health services directly.

Since July 2003, four sporadic community-acquired cases have occurred in Guangzhou, Guangdong Province, China,[132] while three incidents have been attributed to exposures in laboratories.[125,133]

RESERVOIR

The natural reservoir of SARS-CoV has been identified as the Chinese horseshoe bat.[134] Although many animals have been investigated as possible reservoirs,[124,135] bats are well suited to transmit zoonotic disease, as many people in Asia eat bats and use their feces for medicines.

CHILDREN

SARS runs a more benign and shorter clinical course in young children (less than 12 years of age) during the acute phase.[136] Infants born to mothers with the disease did not acquire the infection through vertical transmission. No deaths were reported in children.[137] Children appear to acquire the infection by close-contact household exposure to an infected adult.[138]

Tuberculosis

Tuberculosis (TB) remains a major global public health problem. It is estimated that in 2004, one third of the world's population was infected with the mycobacterium bacillus that causes TB and almost 4 million were smear positive.[139] A number of factors have facilitated the resurgence of tuberculosis. These include the advent of the AIDS epidemic, emigration from countries where prevalence of TB is high, noncompliance of patients, transmission in high-risk environ-

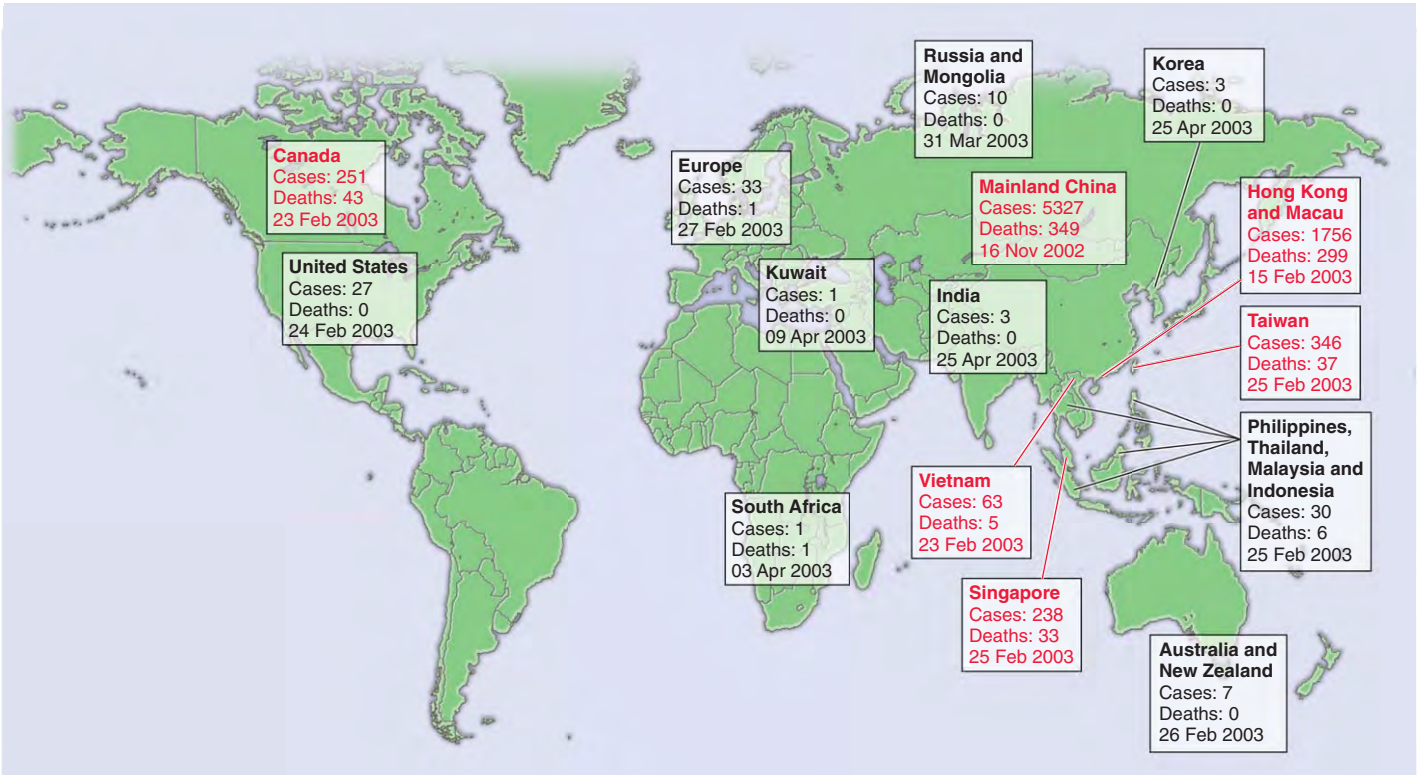

Figure 31-14 The global spread of SARS. The number of probable cases of SARS and the date of onset of the first case in each country (or group of countries) is denoted. The countries denoted in *red* are those where substantial local transmission occurred. (From Peiris JS, Guan Y, Yuen KY: Severe acute respiratory syndrome. Nat Med 10(12 suppl):S88-S97, 2004.)

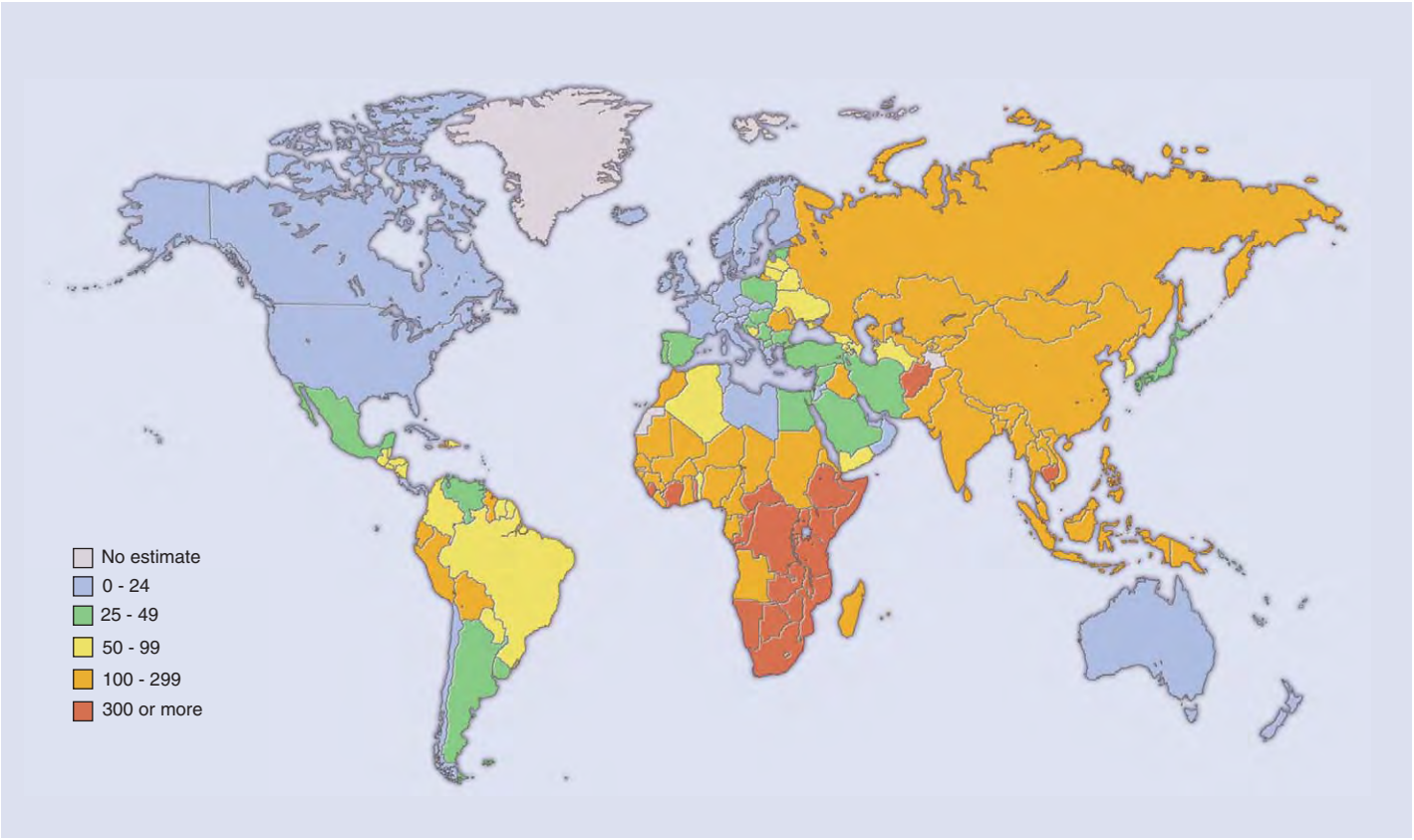

Figure 31-15 Estimated tuberculosis incidence rates, 2003. (From the Global Plan to Stop TB 2006-2015. Geneva, World Health Organization, Actions for Life, 2006.)

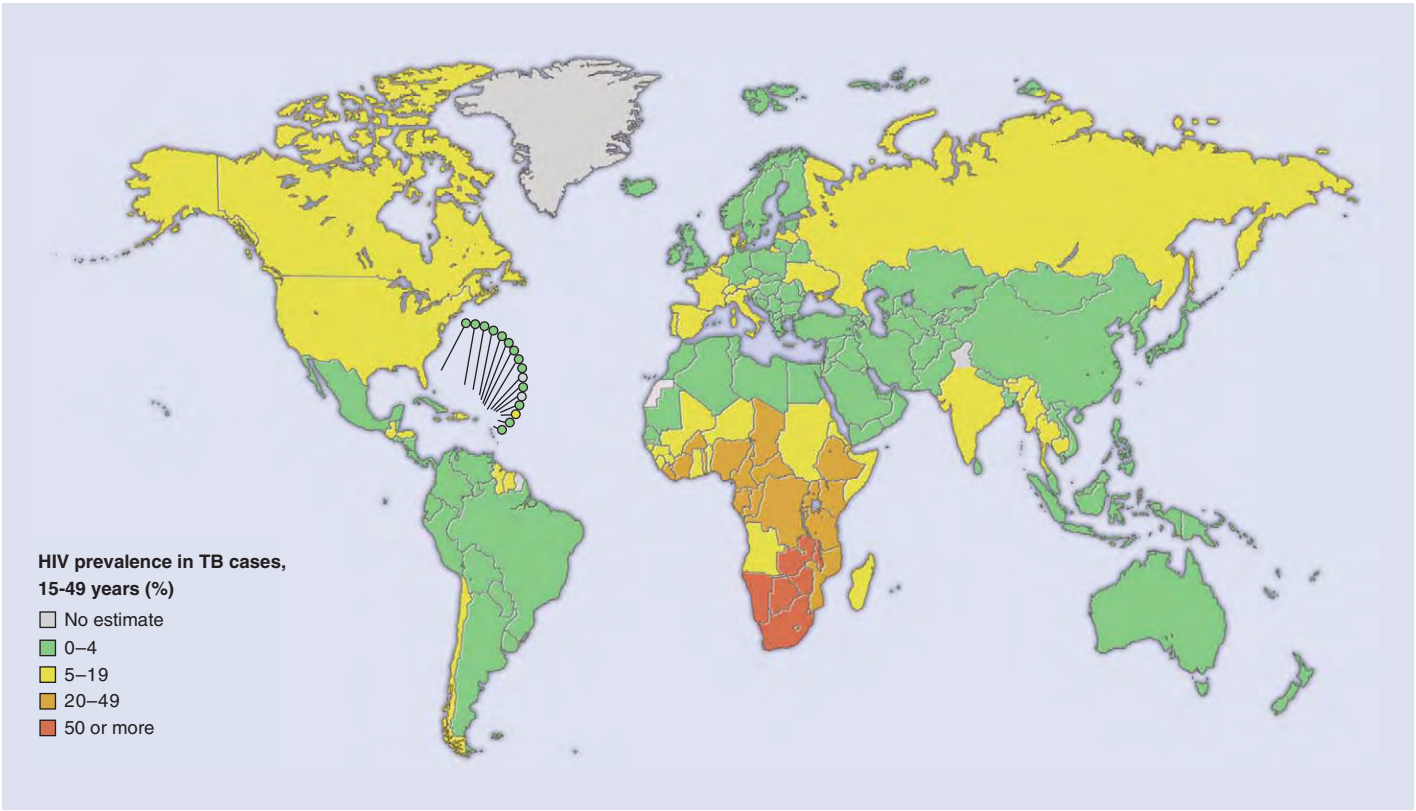

Figure 31-16 Estimated prevalence of HIV infection in TB cases, 2003. (From the Global Plan to Stop TB 2006-2015. Geneva, World Health Organization, Actions for Life, 2006.)

ments, and the coincident increase in the number of cases of multidrug-resistant tuberculosis (MDR-TB).

GLOBAL INCIDENCE

The estimated TB incidence globally is shown in Figure 31-15.[140] The largest number of cases occurs in the Southeast Asia region (190 cases per 100,000 population), which accounts for 33% of incident cases globally; however, in sub-Saharan Africa, the incidence per capita is nearly twice that of Southeast Asia, given by the WHO at 356 cases per 100,000 population in 2004.[139]

The WHO also estimated that 1.69 million deaths (27 deaths per 100,000 population) resulted from TB in 2004.[139] As with cases of disease, the highest number of estimated deaths is in the Southeast Asia region, but the highest mortality per capita (78 deaths per 100,000 population) is in sub-Sahaian, Africa, where HIV has led to rapid increases in the incidence of TB and increases the likelihood of dying from TB (Fig. 31-16).[140] TB accounts for about 13% of AIDS deaths worldwide.[141]

DRUG-RESISTANT TUBERCULOSIS

Drug-resistant TB is on the increase in many parts of the world.[142] The development of resistance is a result of inconsistent or partial treatment of cases. Of particular concern is multidrug-resistant TB, which is defined as resistance to isoniazid and rifampicin, the two most effective anti-TB drugs. It is estimated that 300,000 new cases of multidrug-resistant TB are developing each year.[139]

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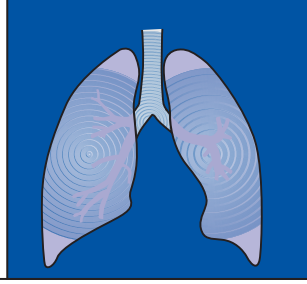

CHAPTER 32 Infections of the Upper Respiratory Tract

M. Innes Asher and Cameron C. Grant

TEACHING POINTS

- Treatment with antibiotics shortens the duration of symptoms and reduces the complications of tonsillitis and pharyngitis, otitis media, sinusitis, deep neck abscesses, epiglottitis, and bacterial tracheitis.
- Over-the-counter medicines for colds are not efficacious.
- Penicillin remains the treatment of choice for *Streptococcus pyogenes* pharyngitis.
- Airway obstruction occurs in deep neck abscesses, viral croup, epiglottitis, bacterial tracheitis, and recurrent respiratory papillomatosis.
- Clinical features and patterns of disease are different from those in adults.

Infections of the upper respiratory tract are very common in children. Their epidemiology is described in Chapter 31. Although infections of the upper respiratory tract often resolve completely without complications, treatment is indicated where it can achieve more rapid resolution of symptoms, prevent the illness becoming more severe, prevent complications, or prevent chronic disease.

The conditions covered in this chapter are the common cold, tonsillitis and pharyngitis, otitis media, sinusitis, deep neck abscesses, viral croup, epiglottitis, bacterial tracheitis, and recurrent respiratory papillomatosis.

THE COMMON COLD

I love the doctors—they are dears;
But must they spend such years and years
Investigating such a lot
Of illnesses which no one's got,
When everybody, young and old,
Is frantic with the common cold?
And I will eat my only hat
If they know anything of that![1]

Epidemiology, Risk Factors, and Pathogenesis

The common cold may be caused by one of over 100 different viral types; the major ones are listed in Box 32-1. The main clinical difference among colds induced by different viruses is in the duration of the incubation period.[2] Other types of organisms occasionally cause a syndrome that can overlap with the common cold. Such organisms include *Mycoplasma pneumoniae*, *Bordetella pertussis*, *Streptococcus pyogenes*, *Coccidiodes immitis*, *Histoplasma capsulatum*, *Chlamydia psittaci*, and *Coxiella burnetii*.[1]

With the use of polymerase chain reaction (PCR)-based assays, the proportion of common colds for which an etiologic organism is identifiable has increased to 70% to 80%. The discovery of human metapneumovirus as a cause of acute respiratory infections suggests that currently unidentified infectious agents cause at least a proportion of the remainder.[1]

Common colds vary in frequency with age and season. They are more frequent in autumn and winter in temperate regions and in the rainy season in tropical regions.[1] Children have more colds per year than do adults and can be expected to have approximately six colds annually from age 2 to 6 years.[3-5] For children, day care attendance increases the risk of illness, with a dose-response effect evident between the number of children in the day care setting and the number of colds.[1,6-8] Among adults, psychological stress is associated with an increased risk of having the common cold.[9] Colds occur less frequently in women who work outside of the home, suggesting that exposure to children is a risk factor for adults.[1,10]

The mode of transmission (hand contact with infected secretions versus small-particle aerosols versus direct hit by large-particle aerosols) varies between viruses. Rhinovirus, the most frequent pathogen, is transmitted mainly by hand contact with infected secretions followed by self-inoculation onto the nasal mucosa or conjunctiva, but it also spreads as an aerosol.[11,12]

The pathophysiology of the common cold is understood mainly from studies of adult volunteers infected with rhinoviruses.[1,11,13] After deposition of the virus on the nasal mucosa or from the conjunctiva via the lacrimal duct, the virus reaches the nasopharynx via mucociliary transport. After binding to specific cell surface receptors, the virus enters the epithelial cell. Once inside the cell, the virus starts to replicate rapidly. The infectious dose is small.[14] Up to 95% of people without serotype-specific antibodies become infected, with 75% of these infections resulting in symptomatic colds.[15]

Infection of nasal mucosal epithelial cells results in vasodilation and increased vascular permeability leading to rhinorrhea and nasal obstruction.[1] Sneezing and increased mucus

BOX 32-1 Viral Causes of the Common Cold

Most Common Cause

Rhinoviruses

Common Causes

Coronaviruses
Influenza viruses*
Parainfluenza viruses*
Respiratory syncytial virus*

Occasional Causes

Adenoviruses*
Enteroviruses*

*Most illnesses caused by these viruses include other symptoms in addition to those that are symptoms of the common cold.[1]

gland secretion occur as a result of increased cholinergic stimulation.[1] In contrast with influenza and adenovirus infection, epithelial destruction is not a feature of rhinovirus infection.[1,13]

Components of the upper respiratory tract other than the nasal cavity are affected by the common cold. Paranasal sinus abnormalities are evident on radiography.[16,17] These abnormalities resolve spontaneously. Eustachian tube dysfunction occurs frequently in both children and adults and predisposes the susceptible individual to otitis media.[18-21]

During the common cold, the greatest concentration of virus is in the nasal secretions, with little found in secretions generated by coughing or talking or in saliva. The greatest amount of virus comes from sneezing, nose blowing, and secretions from the nose transmitted on contaminated hands. Children have a greater concentration of virus in their secretion and tend to shed virus for longer periods than adults. Viral shedding is maximal 2 to 7 days after inoculation, although some shedding may continue for another 2 weeks.

Serum antibody and secretory antibody develop from the infection and appear to be protective against reinfections. Clinically abortive colds may be reinfection colds with early antibody recall.

Impairment of nasal mucociliary transport persists for approximately 1 month after a cold. Children who have four to six colds in a winter may have constantly impaired mucociliary transport.

Clinical Features

The common cold is an acute, highly infectious illness characterized by nasal stuffiness, sneezing, coryza, throat irritation, cough, and little or no fever; it occurs multiple times each year in each person. Although older children have an illness similar to that of adults, in infants, the symptoms and signs may be more varied. The minimal symptoms that define the diagnosis are nasal discharge, nasal obstruction, and throat irritation. At the onset of symptoms, there is a feeling of chilliness on exposure to cold, dryness and irritation in the nose, and a scratchy throat. This progresses rapidly to nasal stuffiness or obstruction, sneezing, watery nasal discharge, throat irritation, watering eyes or eye irritation, coughing, occasional muscular aches, general malaise, anorexia, and, sometimes, low-grade fever.[2] After 1 to 3 days, the nasal secretions may become thicker and purulent. Persistent nasal discharge may lead to excoriation around the nose. If nasal obstruction occurs, it leads to mouth-breathing, aggravating the irritation of the throat. The usual duration of the illness is about 7 days, but lingering nasal discharge may persist for 2 weeks or longer.

In infants, the onset is more likely to be associated with a fever of 38° to 39° C (100.4° to 102.2° F).[1,22,23] The infant may be irritable and restless, and the nasal obstruction may significantly interfere with both feeding and sleeping. Vomiting and diarrhea may also occur.

Diagnosis

If the clinical features and exposure history are specific, then investigations are not indicated. In infants, investigation for alternative diagnoses, including invasive bacterial infections, may be necessary, particularly if fever is a predominant symptom and/or nasal obstruction results in apnea. The early symptoms of many illnesses such as pertussis, epiglottitis, measles, and diphtheria are similar to those of the common cold, but in a short time, the other features of the specific illness appear. Allergic rhinitis may need to be distinguished from the common cold in the child with "recurrent colds." Assessment of the family history, possible allergic triggers, nasal eosinophilia, and serum immunoglobulin E (IgE) concentration help confirm or exclude this diagnosis. In children, intranasal foreign bodies should be searched for if the nasal discharge is atypical in terms of persistence, blood staining, or malodor.[1]

The features of the illness caused by different viruses overlap widely, making clinical differentiation unreliable. Laboratory confirmation of the specific viral cause is of little value to clinical practice with the exception of influenza. Several laboratory methods are available for identification of viruses. Isolation by cell culture is too slow to be clinically relevant. Rapid antigen tests are available for some organisms, for example, influenza virus. In comparison with cell culture, influenza antigen detection in respiratory specimens by immunofluorescent staining has a sensitivity of 70% to 100% and specificity of 80% to 100%. PCR assays are more sensitive than culture, but their laboratory requirements limit clinical applicability.[24] Near patient tests, which produce results within 30 minutes, have highly variable sensitivities and negative predictive values.[25]

Treatment and Prevention

The common cold in children usually resolves quickly, and no specific therapy is indicated in the majority of cases. Although the common cold is a relatively mild and self-limiting illness, it is enormously expensive in terms of lost productivity and money spent on various treatments, the majority of which have minimal or no efficacy.

In infants, nasal obstruction may be relieved by isotonic saline nosedrops, which can moisten irritated nasal mucosa, loosen nasal secretions, and induce sneezing. Gentle aspira-

tion of the nasal secretion using a blunt syringe or suction can provide temporary relief for an infant. Use of concentrated capsules of eucalyptus for inhalation to clear the nose is contraindicated in young children; these can be highly dangerous if applied incorrectly to the face.[26]

Frequent intake of fluid helps relieve the irritated throat. Environmental tobacco smoke aggravates all the symptoms and should be avoided.

The published literature on modalities used for symptomatic relief of cold symptoms has been summarized using systematic reviews as follows:

Antibiotics: In a meta-analysis of six trials that included 1147 patients (children and adults), people receiving antibiotics did no better than did those receiving placebo in terms of cure or persistence of symptoms.[27]

Vitamin C: In studies of adults, beneficial effects of vitamin C have been shown when it is used prophylactically for 2 to 3 months but not when started at the onset of symptoms. However, fewer trials have examined this later use.

In studies of adults, 200 mg or more per day of vitamin C does not reduce the incidence of colds, except in those exposed to brief periods of extreme physical exercise and/or cold environments.[28]

Vitamin C given prophylactically results in a small but significant reduction in the duration and severity of cold symptoms. In studies of children, there is an approximately 14% reduction in duration of symptoms. The severity of symptoms, as measured by "days confined to home" or "days off work or school," is significantly reduced in studies that include both children and adults.[28]

Zinc lozenges: There are no studies specifically of children, although some older children have been included in predominantly adult studies. There is no evidence that zinc lozenges are effective.

Echinacea: Most studies have examined the use of echinacea for treating rather than preventing colds. The results of placebo-controlled trials have been inconsistent, with some showing effect and others not. This variability is likely to be due at least in part to the large variability in composition of products that are sold as "Echinacea."[29]

Nasal decongestants (either oral or intranasal): The efficacy of these in children remains unproved.[5] In adults, a single dose of a nasal decongestant is moderately effective for the short-term relief of congestion.[5] The potential side effects are a concern, especially in young children. In children, they have a measurable sedating effect.[30] Excessive use of sprays and drops with vasoconstrictive medications can lead to rebound obstruction, which prolongs the illness symptoms.

Over-the-counter medicines for acute cough[31]: There is no good evidence that over-the-counter medicines provide any benefit greater than that seen with a placebo. These medications confer no protection against the development of otitis media.[32]

Antitussives: Neither dextromethorphan nor codeine is better than a placebo at reducing cough during the day or night.[33]

Expectorants (Guaifenesin): This has not been adequately studied in children.

Mucolytics (letosteine): One study involving 40 children showed a statistically but not clinically significant difference in symptom score in comparison with placebo (a difference of 0.2 point on a 4-point scale).[34]

Antihistamines as monotherapy: In children and adults, antihistamines do not significantly reduce cold symptoms (nasal congestion, rhinorrhea, sneezing) or alter subjective improvement.[35,36] First-generation antihistamines cause more sedation than does placebo.[35]

Antihistamine decongestant combinations: These are not effective in small children.[35] In older children and adults, a small amount of improvement in general and in nasal symptoms specifically may occur.[30,35,37]

Of the numerous etiologic agents that can cause colds, only for influenza virus is there commercially available antiviral therapy. The newer class of antiviral drugs, the neuraminidase inhibitors (zanamivir and oseltamivir), are effective against both influenza A and B viruses.[38,39] Oral oseltamivir, 2 mg/kg/dose, given twice daily, to children 1 to 12 years old shortens illness duration by 26% and reduces cough, coryza, duration of fever, and new diagnoses of otitis media.[39] In children 5 to 12 years of age, the nasally administered zanamivir has also been shown to decrease symptom duration and severity.[40]

Prevention by immunization is currently possible only for influenza. In addition to the present inactivated vaccine that is given intramuscularly, a live attenuated cold adapted intranasal vaccine has been shown to be efficacious in children.[41-43]

Clinical Course and Prognosis

The uncomplicated common cold has a uniformly excellent outcome with complete recovery. However, complications are common and include acute otitis media, otitis media with effusion, tonsillitis, sinusitis, lower respiratory tract infections, and acute exacerbations of asthma[44] (Box 32-2).

PHARYNGITIS AND TONSILLITIS

Pharyngitis is an inflammatory illness of the mucous membranes and underlying structures of the throat; it is invariably associated with the symptom of sore throat. Most cases of pharyngitis in children are caused by viruses and are benign

BOX 32-2 Common Cold Teaching Points

- Children have more colds than do adults. They have approximately six colds per year from age 2 to 6 years.
- Children are very effective spreaders of colds, having a greater concentration of virus in their secretions and longer duration of viral shedding than do adults.
- In infants, colds are more likely to cause fever, and at initial presentation, the colds may be clinically indistinguishable from serious bacterial infections.
- Vast amounts of money are wasted on over-the-counter products for colds. Meta-analyses of clinical trials have confirmed their lack of efficacy.

self-limiting illnesses. Group A β-hemolytic streptococcus (*S. pyogenes*) is the most important etiologic agent because of its potential to cause rheumatic fever. The prevention of rheumatic fever defines the management of pharyngitis.

Epidemiology, Risk Factors, and Pathogenesis

Pharyngitis includes tonsillitis, tonsillopharyngitis, and nasopharyngitis. The inflammation frequently also involves the nasopharynx, uvula, and soft palate. Pharyngitis with nasal symptoms (sometimes called *nasopharyngitis*) is usually caused by a virus, whereas pharyngitis without nasal symptoms can be caused by a wide variety of infectious agents.

When an infectious agent is inoculated onto the pharyngeal or tonsillar tissue, localized inflammation occurs. This may occur de novo or as a complication of the common cold, when the etiologic agent is more likely to be viral. A list of etiologic agents is presented in Boxes 32-3 and 32-4. *S. pyogenes* causes 15% to 30% of acute pharyngitis in children.[45]

Pharyngitis occurs more frequently during the colder months of the year. In temperate climates, pharyngitis due to *S. pyogenes* infection usually occurs in the winter and early spring.[45] Pharyngitis due to *S. pyogenes* is primarily a disease of children 5 to 15 years old. Group C streptococci are a common cause of pharyngitis in college students.[46] Group C streptococci are also described as the etiologic organism in epidemic pharyngitis spread by contaminated food.[47,48]

The inflammation causes erythema of the pharynx, the tonsils, or both structures. Exudate typically occurs with only some organisms, including adenovirus, herpes simplex virus, β-hemolytic streptococci, *Corynebacterium diphtheriae*, *Arcanobacterium haemolyticum*, Epstein-Barr virus, and *Candida* species. Ulceration is usually seen only with herpes simplex virus and enterovirus.

The pharyngeal involvement may be overshadowed by other symptoms, such as cough and coryza, when, for example, the infecting organism is the parainfluenza virus, and fever, exanthem, and meningitis when the infecting organism is an enterovirus.

The tonsillopharyngeal involvement with marked exudate caused by Epstein-Barr virus looks similar to that caused by *S. pyogenes*. It appears that bacterial adhesion is the cause of the exudate that occurs with this Epstein-Barr virus infection.[49]

Primary and recurrent herpes simplex virus infection occasionally has associated pharyngitis.[50] In almost all instances, there are herpes lesions in the anterior mouth, externally around the mouth, and at the mucocutaneous border.

Clinical Features

Children of any age can develop pharyngitis and tonsillitis. The onset is usually sudden with fever, sore throat, and anorexia. There may be headache, nausea, vomiting, lassitude, and sometimes abdominal pain. With viral infection, there are often other signs of respiratory tract infection, with more or less systemic involvement. The cervical lymph nodes are enlarged and tender. There is moderate to severe pharyn-

BOX 32-3 Viral Agents in Pharyngitis and Tonsillitis

Common Viral Causes

Adenovirus types 1 to 7, 7a, 9, 14 to 16
Coronavirus
Enteroviruses: coxsackievirus types A and B, echovirus type A
Epstein-Barr virus
Influenza virus types A and B
Parainfluenza virus types 1 to 4
Respiratory syncytial virus

Less Common Viral Causes

Cytomegalovirus
Herpes simplex virus
Measles virus
Poliovirus
Reovirus
Rhinoviruses
Rotaviruses
Rubella virus

BOX 32-4 Other Agents in Pharyngitis and Tonsillitis

Common Bacterial Causes

Streptococcus pyogenes

Less Common Bacterial Causes

Actinomyces spp.
Bacteroides melaninogenicus
Bacteroides spp.
Borrelia spp.
Corynebacterium diphtheriae
Corynebacterium pyogenes
Corynebacterium ulcerans
Francisella tularensis
Fusobacterium spp.
Haemophilus influenzae
β-Hemolytic streptococci B, C, and G
Legionella pneumophila
Leptospira spp.
Neisseria gonorrhoeae
Neisseria meningitidis
Peptostreptococcus spp.
Salmonella typhi
Streptobacillus moniliformis
Streptococcus pneumoniae
Treponema pallidum
Yersinia enterocolitica

Other Organisms

Candida spp.
Chlamydia pneumoniae strain TWAR
Coxiella burnetii
Mycoplasma hominis
Mycoplasma pneumoniae
Toxoplasma gondii

geal erythema, and there may be follicles, ulcers, petechiae, and generalized exudate. Petechial lesions on the soft palate may occur with pharyngitis due to *S. pyogenes*, Epstein-Barr virus, measles virus, and rubella virus.

In all cases of acute pharyngitis, streptococcal disease must be considered. Various clinical factors (exposure, season, incubation period, age of patient, and associated clinical findings) may distinguish among causative organisms in large epidemiologic studies, but in the individual child, the clinical distinction of streptococcal pharyngitis from viral pharyngitis is unreliable. If there is an obvious nasal infection, ulceration, or conjunctivitis, the etiology is most likely viral. In a child under the age of 4 years, pharyngitis with no exudate is almost always viral. In a child older than 4 years of age, pharyngitis with exudate or fever is most likely caused by *S. pyogenes*, but other bacteria may mimic this condition.[11,12] The clinical features of pharyngitis due to group A, C, and G β-hemolytic streptococci are similar.[45] The clinical and epidemiologic features that differ in pharyngitis due to *S. pyogenes* versus a viral cause are shown in Boxes 32-5 and 32-6 (see also Fig. 32-1).

Diagnosis

A throat swab is necessary to determine the presence of *S. pyogenes*. Identification can be with either culture or a rapid antigen detection test. For both, an adequate swab of the inflamed tonsillar area is required and the manner in which the swab is obtained is the main determinant of diagnostic accuracy.[51] The surfaces of both tonsils and the pharyngeal wall should be swabbed. Other areas of the mouth and pharynx should not be swabbed. If collected in this manner, a single swab has a sensitivity of 90% to 95% for the detection of *S. pyogenes* in the pharynx.[45,52]

BOX 32-5 Clinical and Epidemiologic Features Suggesting *Streptococcus pyogenes* Pharyngitis

Sudden onset
Sore throat
Fever
Scarlet fever rash
Headache
Nausea, vomiting, and abdominal pain
Inflammation of pharynx and tonsils and uvula
Patchy discrete exudates
Palatal petechiae
Excoriated nares (especially in infants)
Tender, enlarged anterior cervical nodes
Patient age 5 to 15 years
Presentation in winter or early spring
History of exposure

Modified from Gerber MA: Diagnosis and treatment of pharyngitis in children. Pediatr Clin North Am 52:729-747, 2005; and Bisno AL, Gerber MA, Gwaltney JM, et al: Practice guidelines for the diagnosis and management of group A streptococcal pharyngitis. Clin Infect Dis 35:113-125, 2002.

BOX 32-6 Clinical and Epidemiologic Features Suggesting Viral Pharyngitis

Conjunctivitis
Coryza
Cough
Hoarseness
Anterior stomatitis
Discrete oral ulcers
Diarrhea
Characteristic exanthems

Modified from Gerber MA: Diagnosis and treatment of pharyngitis in children. Pediatr Clin North Am 52:729-747, 2005; and Bisno AL, Gerber MA, Gwaltney JM, et al: Practice guidelines for the diagnosis and management of group A streptococcal pharyngitis. Clin Infect Dis 35:113-125, 2002.

The throat swab should be incubated for 18 to 24 hours on a sheep blood agar plate. Agar plates that are negative at 24 hours should be reexamined at 48 hours.[45]

Rapid antigen detection tests have been developed because of this 24- to 48-hour delay before a throat swab can inform clinical management. The results may be obtained in about 10 minutes. Most available rapid antigen detection tests have specificities of 95% or greater, and thus a positive result is a very good indicator of the need to treat.[53] Sensitivities range from 80% to 90%, so a negative antigen test does not exclude *S. pyogenes* infection.[53] When *S. pyogenes* pharyngitis is suspected clinically but the rapid diagnostic test is negative, a throat swab for culture should be obtained.[24] A large proportion of false-negative rapid antigen tests are true infections rather than *S. pyogenes* carriage.[54] Because of the limited number of direct test-to-test comparisons that have been performed, the relative sensitivities of different rapid antigen test have not been established.[45]

A positive culture or rapid antigen test for *S pyogenes* cannot differentiate a child with a true infection from another with a symptomatic viral pharyngitis who is a *S. pyogenes* carrier.

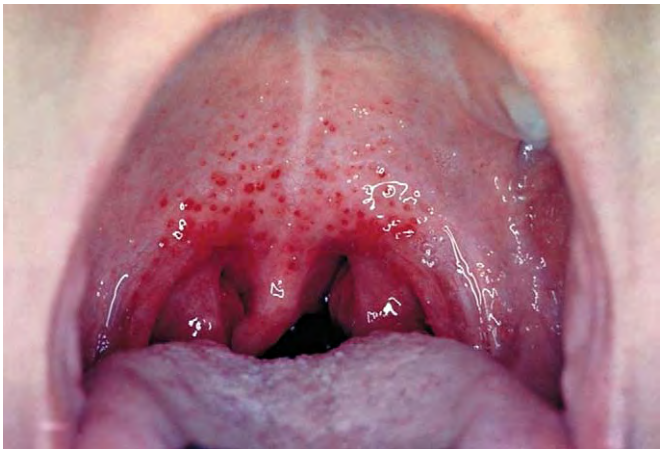

Figure 32-1 Palatal petechiae in a child with *Streptococcus pyogenes* pharyngitis.

Treatment

Symptomatic relief may be obtained from drinking warm fluids or, in the older child, saltwater gargles. An analgesic such as acetaminophen is appropriate. Simple lemon-based throat lozenges may be soothing, but ones that contain potentially toxic substances should be avoided. Decongestants and antihistamines have no place in the treatment of pharyngitis and tonsillitis.

Antibiotics are used to treat symptomatic pharyngitis caused by infection with *S. pyogenes*. The aim is to prevent the development of rheumatic fever. If the rapid antigen test and culture are both negative, then antibiotics should be withheld or, if already started, discontinued.

In addition to preventing rheumatic fever, treatment of *S. pyogenes* pharyngitis reduces the duration of symptoms and the risk of spread and enables quicker return to school and work.[55]

Several different antibiotics are effective, including penicillin, ampicillin and amoxicillin, many cephalosporins, macrolides, and clindamycin. Antimicrobial therapy options for *S. pyogenes* pharyngitis are summarized in Table 32-1. Penicillin remains the recommended treatment because of its proved efficacy, narrow antimicrobial spectrum, low cost, and excellent safety profile.[56] *S. pyogenes* has never developed resistance to penicillins or cephalosporins. The minimum inhibitory concentration of penicillin has not increased over the past 50 years.[45,57]

Penicillin can be effective in preventing rheumatic fever even when therapy is started up to 9 days after the onset of the acute illness. Although the conventional oral dosage regimen is penicillin V, 250 mg 3 to 4 times a day,[24] a twice-daily dose of 250 mg, if reliably given, is as effective.[58] In children over 12 years of age, a higher dose of 500 mg twice a day is recommended.[58] Intramuscular benzathine penicillin is very effective and should be considered for children who are particularly unlikely to complete a course of oral treatment.

Although the efficacy of penicillin in eliminating *S. pyogenes* from the tonsils and pharynx has not diminished after 40 years of use,[59] the failure rate in practice may be at least as high as 18% in certain communities. Ampicillin and amoxicillin are associated with a 95% risk of skin rash in infectious mononucleosis[24]; therefore, they are not recommended in the treatment of pharyngitis.

The course of oral antibiotic must be 10 days; courses of shorter duration are associated with lack of effective treatment. A child must complete a full 24 hours of therapy before returning to school or day care; otherwise, he or she remains infectious to other children.[60]

Both suppurative and nonsuppurative (acute rheumatic fever, acute post streptococcal glomerulonephritis, and post streptococcal reactive arthritis) complications can develop from pharyngitis.

Scarlet fever is a streptococcal pharyngitis with a characteristic rash. The rash occurs if the *S. pyogenes* causing the infection produces a pyrogenic (erythrogenic) toxin and infects an individual who does not have antitoxin antibodies. The rash is either the first sign of the illness or occurs within 24 to 48 hours of illness onset. It begins around the neck and chest, spreads downward and is often more intense in the skin creases of the neck, axillae, elbows, groins, and knees (Pastia's lines). The palms and soles are spared as is the face, where there is characteristic circumoral pallor and flushed cheeks. The rash is diffuse, bright red, papular, and rough to the touch. The sandpaper texture is caused by occlusion of sweat glands. The rash fades over a week and is followed by desquamation for several weeks. In addition to palatal petechiae, the tongue has a white strawberry (yellowish white coating through which the red papillae are seen) and then, when the coating disappears, a red strawberry appearance (red swollen papillae).[45,61]

Clinical Course and Prognosis

Pharyngitis is self-limited, lasting 4 to 10 days, and it has an excellent prognosis. However, in 0.3% to 3.0% of untreated *S. pyogenes* throat infections, the serious complication of rheumatic fever results. Suppurative involvement of both adjacent and more distant tissue is a well-recognized complication of *S. pyogenes* pharyngitis.[62]

Table 32-1
Antimicrobial Therapy for *Streptococcus pyogenes* Pharyngitis

Route of Administration, Antimicrobial Agent	Dosage	Duration
Oral		
Penicillin*	Children: 250 mg bid or tid	10 days
	Adolescents and adults: 250 mg tid or qid	10 days
	Adolescents and adults: 500 mg bid	10 days
Intramuscular		
Benzathine penicillin G	1.2×10^6 U (for patients ≥27 kg)	1 dose
	6.0×10^5 U (for patients <27 kg)	1 dose
Mixtures of benzathine and procaine penicillin G	Varies with formulation†	1 dose
Oral, for Patients Allergic to Penicillin		
Erythromycin	Varies with formulation	10 days
First-generation cephalosporin‡	Varies with agent	10 days

*Amoxicillin is often used in place of oral penicillin V in young children because of the acceptance of the taste of the suspension, not because of any microbiologic advantage.
†Dose should be determined on basis of benzathine component.
‡These agents should not be used to treat patients with immediate-type hypersensitivity to β-lactam antibiotics.
Modified from Gerber MA: Diagnosis and treatment of pharyngitis in children. Pediatr Clin North Am 52:729-747, 2005; and Bisno AL, Gerber MA, Gwaltney JM, et al: Practice guidelines for the diagnosis and management of group A streptococcal pharyngitis. Clin Infect Dis 35:113-125, 2002.

Follow-up cultures should be performed in children who have had rheumatic fever.[45] Such testing should also be considered in patients living in communities where there are outbreaks of *S. pyogenes* infections, post streptococcal glomerulonephritis, or rheumatic fever.[63] Follow-up throat cultures are not indicated in patients who have completed an appropriate antibiotic course and are asymptomatic. If tested, most of such children in whom *S. pyogenes* is identified are carriers.[63]

Tonsillectomy is sometimes considered in the child with recurrent pharyngitis. The frequency of symptomatic episodes diminishes with time whether or not tonsillectomy is performed. Tonsillectomy results in a small additional reduction in number of symptomatic episodes, days of symptoms, and days of school missed[64] (Box 32-7).

RETROPHARYNGEAL, PARAPHARYNGEAL, AND PERITONSILLAR ABSCESSES

Deep abscesses in the neck may cause serious problems because of local pressure, local destruction, or airway obstruction. They are classified by location into peritonsillar abscess (also known as *quinsy*), retropharyngeal abscess, and parapharyngeal abscess. Multiple abscess types can coexist. They have become sufficiently uncommon that they can be overlooked in the differential diagnosis when a young child presents with nonspecific symptoms of sepsis or of an acute pharyngeal infection. They have the potential to be catastrophically fatal or to result in significant morbidity if not detected early.[65]

BOX 32-7 Pharyngitis and Tonsillitis Teaching Points

- Most cases of pharyngitis in children are caused by viruses and are benign self-limiting illnesses.
- The prevention of rheumatic fever defines the management of pharyngitis.
- In the individual child, the clinical distinction of streptococcal pharyngitis from viral pharyngitis is unreliable.
- The manner in which the throat swab is obtained is the main determinant of diagnostic accuracy.
- Penicillin remains the recommended treatment because of its proved efficacy, narrow antimicrobial spectrum, low cost, and excellent safety profile.
- Tonsillectomy results in a further small reduction in number of symptomatic episodes of tonsillitis, in addition to the decrease in frequency that occurs with time without tonsillectomy.

Epidemiology, Risk Factors, and Pathogenesis

Key features and differences between these abscess types are summarized in Table 32-2.

RETROPHARYNGEAL ABSCESS

An abscess can form in the retropharyngeal space, which is a potential space immediately anterior to the pre-

Table 32-2
Clinical Features of Retropharyngeal, Parapharyngeal, and Peritonsillar Abscesses

	Usual Age	Sites of Origin	Location	Clinical Findings	Complications/Extension Site	Management
Retropharyngeal abscess	<4 yr	Pharyngitis, dental infection, trauma	Between posterior pharynx and prevertebral fascia	Unilateral posterior pharyngeal bulging; neck hyperextension, drooling, respiratory distress	Spontaneous rupture and aspiration; contiguous spread to posterior mediastinum, parapharyngeal space	Antibiotics, drainage; artificial airway
Parapharyngeal abscess	>8 yr, adolescents, adults	Tonsillitis, otitis media, mastoiditis, parotitis, dental manipulation	Anterior and posterior pharyngomaxillary space	Anterior compartment: swelling of the parotid area; trismus; tonsillar prolapse. Posterior compartment: septicemia; minimal pain or trismus	Carotid erosion; airway obstruction; intracranial, lung, contiguous spread to mediastinum; septicemia	Antibiotics, drainage; artificial airway
Peritonsillar abscess	Adolescents, adults	Tonsillitis	Tonsillar capsule, and space below superior constrictor muscle	Swelling of 1 tonsil, uvular displacement; trismus, muffled voice	Spontaneous rupture and aspiration; contiguous spread to parapharyngeal space	Antibiotics, drainage

From Brook I: Microbiology and management of peritonsillar, retropharyngeal, and parapharyngeal abscesses. J Oral Maxillofac Surg 62:1545-1550, 2004.

vertebral fascia. It extends inferiorly from the skull base for the length of the pharynx.[66] This space receives lymphatic drainage from many surrounding structures, including the middle ear, pharynx, nasopharynx, nose, and paranasal sinuses.[67]

The retropharyngeal space is continuous laterally with another potential space, the parapharyngeal space. The fascia that separates these two spaces is an ineffectual barrier to the spread of infection.[65] Infection may result from suppurative adenitis of the lymph nodes in the retropharyngeal space, or penetrating trauma, or foreign body aspiration.[68-70]

PARAPHARYNGEAL ABSCESS

The parapharyngeal space (or lateral pharyngeal or pharyngomaxillary space) is in the upper neck above the hyoid bone. It is an inverted cone-shaped potential space that extends from the hyoid bone to the base of the skull. Medially, it is bound by the pretracheal fascia, and laterally, by the pterygoid muscles and mandible.[71] Anteriorly, it is bound by the submandibular space, and posteriorly, by the retropharyngeal space.[72] The clinical manifestations of a parapharyngeal abscess are determined by the structures involved around the abscess cavity. An abscess in the posterior component of the space may result in medial displacement of the lateral pharyngeal wall. Extension can result in serious local nerve and life-threatening vascular complications (the internal carotid artery, internal jugular vein, cranial nerves IX, X, XI, and XII, and the sympathetic chain pass posteriorly through the parapharyngeal space).[73] An anterior compartment abscess can cause trismus from irritation of the internal pterygoid muscle. The source of the abscess is often unclear, but it seems likely to result from extension of infection from nearby tissues.

PERITONSILLAR ABSCESS

The peritonsillar space is limited medially by the fibrous wall of the tonsil capsule and laterally by the superior constrictor muscle.[74] Pus may be found in a single pocket or in several pockets. The majority occur following tonsillitis, presumably from local extension of the infection through the tonsillar capsule.[75] The three types of abscess have similar microbiology. The microbiology reflects the flora of the oropharynx and nasopharynx. Most are polymicrobial infections with an average number of five isolates.[71] Anaerobic bacteria can be isolated from most abscesses if appropriate culture techniques are used.[71] The predominant anaerobic organisms are *Prevotella*, *Porphyromonas*, *Fusobacterium*, and *Peptostreptococcus* spp.[71] Retropharyngeal abscesses in young children are more likely to have pathogenic aerobic isolates, most frequently, *S. pyogenes*, *Staphylococcus aureus*, and *Haemophilus* species.[71,76]

Retropharyngeal Abscess

CLINICAL FEATURES

The clinical presentation of a retropharyngeal abscess can be very nonspecific, particularly in younger children. Torticollis is a key clinical sign, particularly in combination with fever and dysphagia.[65,67,77] Other clinical manifestations include drooling, airway stridor, dyspnea, tachypnea, stiff neck, and ipsilateral cervical adenopathy. There is sometimes midline or unilateral swelling of the posterior pharynx. Presenting symptoms and signs in infants include neck swelling, fever, dysphagia, and stridor.[65]

DIAGNOSIS

An acute inflammatory response will be demonstrable with measurement of, for example, the peripheral white blood cell count and C-reactive protein, but radiologic investigation is necessary to confirm the diagnosis.[65]

A lateral neck radiograph can yield diagnostic information. To prevent the false appearance of a retropharyngeal mass when none exists, it is important that the neck be in true lateral orientation and in extension and the image be obtained on full inspiration.[78] The lateral neck radiograph may show an increase in the thickness of the soft tissue space anterior to the cervical spine (>7 mm at the level of the second and >14 mm at the sixth cervical vertebra)* with narrowing of the oropharyngeal aiway[65,79] (Fig. 32-2). Other radiographic signs include straightening of the cervical vertebra, reversal of the normal lordotic curve of the cervical spine, and presence of air in the soft tissues.[80] A negative ultrasound examination cannot exclude a retropharyngeal abscess.[65] A computed tomography (CT) scan is the preferred investigation for distinguishing deep neck abscesses from cellulitis of the neck and for defining any extension into adjacent areas.[67] However, even with a CT scan, it is not always possible to differentiate cellulitis from abscess[78,81,82] (Fig. 32-3).

Magnetic resonance imaging (MRI) has the potential to provide better definition of any complications such as venous thrombosis and impending carotid artery erosion or rupture.[65,72]

TREATMENT

Intravenous antibiotics and incision and drainage are the necessary treatments. Intubation and, rarely in severe cases, tracheostomy may be necessary to secure the airway.[65,72,75,84]

Antibiotic choice needs to acknowledge the polymicrobial nature of the infection and the frequent presence of one or more anaerobes. Appropriate first-line choices include amoxicillin–clavulanic acid, clindamycin + cefuroxime, ceftriaxone plus metronidazole, gentamicin, and ampicillin plus sulbactam.[65,75,84]

The decision to operate should be based on the clinical course, including response to antimicrobial therapy, rather than just on the CT scan findings.[65] Antimicrobial therapy alone may be sufficient in children without severe systemic toxicity, who have no respiratory difficulties, who are able to swallow their secretions adequately, and in whom airway examination by indirect mirror or direct flexible endoscopy confirms a lack of airway compromise.[73,82]

*In adults these measurements are greater than 7 mm at the level of the second and greater than 22 mm at the sixth cervical vertebra.[79]

If the abscess is medial to the great vessels and confined to the retropharyngeal space, the abscess can be drained intraorally.[72,85,86] Large abscesses, particularly those that extend laterally or that involve other spaces in the neck, may need external drainage.[75] External drainage in children has the potential to damage important structures such as the great vessels and cranial nerves VII, IX, X, XI, and XII.[65] Successful drainage of uniloculated abscesses using ultrasound and CT to guide either needle aspiration or catheter insertion has been reported.[87,88]

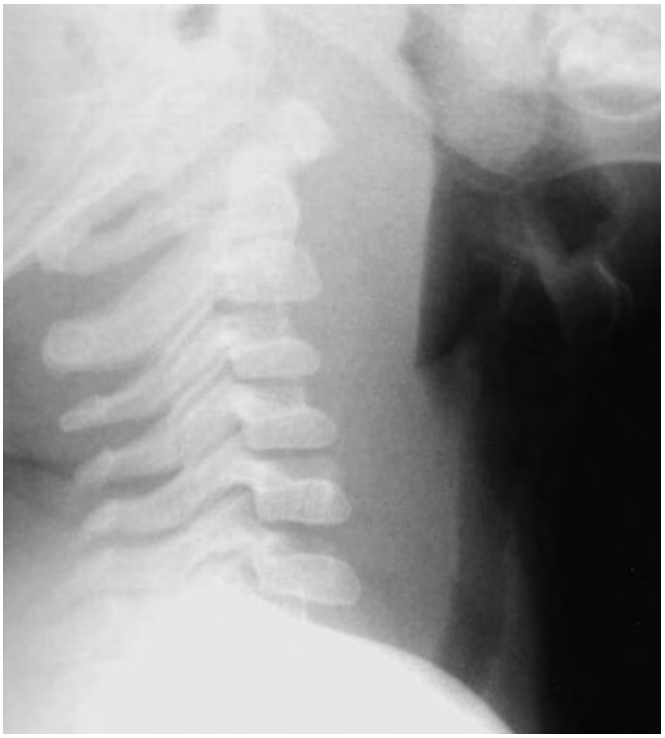

Figure 32-2 Lateral neck radiograph showing increased thickness of the retropharyngeal space.

Abscesses can extend laterally, posteriorly into the posterior mediastinum, and cranially, causing a cerebral abscess or meningitis.[71] Abscesses left untreated can rupture into the pharynx, leading to aspiration. Direct pressure, sudden rupture, or hemorrhage can all result in asphyxia. Death can occur from aspiration, airway obstruction, erosion of a major vessel, extension into the posterior mediastinum, or from dissemination and sepsis.[71]

Other complications include abscess recurrence (1% to 5%), epiglottitis, empyema, pyopneumothorax, pneumomediastinum, and purulent pericarditis.[65,83]

Peritonsillar Abscess

CLINICAL FEATURES

Clinical features include sore throat (occasionally with unilateral pain), malaise, low-grade fever, chills, dysphagia, and reduced oral intake. Trismus can result from irritation and reflex spasm of the internal pterygoid muscle. A muffled voice can result from edema, impairing movement of the palate. There may be signs of toxicity, drooling, and sometimes dehydration. The soft palate and uvula are displaced away from the affected side by swelling. The tonsil is displaced medially, and there is ipsilateral tender cervical adenopathy. Untreated peritonsillar abscess may spontaneously rupture into the mouth or extend into the parapharyngeal space with potentially fatal complications.

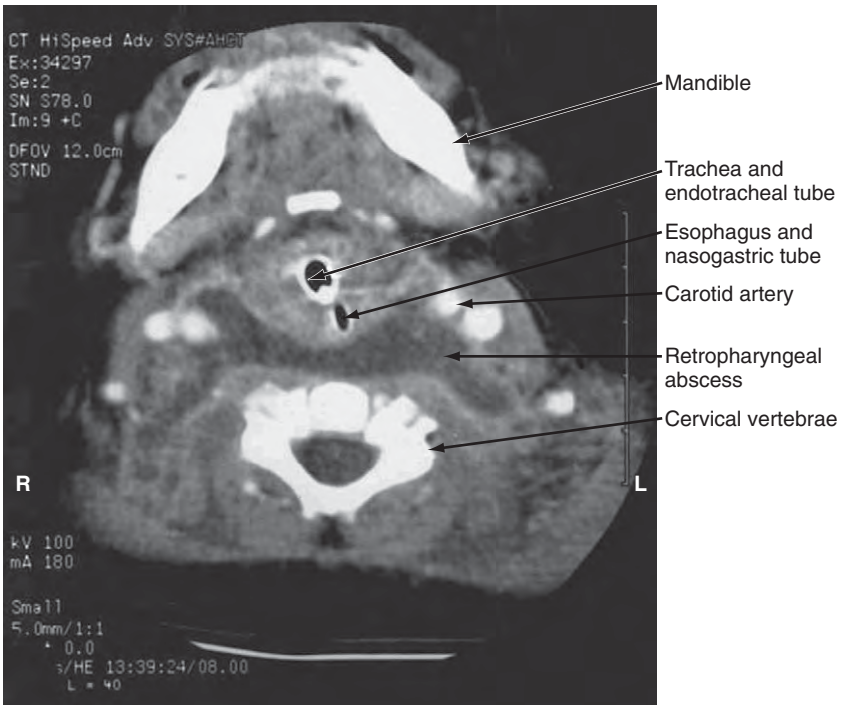

Figure 32-3 Computed tomography scan of a 6-month-old child at the level of mandible demonstrating a retropharyngeal abscess. (From Cheema B, Grant CC, Mahadevan M, Beca J: An infant with a persistent empyema. Acta Paediatr 88:1168-1171, 1999.)

DIAGNOSIS

Identification of the organisms from aspirated pus is highly desirable. The peripheral white blood cell count is elevated, with a predominance of neutrophils.

TREATMENT

A combination of broad-spectrum parenteral antibiotic therapy that is active against anaerobes and drainage of the abscess is required.[75] Needle aspiration is also effective definitive therapy.[75,89] Tonsillectomy can be performed either during the same procedure or after an interval. It is indicated in those presenting with a peritonsillar abscess who have a history of recurrent tonsillitis, who have recurrent peritonsillar abscess, or who have tonsillar hypertrophy causing airway obstruction.[75]

Parapharyngeal Abscess

CLINICAL FEATURES

Clinical features include tender cervical swelling, induration and erythema of the side of the neck, sore throat, dysphagia, trismus, hoarseness, malaise, chills, and fever, which may be low grade. In addition to evidence of toxicity, there may be respiratory distress, medial displacement of the lateral pharyngeal wall and inferior tonsil pole, and drooling. Sometimes the presentation is of a high cervical mass palpable in the neck that progresses to fluctuance. Other signs arise if there is further extension or complications. Initially, a parapharyngeal abscess may be difficult to differentiate from a peritonsillar abscess, but the child with the latter is usually less toxic and has obvious palatal fluctuance.

DIAGNOSIS

The peripheral white blood cell count is elevated, with a predominance of neutrophils. Radiographs may be helpful. A submental vertex skull radiograph typically shows pharyngeal fullness on the side of the abscess. An anteroposterior view of the upper airway shows ipsilateral edema and obliteration of the pyriform sinus. As with retropharyngeal abscesses, a CT scan is able to localize the inflammatory process to the parapharyngeal space but cannot always differentiate an abscess from cellulitis.[82,90]

TREATMENT

The definitive treatment is incision and drainage and intravenous antibiotic therapy. In patients with larger abscesses or an unstable airway, emergency drainage with postoperative airway management, including intubation for several days, is indicated.[90] In the stable child, drainage can be deferred for 24 to 48 hours to determine whether intravenous antibiotics alone are sufficient to treat the infection.[90] Children with abscesses that are limited to this space and who demonstrate clinical improvement with intravenous antibiotics can be managed without drainage.[73] If drainage is required, this can be intraoral rather than external in most, unless the abscess is lateral to the great vessels or involves multiple spaces.[91]

Parapharyngeal abscesses can cause life-threatening complications, including internal carotid artery pseudoaneurysm or rupture, internal jugular vein thrombophlebitis, mediastinitis, and dysfunction of cranial nerves IX to XII (Box 32-8).[90,92-94]

BOX 32-8 Retropharyngeal, Parapharyngeal, and Peritonsillar Abscesses Teaching Points

- Deep neck abscesses are potentially fatal infections that cause significant morbidity.
- Multiple abscess types can coexist.
- The deep neck potential spaces are in close proximity to vital structures, including the airway, carotid arteries, and many cranial nerves.
- Retropharyngeal abscesses are more common in the preschool-age group, and parapharyngeal and peritonsillar abscesses are more common in older children and adolescents.
- The three types of abscess have similar microbiology; most are polymicrobial infections.
- The clinical presentation of a retropharyngeal abscess can be very nonspecific, particularly in younger children. Torticollis is a key clinical sign, particularly in combination with fever and dysphagia. A lateral neck radiograph can be diagnostic, but care needs to be taken to perform it correctly. Even with a CT scan, it can be difficult to differentiate an abscess from cellulitis.
- A peritonsillar abscess usually presents with a sore throat, with systemic signs of infection. Trismus and a muffled voice can be present. The soft palate and tonsil are usually displaced by the abscess.
- A parapharyngeal abscess presents with dysphagia, trismus, and hoarseness and tender cervical swelling, which is indurated. It can sometimes be difficult to differentiate clinically from a peritonsillar abscess. A CT scan is required to define the extent of the abscess and the potential for complications.
- All abscess types require intravenous antibiotics. Anaerobic cover must be provided.
- Drainage is frequently required. The decision to drain and timing of surgical drainage are determined by the clinical course.

OTITIS MEDIA

Otitis media is a very common condition in childhood. There are three categories of otitis media: *acute otitis media*, *otitis media with effusion* (secretory otitis media), and *chronic suppurative otitis media*. The widespread use of antibiotics for acute otitis media in the developed world has drastically reduced the previously fairly common suppurative complications of otitis media, but otitis media with effusion has become more common.

Epidemiology, Risk Factors, and Pathogenesis

A higher rate of acute otitis media and chronic suppurative otitis media is found in children in developing countries[95] and in indigenous populations in developing countries, including

New Zealand Maori,[96] Australian Aborigines, Alaskan Inuit, and North American Indians.

Acute otitis media is an acute infection of the middle ear, and most children have at least one episode by the age of 7 years.[97] Acute otitis media is particularly common in the preschool-age child and more common in boys than girls. Exclusive breastfeeding for at least 4 months appears to protect against otitis media in the first 12 months of life.[98] The increased environmental exposure to respiratory tract infections in day care centers increases the risk of acute otitis media.[99] Side-stream smoking increases the risk of otitis media with effusion and recurrent acute otitis media.[100]

Acute otitis media may occur de novo; more commonly, it occurs as a complication of the common cold. It may occur in the context of infection with recognized respiratory viruses such as respiratory syncytial virus, influenza viruses, adenoviruses, parainfluenza viruses, enteroviruses (coxsackievirus, echovirus), rhinoviruses,[101] and even herpes simplex virus type 1 and cytomegalovirus.[102] Viral infection in isolation is a rare cause of otitis media (5%), but up to 20% of cases are combined viral and bacterial infections.[101] The remainder are caused by bacteria alone. Bacterial causes of acute otitis media are listed in Box 32-9.

Two or more organisms are found in about 7% of cases. A different organism may be found in each ear in about 20% of children with bilateral otitis media. In neonates, there may be a higher incidence of *S. aureus* and gram-negative bacilli than in older children.[103]

The organisms isolated from acute otitis media with tympanostomy tubes are different in prevalence from acute otitis media with an intact tympanic membrane, being mainly *Streptococcus pneumoniae*, *S. aureus*, *Haemophilus influenzae*, *Pseudomonas aeruginosa*, *Moraxella catarrhalis*, anaerobes, and fungi.[104-106]

Acute otitis media occurs when viral infection causes respiratory epithelial injury in the nasopharynx, which is colonized with pathogenic bacteria, leading to hyperemia and edema of the eustachian tubes with consequent obstruction. Bacteria may arise in the middle ear by positive or negative forces through the eustachian tube or occasionally through the bloodstream or by direct spread through a damaged tympanic membrane. The inflammation of the tympanic membrane and infected inflammatory exudate in the middle ear are caused primarily by bacteria, polymorphonuclear leukocytes, and edema. The eustachian tubes are believed to play a part in the pathophysiology of this process. The eustachian tubes in a young child are shorter, wider, straighter, and more horizontal and patulous than in the older child, allowing more ready access of organisms to the middle ear.

Otitis media with effusion is the presence of fluid in the middle ear without signs or symptoms of acute ear infection. It can result from prolonged negative pressure in the middle ear after viral infection, and stimulation of inflammatory mediators can promote fluid leakage from the mucous membrane. Persistent middle ear fluid results in decreased mobility of the tympanic membrane and serves as a barrier to sound transmission.[95] Recurrence of bilateral otitis media with effusion after tympanostomy tube placement was more likely in children with a combination of low IgA or IgG2 levels with poor eustachian tube functioning and decreased levels of mannose-binding lectin.[107] However, eustachian tube functioning is not predictive of risk of recurrence of otitis media with effusion.[108] Eustachian opening and closing functions are dynamic and highly variable in ears with otitis media with effusion.[109]

Chronic suppurative otitis media is a stage of ear disease in which there is ongoing chronic infection of the middle ear without an intact tympanic membrane (presence of a perforation or tympanostomy tube).[95] It is one of the most common infectious diseases of childhood and is most common in developing countries, in certain high-risk groups in developed nations, and among children who have had tympanostomy tubes inserted.[95] Risk factors that have been attributed to the high rates of chronic suppurative otitis media are lack of breastfeeding, overcrowding, poor hygiene, poor nutrition, passive smoking, high rates of nasopharyngeal colonization with potentially pathogenic bacteria, and inadequate health care.[95] Bacteria isolated in chronic suppurative otitis media are listed in Box 32-10.

BOX 32-9 Bacterial Causes of Acute Otitis Media and Bacteria Found in Otitis Media With Effusion

Common Causes

50% *Streptococcus pneumoniae* serotypes 1, 3, 4, 6, 7, 9, 14, 15, 18, 19, and 23
25% Nontypable *Haemophilus influenzae* and *H. influenzae* type b
25% *Moraxella catarrhalis*

Rare Causes

Mycoplasma pneumoniae
Chlamydia trachomatis
Chlamydia pneumoniae
Enteric bacteria
Staphylococcus aureus
Staphylococcus epidermidis
Streptococcus pyogenes
Pseudomonas aeruginosa

BOX 32-10 Bacterial Isolates in Chronic Suppurative Otitis Media

Enteric gram-negative bacilli
Mixed aerobic and anaerobic bacteria
Mycobacterium tuberculosis
Pseudomonas aeruginosa
Staphylococcus aureus

Clinical Features

Acute otitis media typically presents with generalized symptoms of malaise, earache, and often fever. An older child

complains of muffled hearing, a sense of fullness, and discomfort of the ear. In a younger child, there are more likely to be systemic signs such as high fever, nausea, vomiting, loss of appetite, malaise, generalized muscle pain, nasal congestion, flushed face, and, occasionally, diarrhea and restlessness. The pain may be severe and accentuated by swallowing, and occasionally there may be throbbing tinnitus. The fever, pain, deafness, and tinnitus may worsen, and there may be tenderness over the mastoids, but there is immediate relief of pain and systemic symptoms if the drum ruptures and the pus drains.

The clinical suspicion of otitis media is confirmed by appropriate otoscopic examination. Typical signs of acute otitis media are retraction, diminished light reflex, and poor mobility of the drum. The light reflex may completely disappear, and the drum becomes opaque. There is injection of vessels around the margin of the tympanic membrane and adjoining external auditory canal skin. The tympanic membrane moves but less freely with insufflation, and such movement is painful. The drum becomes red, and the pars tensa becomes thick and convex and bulges, with loss of landmarks. In young children, there may be swelling of the posterosuperior aspect of the adjacent external auditory canal skin. As the condition progresses, the drum becomes convex, tense, and whitish, and it bulges, with no mobility and hyperemic vessels on the periphery. There may be yellowish necrotic areas. The drum may rupture in the pars tensa, causing a gush of purulent material, blood, or serosanguineous fluid. Drainage usually stops after 1 to 2 days and the perforation becomes dry. The perforation is generally small and does not enlarge, and after the infection subsides, it usually heals completely (Fig. 32-4).

Although viral infection may be associated with otitis media, there is no clinical way of distinguishing between viral and bacterial otitis media. If purulent conjunctivitis is also present, acute otitis media is most likely due to nontypable *H. influenzae,* and these clinical signs in combination should influence antibiotic choice. *M. pneumoniae* is a more likely cause if pneumonia is present.

Otitis media with effusion causes fluctuating hearing loss, which may have an adverse effect on speech, language, and cognitive development, although there seems to be a catch-up to normal by age 7 years. The clinical suspicion is confirmed by persistence of middle ear effusion without signs of inflammation. Cases may occur with infection, tubal obstruction, allergic or immunologic disorders, enlarged adenoids, or, rarely, nasopharyngeal tumors.

In chronic suppurative otitis media, the cardinal feature is chronic otorrhea, which is often smelly. Hearing loss occurs in 96% and is more severe than in otitis media with effusion.[95]

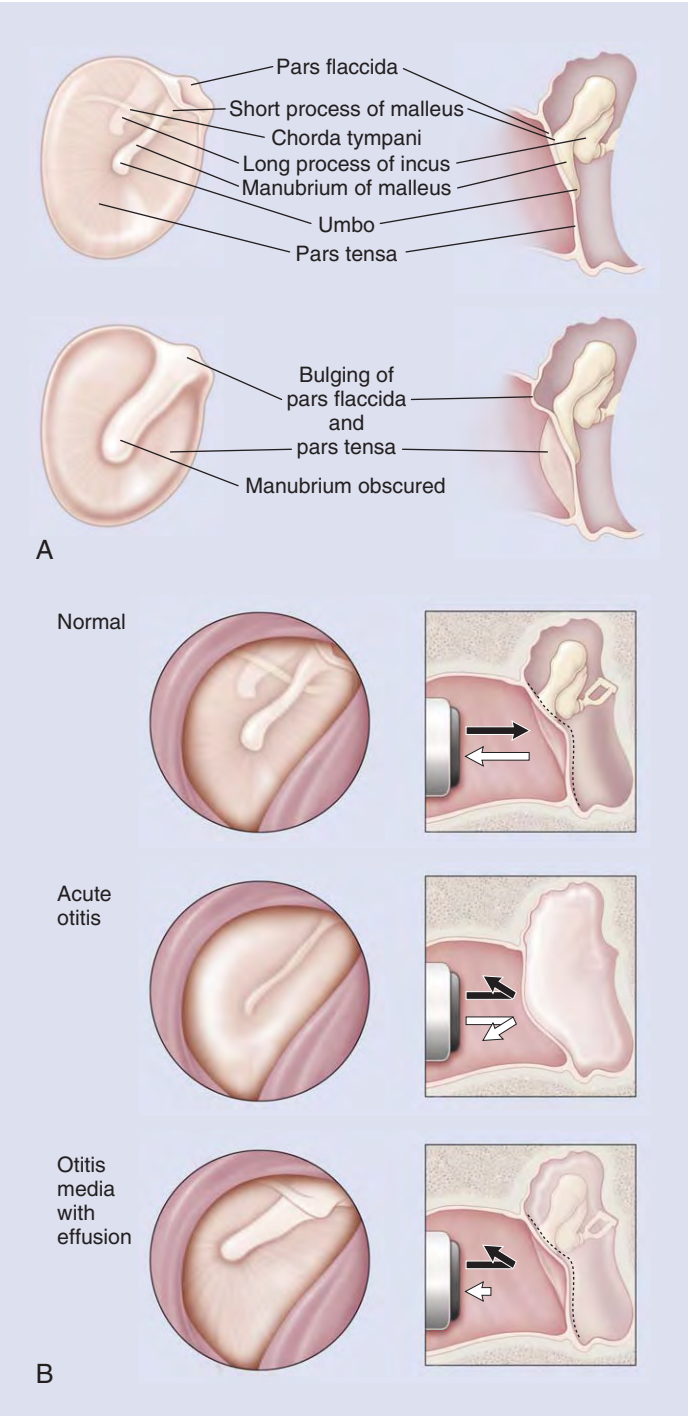

Figure 32-4 **A,** Visual assessment of middle ear status: normal and bulging. **B,** Visual assessment of tympanic membrane: normal, acute otitis media, otitis media with effusion. (From Pelton SI: Otoscopy for the diagnosis of otitis media. Pediatr Infect Dis J 17:540-543; discussion 580, 1998.)

Diagnosis

When acute otitis media has classic symptoms and signs, making the diagnosis from clinical features is not difficult. However, uncommonly, acute otitis media may have no localizing symptoms or less impressive signs of inflammation. Sometimes, the tympanic membrane is difficult to visualize. In this situation, the clinical distinction between acute otitis media and otitis media with effusion is difficult. The critical distinguishing factors are signs of acute inflammation versus otoscopic evidence of middle ear effusion. If otoscopic examination cannot be satisfactorily completed, tympanometry is indicated.

A strong light source and adequate magnification are necessary. Where possible, debris in the canal is removed. The

mobility of the drum should be tested, by occluding the external canal completely with a large ear speculum and using pneumatic otoscopy, permitting the application of positive and negative pressure. Visualization of the tympanic membrane and assessment of mobility are the standard for the diagnosis of otitis media.[110]

There is a poor correlation between qualitative and semiquantitative cultures of the nose and throat and those of the middle ear. Tympanocentesis is the only reliable way of detecting middle ear pathogens, but it is primarily a research tool and is seldom done in clinical practice.

Tympanometry gives an objective, reproducible measure of middle ear function. It is particularly useful in situations in which otoscopy is difficult or unreliable. In the infant under 6 months of age, it can be unreliable because of collapsing ear canals. Normative values have been established for 7- to 24-month-old children.[111] The findings of whether there are signs of acute inflammation are of a type B (flat) tympanogram or C2 (peak at less than –200 mm H_2O). Tympanometry is at least as sensitive in detecting middle ear fluid as pneumatic otoscopy[112] (Fig. 32-5).

Clinicians should document the laterality, duration of effusion, and presence and severity of associated symptoms in the child with otitis media with effusion at each assessment.[113] Children with otitis media with effusion who are at risk for speech, language, or learning problems need to be distinguished from all other children with otitis media with effusion. Those at risk include children with permanent hearing loss independent of otitis media with effusion, suspected or diagnosed speech and language delay or disorder, autism-spectrum disorder, syndromes such as Down syndrome that include cognitive, speech, and language delays, uncorrectable visual impairment, cleft palate with or without associated syndrome, and developmental delay.[113] In such children intervention may be required more promptly. In healthy children not at risk, watchful waiting for 3 months from the date of effusion onset (if known) or diagnosis (if onset is unknown) is recommended.[113]

The symptoms of acute otitis media need to be distinguished from those of acute systemic illness. The specific diagnosis can usually be made by noting the general symptoms and performing an adequate and complete inspection of the tympanic membrane. There can be difficulties when the external canal or debris within it does not allow adequate visualization.

Ear pulling in the absence of other symptoms is not related to ear infection.[114] Hyperemia of the tympanic membrane can occur with crying, trauma to the external auditory canal, or mild upper respiratory tract infections. These situations can be distinguished from acute otitis media because other abnormal features of the drum, in particular reduced mobility, would be lacking in them. Acute bullous myringitis can occur with acute otitis media. It causes more severe symptoms with blisters on the tympanic membrane, but it has a good clinical outcome.[115] Otalgia may be caused by referred pain from infections in the adenoids, tonsils, teeth, nasopharynx, hypopharynx, or larynx through the tenth cranial nerve. Tumors of the palate, nasopharynx,

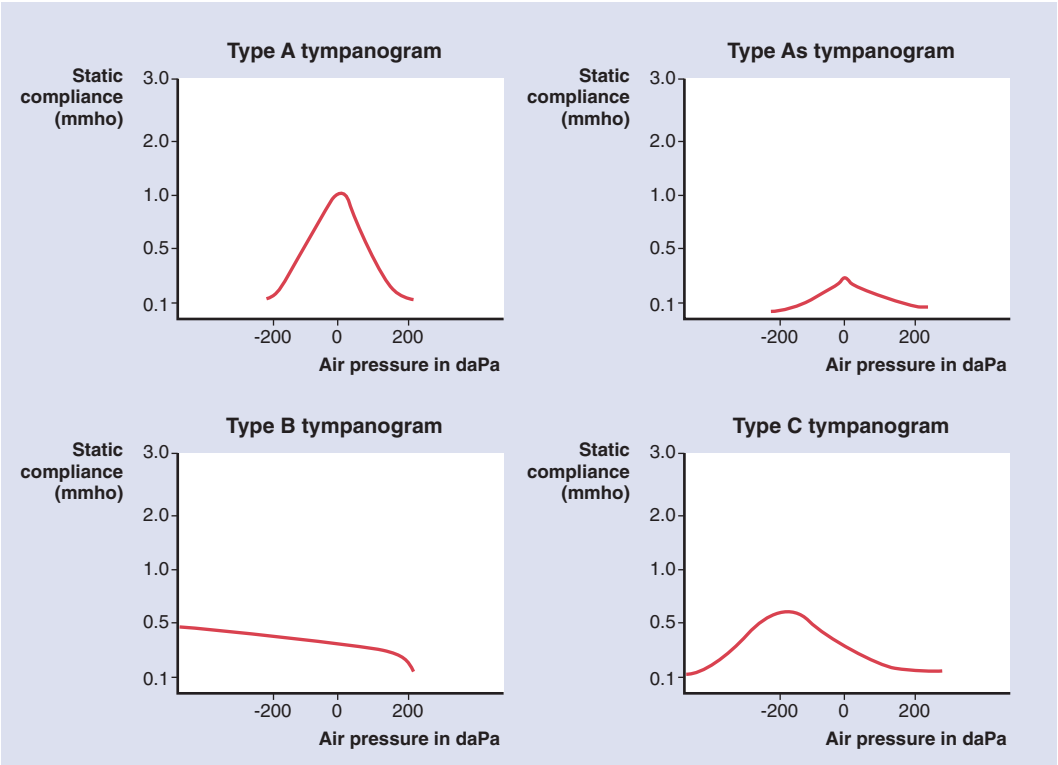

Figure 32-5 Tympanogram: classification system for low-frequency tympanograms. Based on Jerger (1970). (From Harris PK, Hutchinson KM, Moravec J: The use of tympanometry and pneumatic otoscopy for predicting middle ear disease. Am J Audiol 14:3-13, 2005.)

or base of the skull eventually occlude one or both eustachian tubes.

Treatment

The goals of treatment are to shorten the duration of symptoms of acute otitis media, to prevent complications, to prevent progression to chronic suppurative otitis media, and to prevent long-term hearing loss.

ACUTE OTITIS MEDIA

The management of acute otitis media varies within the Western world,[116] but the development of evidence-based guidelines may lead to a more standardized approach. In the past decade, several randomized controlled trials and meta-analyses have advanced knowledge about treatment strategies for this condition and otitis media with effusion.

All randomized clinical trials of antibiotic use for acute otitis media are from developed countries. They have shown that about 15 children needed to be treated to prevent one child from having pain on days 2 to 7 (no benefit on day 1). The effect on hearing is inconclusive.[117] Antibiotic use in groups where mastoiditis is common may reduce the risk of its development.[118]

Patients with acute otitis media are treated as outpatients if there is no systemic infection, unless there is frequent vomiting requiring hospital care. Children should be allowed to rest until the fever has resolved for 24 hours. Pain relief with acetaminophen is indicated. The complications of bacterial otitis media can be so serious that every child with acute inflammation should be seriously considered for antibiotics. The only indication for withholding antibiotics is a situation in which there is redness and no other sign of inflammation and the child can be reliably monitored every 1 to 2 days by otoscopy, with the parent bringing the child between visits if the condition deteriorates. The indications for antibiotics are absolute in children under the age of 6 months, regardless of symptoms, and in children of any age who have severe symptoms such as fever or vomiting. Observation with monitoring is allowable for nonsevere illness.

The choice of antibiotics for acute otitis media is determined by the known likely pathogens and local sensitivity patterns. Other factors influencing choice of therapy include the age of the patient, likelihood of compliance with the dosing frequencies, hypersensitivity to antibiotics, the cost of the antibiotics, and the patient's previous experience with the medication.[119] As illustrated in Figure 32-6, amoxicillin, 80 mg/kg/day in three divided doses, is the usual first choice of treatment.[120] If the patient is allergic to penicillin, trimethoprim-sulfamethoxazole is the usual alternative (8 mg of trimethoprim and 40 mg of sulfamethoxazole per kilogram per day in two doses). If the child has had no symptomatic response within 3 days, a change of an antibiotic is indicated. Alternatives are amoxicillin-clavulanate potassium, 40 mg/kg/day in three doses; cefixime, 8 mg/kg/day in one or two doses[121]; and erythromycin-sulfisoxazole, 50 mg/kg/day in four doses. Cefaclor (40 mg/kg/day in two or three doses) is less efficacious. If the child is vomiting, a single intramuscular dose of ceftriaxone, 50 mg/kg/day, is as effective as 10 days of oral amoxicillin.[122] All these antibiotic regimens seem to have comparable efficacy in resolving the clinical features of acute otitis media. Paradoxically, there can be a good clinical response to amoxicillin despite the presence of middle ear pathogens that produce β-lactamase. In acute otitis media in the neonate, special vigilance is required because infection may progress. If there is accompanying systemic infection, hospital admission with parenteral therapy covering *S. aureus* and gram-negative bacilli is indicated.

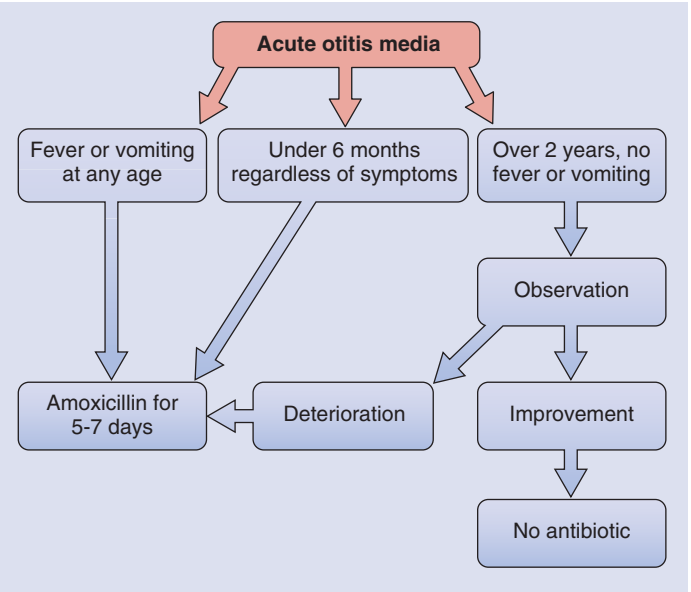

Figure 32-6 Antibiotics for acute otitis media.

When antibiotics are given early, the length of the symptomatic period may be reduced, and the infection is usually arrested before the drum ruptures. Immediate antibiotic treatment brings more rapid relief of pain and malaise compared with delaying the onset of treatment by 48 hours.[123] Early eradication of pathogens from middle ear fluid during antibiotic treatment of acute otitis media is associated with improved clinical outcome.[124] However, improved clinical outcome does not necessarily predict bacteriologic outcome. Bacteriologic failure occurs most often in children under 18 months of age.[125] Incomplete eradication could be one reason that otitis media with effusion may develop.

There is no consistent evidence from randomized, controlled trials that nasal decongestants, mucolytic agents, or antihistamines help prevent or treat any form of otitis media.[126] Intranasal steroids given to children with viral upper respiratory infections do not provide symptomatic relief or decrease episodes of acute otitis media and may even increase this undesired outcome.[127]

Myringotomy is indicated when there is severe, persistent pain and failure to respond to initial antibiotic therapy or when there is a complication of otitis media with an intact drum or persistent conductive hearing loss. In clinical practice, myringotomy is seldom performed despite these indications.

The role of adenoidectomy and adenotonsillectomy in reducing recurrence of acute otitis media is not established. Coyte and colleagues[128] found that among children over 2 years old, adenoidectomy and adenotonsillectomy at the time of insertion of tympanostomy tubes reduced the likelihood of additional hospitalizations and operations related to otitis

media. However, Hammaren-Malmi and colleagues[129] found in children 1 to 4 years of age that adenoidectomy did not reduce the incidence of acute otitis media in children who have recurrent acute otitis media, or otitis media with effusion with tympanostomy tubes. Paradise and colleagues[130] found that in children with recurrent acute otitis media with or without otitis media with effusion, that adenoidectomy and adenotonsillectomy showed limited short-term benefit but did not recommend it as a first intervention because of adverse events and cost.

Following interventions by an otolaryngologist, there was a significant disease-specific improvement in quality of life, physical suffering, emotional distress, and caregiver concerns, regardless of the treatment given.[131,132]

Adjuvant treatment with prednisone 2 mg/kg/day versus placebo for 3 days has been shown in a randomized controlled trial to reduce the duration of otorrhea from 3 days to 1 day in children also treated with amoxicillin/clavulanate who have acute otitis media with tympanostomy tubes.[133]

Myringotomy with insertion of tympanostomy tubes is indicated for persistent otitis media with effusion with hearing loss, taking into account that in an otherwise healthy child 50% of cases resolve spontaneously. The timing of tympanostomy tube insertion depends on the clinical risk of the child (Fig. 32-7). Tympanostomy tube insertion has become very common and is the main reason a child in the United States receives a general anesthetic. Waiting for spontaneous resolution in otherwise healthy children may reduce the number of children receiving this operation. If otitis media with effusion has been present for 9 to 12 months with decreased hearing, tympanostomy tubes are indicated. This can result in improvement in hearing (average, 12 decibels [dB]) in the short term, but there is no evidence that there is a beneficial effect on development or behavior. At the time of insertion of tympanostomy tubes, the clinician should conduct a preoperative assessment, including a developmental assessment, history of hearing difficulty or speech or learning problems, documentation of actual hearing impairment, and pneumatic otoscopy and tympanometry.

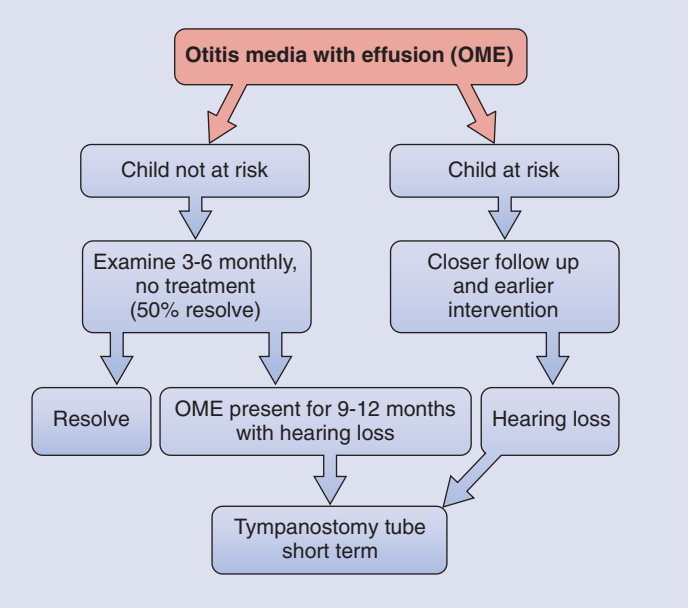

Figure 32-7 Management of otitis media with effusion (OME).

Anesthetic complications of bilateral tympanostomy tube placement in a tertiary care children's hospital are infrequent, and all can be successfully treated. A minor adverse event occurred in 9% (agitation or prolonged recovery) and a major event occurred in 1.9% (upper airway obstruction or laryngospasm), most commonly in a child with an acute or a chronic illness.[134]

In otherwise healthy children younger than 3 years of age who have persistent otitis media with effusion, prompt insertion of tympanostomy tubes does not improve developmental outcomes at 3 and 6 years of age.[135,136]

Sequelae of tympanostomy tubes are common but are generally transient (otorrhea) or cosmetic (tympanoslerosis or focal atrophy). Nonetheless, the high incidence suggests the need for ongoing surveillance of all patients with indwelling tubes and for a reasonable time period after tube extrusions. Long-term tubes should be used rarely for unusually severe cases.[137] Acute otitis media with tympanostomy tubes responds better to topical antibiotics than oral antibiotics[138,139] (Box 32-11).

Eustachian tube inflation by mechanical means, using nasal balloons (Otovent), appears to be associated with short-term improvement in otoscopic findings in 3- to 10-year-old children compared with findings in controls.[140] Its place in the treatment of otitis media with effusion has yet to be established.

The components of treatment of chronic suppurative otitis media include aural toilet, topical antibiotics, and closure of prolonged tympanic perforation. There are few randomized controlled trials for this condition. Treatment of chronic suppurative otitis media with aural toilet and topical antibiotics, particularly quinolones, is effective in resolving otorrhea and eradicating bacteria from the middle ear.[141] Aural toilet is ideally performed using the microscope and microinstruments to mechanically remove debris. Topical quinolone antibiotics can clear aural discharge better than no drug treatment or topical antiseptics. Studies are inconclusive regarding any differences between quinolone and nonquinolone antibiotics.[142] Topical antibiotics are more effective than oral antibiotics, probably because a higher local concentration of antibiotic is achieved.

Clinical Course and Prognosis

Chronic perforation without otorrhea can occur as a complication of acute otitis media or after tympanostomy extrusion.[95]

BOX 32-11 Tympanostomy Tubes

This is the most common operation in childhood in developed countries.

Complications include
- Anesthetic risks
- Purulent discharge
- Granulation tissue
- Chronic perforation
- Retraction pockets
- Atrophic scars
- Tympanosclerosis

Eighty percent of children with acute otitis media settle spontaneously in 7 days.[118] Intracranial or intratemporal complications can occur with acute otitis media. Antibiotic therapy is indicated to prevent these serious bacterial complications. Extension of inflammation and infection beyond the mucoperiosteal lining of the middle ear may result in mastoiditis or meningitis (especially with *H. influenzae*). The symptoms and signs of acute mastoiditis may be subtle, especially if they are partially treated by antibiotics or if the tympanic membrane is ruptured. The recurrence of pain and the presence of copious purulent discharge associated with low-grade fever suggest mastoiditis. Usually, there is tenderness over the mastoid process, and there may be edema of the mastoid periosteum, sometimes with postauricular pitting. In the external auditory canal, there is a sagging bulge in the posterior superior wall.

After acute otitis media, up to 20% of cases progress to otitis media with effusion. Some 50% of such patients recover after 3 months, but in about 5% the condition persists after 12 months. A large number of cases are transient, with episodes varying in duration and severity. Sometimes, there is recurrence of otitis media with effusion when acute otitis media does not recur.

In children with tympanostomy tubes for otitis media with effusion, 50% to 83% have episodes of otorrhea,[106] mostly nonsevere and self-limited, reflecting secondary inflammation of the eustachian tube and middle ear during viral upper respiratory infection.[137] These simple cases of otorrhea are inevitable and cannot be prevented by water precautions, prophylactic drops, or changes in surgical technique. Management with ototopical antibiotic drops such as ofloxacin alone is sufficient to treat purulent otorrhea.[138]

The hearing level at 14 years of age of healed ears after tympanostomy tubes is normal. In ears showing abnormalities (perforation, pars tensa retraction, otitis media with effusion) 25% have varying degrees of hearing loss.[143]

Prevention

The advent of pneumococcal vaccines has led to investigation of their role in the prevention of acute otitis media where 50% of bacterial causes are due to *S. pneumoniae*. A small benefit has been shown for pneumococcal polysaccharide vaccine in children over 2 years of age who have had previous episodes of acute otitis media.[144] There was also a small reduction in risk of recurrent disease with pneumococcal conjugate vaccine. An 11-valent pneumococcal vaccine conjugated with *H. influenzae*–derived protein D, given at 3, 4, 5, and 12 to 15 months of age, has been shown to have an efficacy of 34% against first episodes of otitis media in the first 2 years of life (95% confidence interval, 21% to 44%).[145]

Efforts to prevent chronic suppurative otitis media should be directed toward improvement in health care and living conditions in all populations that have a high prevalence of chronic suppurative otitis media, encouragement of breastfeeding, and reduction of cigarette smoking exposure.[95]

Pitfalls and Controversies

In neonates, otitis media may be overdiagnosed. The tympanic membrane often appears thickened and opaque during the first few weeks of life and lies in an extremely oblique position, making it difficult to distinguish it from the canal wall. The ear canal is particularly compliant, with positive pressure simulating the movement of the tympanic membrane.

There is frequently a gap in training in pneumatic otoscopy for most clinicians due to the lack of easy-to-use dual-headed equipment to enable training and evaluation of medical personnel. These skills can be learnt and result in high sensitivity and specificity.[110]

The method of use of antibiotics for acute otitis media and tympanostomy tubes for otitis media with effusion used to be highly controversial. However, many well-conducted randomized controlled trials and evidence-based Cochrane reviews have clarified most of the contentious issues. The challenge is to disseminate this knowledge to achieve evidence-based practice (Box 32-12).

BOX 32-12 Otitis Media Teaching Points

- In acute otitis media, there is acute inflammation with 5% viral only, 75% bacterial only, and 20% both bacterial and viral. The most common organism is *Streptococcus pneumoniae,* and the first-line antibiotic is amoxicillin.
- In otitis media with effusion, there is middle ear effusion, and up to 20% of cases of acute otitis media progress to otitis media with effusion.
- In chronic suppurative otitis media including perforation, there is otorrhea and deafness. This is an important public health problem.

ADENOIDECTOMY AND TONSILLECTOMY

Elective surgical removal of the tonsils and adenoids was once widely performed, usually with the hope of reducing the frequency of recurrent sore throats, but the rate for this surgery has fallen over the past three decades. However, it remains the most common major operation in children in the United States, although the scientific basis of this practice is not well established.[146] Children aged 3 to 8 years normally have up to nine respiratory tract infections a year. Prospective objective monitoring of symptoms demonstrates lower rates than frequency of symptoms recalled. In severely affected children with frequent, well-documented episodes of sore throat,[147] tonsillectomy reduces the occurrence of throat infection.[147] In children moderately affected with recurrent throat infection, however, the modest benefit conferred by tonsillectomy or adenotonsillectomy does not justify the inherent risks, morbidity, and cost of the operations.[148] Adenotonsillectomy was no more efficacious than tonsillectomy alone.[148]

The most important indication for adenotonsillectomy is obstructive sleep apnea, which can be serious and even life threatening. Removal of both tonsils and adenoids is usually of marked clinical benefit.[149,150] Tonsillar or adenoidal size is not always a reliable indicator of the potential benefit of tonsillar removal.

BOX 32-13 Adenoidectomy and Tonsillectomy Teaching Points

- The main indication for adenoidectomy and tonsillectomy is obstructive sleep apnea.
- Adenoidectomy and adenotonsillectomy are not recommended for prevention of recurrent otitis media.
- Tonsillectomy may be beneficial in children with recurrent severe tonsillitis.

Adenoidectomy has been used in children with otitis media, in an attempt to reduce recurrence of acute otitis media and persistence or recurrence of otitis media with effusion, but the indications remain unclear. Although adenoidectomy and bilateral myringotomy (without tympanostomy tubes) were beneficial in children 4 to 8 years old who were severely affected by otitis media with effusion,[151] adenoidectomy did not reduce the occurrence of acute otitis media in children who have recurrent acute otitis media, or otitis media with effusion with tympanostomy tubes.[129] Among children over 2 years old, adenoidectomy and adenotonsillectomy at the time of insertion of tympanostomy tubes for otitis media with effusion reduced the likelihood of additional hospitalizations and operations related to otitis media.[128] In a further study of children with recurrent acute otitis media, with or without otitis media with effusion, adenoidectomy and adenotonsillectomy showed limited short-term benefit and could not be recommended as a first intervention because of adverse events and cost[130] (Box 32-13).

SINUSITIS

Sinusitis is a bacterial infection of the paranasal sinuses that uncommonly complicates the common cold. The use of antibiotics dramatically reduces the occurrence of complications of sinusitis.

Epidemiology, Risk Factors, and Pathogenesis

In children, sinusitis almost always occurs as a complication of the common cold in developmentally aerated sinuses. It is more common in boys than in girls. The viral infection inflames the mucosa and causes damage to nasal ciliated epithelial cells, encouraging infection with bacteria colonizing the upper respiratory tract. Infection can occur in any of the paranasal sinuses as they develop (Box 32-14). Although the full development of the frontal sinuses may take 20 years, sinusitis can occur at any age.

The four-paired paranasal sinuses communicate with the anterior nose, with which they form a system of narrow channels. The mucosa of the sinuses, like that of the nose, is a continuous ciliated columnar epithelium with goblet cells and is covered in part by a mucous blanket. A continual flow of mucus from the frontal, maxillary, and anterior ethmoid sinuses is propelled toward the ostia and then posteriorly to the nasopharynx. The mucus contains IgA, IgG, IgM, and lysozyme, and the paranasal sinuses are usually sterile. Damage to mucociliary function allows the inoculation of large numbers of pathogens into the sinuses, which causes infection. Once started, sinus infection is aggravated by further inflammation of the ostia of the sinuses, resulting in progressive obstruction. Irritants, such as swimming underwater and drying of the mucosa during winter in cold climates, can set the stage for sinus infection. Host factors predisposing to sinusitis are listed in Box 32-15.

BOX 32-14 Development of Sinuses

Birth: ethmoid sinuses aerated but small
Birth: maxillary sinuses aerated but small
1 to 2 years: sphenoidal sinus aerated
5 to 7 years: frontal sinuses aerated
Developmentally poorly aerated sinuses appear radiologically opaque

The organisms causing sinusitis are listed in Box 32-16. The most common causes are *S. pneumoniae*, *H. influenzae*, and *M. catarrhalis*. These organisms, along with *S. aureus* and *S. pyogenes*, account for over 90% of cases of sinusitis in children. In adolescents, penicillin-sensitive anaerobes become more common. There may be a vast array of enteric gram-negative and other bacilli recovered, mostly from those who have had antibiotic therapy before culture.[152,153]

Clinical Features

Acute sinusitis is heralded by failure of common cold symptoms to resolve after 10 days.[153,154] Older children have more specific complaints than younger children. Sometimes, the sinusitis can be more acute with severe initial symptoms: fever greater than 39° C and purulent nasal discharge. Acute sinusitis involves symptoms persisting from 10 to 30 days, and after this time, it is usually categorized as chronic. However, an international consensus panel has suggested that the term *rhinosinusitis* be used instead of *sinusitis* because of the coexistence of rhinitis and that the term *chronic* be reserved for those with symptoms persisting beyond 12 weeks.[155]

The main symptom is rhinorrhea (80%), which is frequently purulent but can be serous or watery. In a minority of patients, there is fever, cough (especially at night), pain, headache, sore throat, periorbital swelling, vomiting, and, occasionally, malodorous breath. Sinus tenderness is uncommon in children. Posterior pharyngeal pus is not usually seen in acute sinusitis and is very uncommon in chronic sinusitis. Periorbital swelling is usually a sign of acute ethmoid sinusitis. Acute sinusitis is more frequently unilateral, and chronic

BOX 32-15 Host Factors in Sinusitis

Common cold
Respiratory allergies
Defects of ciliary function
Cystic fibrosis
Immunodeficiency
Anatomic abnormalities
Gastroesophageal reflux

BOX 32-16 Organisms Causing Sinusitis

Most Common

Haemophilus influenzae
Moraxella catarrhalis
Streptococcus pneumoniae

Less Common

Acinetobacter spp.
Alcaligenes spp.
Citrobacter spp.
Diphtheroids
Eikenella corrodens
Enterococci
Escherichia coli
Haemophilus spp.
Klebsiella pneumoniae
Neisseria spp.
Proteus spp.
Pseudomonas aeruginosa

Rare

Serratia spp.
Staphylococcus aureus
Staphylococcus epidermidis
Streptococcus pyogenes
α-Hemolytic and nonhemolytic streptococci

Anaerobic Bacteria

Bacteroides spp.
Bifidobacterium spp.
Fusobacterium spp.
Peptococcus spp.
Peptostreptococcus spp.
Propionibacterium spp.
Veillonella spp.

Other organisms

L-forms
Mixed: aerobes and anaerobes
Mixed: *Haemophilus influenzae* with other organisms
Mycoplasma pneumoniae
Other (rhinovirus, adenovirus, *Aspergillus* spp., other fungi)

Fungi

Aspergillus spp.
Bipolaris spp.
Curvularia lunata
Drechslera spicifera
Zygomycetes

sinusitis is usually bilateral. In chronic sinusitis, the symptoms may be minimal: vague unwellness with some persistent signs of upper respiratory tract infection.

Diagnosis

The diagnosis is usually made on clinical grounds alone. In acute sinusitis, clinicians seldom undertake investigations. If investigations are undertaken, nasal culture reveals the organism in the majority of cases, but it should be obtained with careful technique. A vasoconstrictor such as phenylephrine hydrochloride 0.25% should be applied to the anterior nose, and bilateral cultures should be obtained under direct vision using a wire cotton swab touching material as it comes from the sinus ostium. In children who have neurologic complications or in whom treatment fails, antral puncture for aerobic and anaerobic culture can identify the organism.

In acute sinusitis, the number of band neutrophils may be increased. Some cases of sinusitis have an elevated erythrocyte sedimentation rate.

The differential diagnosis includes chronic nasal allergy, foreign bodies in the nose, cysts in the maxillary antra, nasal structural defects, palatal defects, dental infections, and infection of the adenoids.

Sinus radiographs are not sensitive or specific in diagnosing sinusitis.[156] CT scans are more sensitive than radiographs in chronic sinusitis but have low specificity. CT scans are indicated when there are complications or surgery is contemplated.[155,157,158] Ultrasonography is of doubtful value unless there is one normal air-filled maxillary sinus for comparison.

In chronic sinusitis poorly responsive to treatment, clinicians should consider investigation for underlying abnormalities of host defense.

Treatment

The goals of treatment are to reduce symptoms rapidly and to reduce the possibility of persistence of symptoms. Antibiotics should not be started if symptoms are improving.[159] Analgesics such as acetaminophen may be useful for controlling headache, pain, or fever. The primary treatment is antibiotics. Amoxicillin, 40 mg/kg/day in three doses, is adequate for the majority of *S. pneumoniae*, *H. influenzae*, and *M. catarrhalis* infections. A brisk response to treatment is expected in 3 to 4 days, in which case a 10-day course of treatment is satisfactory.[160,161] The benefits are modest: eight children must be treated to achieve one additional cure.[160] In communities with β-lactamase–producing *H. influenzae* and *M. catarrhalis*, the following antibiotics should be considered: amoxicillin–clavulanate potassium (40 mg/kg/day in three doses), trimethoprim-sulfamethoxazole (8 mg of trimethoprim and 40 mg of sulfamethoxazole per kilogram per day in two or three doses), and cefaclor (40 mg/kg/day in three doses).

Vasoconstrictive drugs are often used locally or systemically in an attempt to relieve obstruction at the sinus ostia to help establish drainage, but there is no evidence supporting their effectiveness.[161] Because topical medications can cause rebound vasodilation, these medications should be used only when there is considerable pain and then for no longer than 3 days.

Saline irrigation may have a role in the management of symptoms of chronic sinusitis,[162] but further studies are required.

Clinical Course and Prognosis

The outlook of sinusitis in otherwise healthy children receiving adequate treatment is excellent. Untreated sinusitis can

progress to orbital infection, meningitis, osteomyelitis, cavernous sinus thrombosis, and abscesses of the epidura, subdura, or brain.[163]

If the sinusitis is recurrent, fails to improve, or has more serious clinical features with high fever or periorbital swelling, consider amoxicillin–clavulanate potassium (40 mg/kg/day in three doses), trimethoprim-sulfamethoxazole (8 mg of trimethoprim and 40 mg of sulfamethoxazole per kilogram per day in two or three doses), and cefaclor (40 mg/kg/day in three doses).

If there are bacterial complications of sinusitis, the child should be hospitalized and given parenteral antibiotics. Initially, intravenous cefuroxime (100 mg/kg/day in three divided doses) is recommended; however, if *S. aureus* is a major concern, oxacillin or nafcillin should be added. Therapy should be adjusted on the basis of response to treatment and the results from culture.

Surgical drainage is rarely necessary in children. Fiberoptic endoscopic sinus surgery has replaced more invasive approaches. It is indicated only if there is lack of response to maximal medical therapy and continuing symptoms or in specific situations (Box 32-17). Optimal medical management, including 2 to 6 weeks of adequate antibiotics (intravenous or oral) and treatment of concomitant diseases, is indicated for uncomplicated sinusitis before medical treatment is regarded as failed, and surgery is recommended.

Pitfalls and Controversies

The relationship between sinus disease and lower respiratory tract infections and asthma has caused debate because of the lack of controlled studies. Nevertheless, treating sinus disease may be associated with improvement in concurrent lower respiratory tract symptoms through improved nasal airway or the direct effects of antibiotics on the lower airways[156] (Box 32-18).

BOX 32-17 Indications for Surgery

Complete nasal obstruction in cystic fibrosis due to massive polyposis or closure of the nose by medialization of the lateral nasal wall
Antrochoanal polyp
Intracranial complications
Mucoceles and mucopyoceles
Fungal sinusitis
Dacryocystorhinitis due to sinusitis and resistant to appropriate medical treatment
Chronic rhinosinusitis that persists despite optimal medical management and after exclusion of any systemic disease; endoscopic sinus surgery is a reasonable alternative to continuous medical treatment

From Clement PA, Bluestone CD, Gordts F, et al: Management of rhinosinusitis in children: Consensus meeting, Brussels, Belgium, September 13, 1996. Arch Otolaryngol Head Neck Surg 124:31-34, 1998.

BOX 32-18 Sinusitis in Children Teaching Points

- Acute sinusitis symptoms are present 10 to 30 days after common cold.
- Chronic sinusitis symptoms persist past 30 days.
- Main symptom is rhinorrhea.
- Sinus tenderness is uncommon in children.
- Postpharyngeal pus is seldom seen.
- First-line antibiotic is amoxicillin.
- Outlook is excellent in healthy children.

VIRAL CROUP

Viral croup is common, affecting approximately 15% of children. Although epiglottitis is less common, it is still necessary to consider this and other alternative diagnoses such as congenital airway abnormalities, foreign body, and bacterial tracheitis.

Many children with croup require no specific treatment. Oxygen, single-dose glucocorticoids, and inhaled epinephrine are effective therapies for those who have more significant airways obstruction.

Epidemiology, Risk Factors, and Pathogenesis

Acute upper airway obstruction in children is most commonly due to a viral infection causing laryngotracheitis or spasmodic croup. The term *acute laryngotracheitis* defines the site of inflammation, which always involves the larynx and trachea; if it is believed to extend to the bronchi, the name *laryngotracheobronchitis* is used. Spasmodic croup and recurrent croup are often regarded as separate diagnoses but may be part of the spectrum of the same condition.

Viral croup (which when used in this chapter will refer to both acute laryngotracheitis and spasmodic croup) is uncommon in the first 6 months of life. Under this age, preexisting abnormalities of the upper airway such as subglottic stenosis or hemangioma should be considered. These lesions may also be the cause of prolonged stridor because viral croup rarely lasts longer than 10 to 14 days.

Viral croup is a very common condition, affecting about 15% of children. The annual incidence of croup in children younger than 6 years old is between 1.5% and 6%.[164] It is most common between 6 months and 5 years of age, with a peak prevalence in the second year of life; the youngest reported patient is 3 months old.[165] The full picture of viral croup is rare over the age of 10 years. Boys are affected more often than are girls.

The symptoms and signs result from inflammation in the larynx, trachea, and sometimes the bronchi. They are almost always caused by viral infection. The causative viruses are listed in Box 32-19.

The parainfluenza viruses cause most cases of croup, with type 1 being most common, type 3 less common, and type 2 infrequent. Respiratory syncytial virus and several of the adenoviruses infrequently cause croup, as does influenza virus type A, which induces a particularly severe form.[166] Rhinoviruses, enteroviruses, herpes simplex virus, and reovirus

BOX 32-19 Viral Causes of Acute Laryngotracheitis

Common Causes

Influenza virus types A and B
Parainfluenza virus types 1 to 3
Respiratory syncytial virus

Uncommon Causes

Adenoviruses
Enteroviruses
Herpes simplex virus
Morbilli (measles) virus
Reovirus
Rhinoviruses

Viral, Bacterial, and Fungal Causes in an Immunodeficient Host

Candida albicans
Candida spp.
Herpes simplex virus type 2 (neonate)
Pseudomonas aeruginosa

have been associated with mild cases of croup. Morbilli (measles) virus may cause upper airway obstruction resulting from laryngotracheitis, sometimes severe enough to require intubation, and there may be complicating bacterial tracheitis. Rarely, the vesicular eruption of varicella may involve the larynx. Mild "viral" croup may also be caused by *M. pneumoniae* infection.

Primary bacterial croup is now uncommon. Immunization resulted in a rapid decline in croup due to C. *diphtheriae* infection. Bacterial croup became uncommon with the introduction of antibiotics.[167] Diphtheria must be considered if the child has not been immunized against C. *diphtheriae*. This organisms may cause a membranous obstructive laryngitis. In most cases now where bacterial infection occurs, this is secondary to a preceding viral infection. *S. aureus* is the most common bacteria implicated in this way. Others include *S. pyogenes*, *S. pneumoniae*, *H. influenzae*, and *M. catarrhalis*.[167]

Seasonal variability in croup reflects the epidemiology of the different etiologic viruses. Parainfluenza type 1 causes outbreaks of croup in autumn and croup due to parainfluenza type 3 occurs in spring. The seasonality of croup due to parainfluenza type 2 is more variable.[167,168]

After inhalation of the virus, the cells of the local respiratory epithelium become infected. There is marked edema of the lamina propria, submucosa, and adventitia accompanied by cellular infiltration with histiocytes, lymphocytes, plasma cells, and polymorphonuclear leukocytes.

There is redness and swelling of the involved airway, most marked in the lateral walls of the trachea just below the vocal cords. The subglottic trachea is surrounded by the fixed cricoid cartilage, forcing the inflammatory swelling to encroach on the internal airway lumen, narrowing it or reducing it to a slit (Fig. 32-8). The infant's glottis and subglottic region are normally narrow, and a small decrease in diameter results in a large increase in airway resistance and a decrease in airflow. As the airway diameter enlarges with growth, the impact of the subglottic airway swelling is reduced.

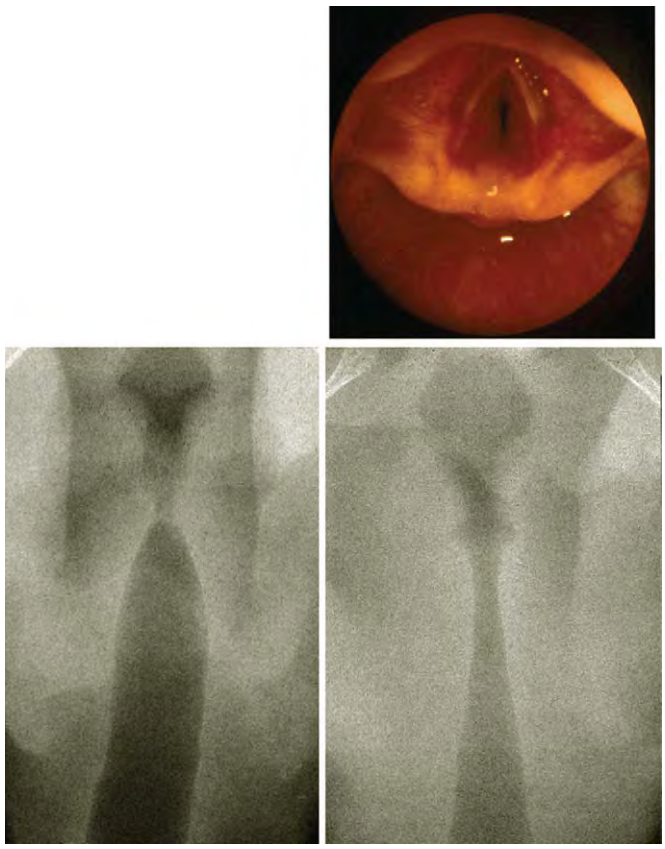

Figure 32-8 Endoscopic view of subglottic edema in viral croup (*top*). Radiologic presentation of subglottic edema in viral croup (*bottom right*) compared with normal trachea (*bottom left*). (From Hammer J: Acquired upper airway obstruction. Paediatr Respir Rev 5:25-33, 2004.)

In spasmodic croup, the direct laryngoscopic appearance shows pale, watery edema of subglottic tissues. There is an association with the same viruses that cause acute laryngotracheitis, but evidence suggests that the response to these viruses may be atopic rather than cytopathic.[167] Spasmodic croup occurs more frequently in children who are atopic.

Clinical Features

Typically, the illness starts with rhinorrhea, sore throat, and mild fever for a few days. Then the child develops a characteristic barking cough, hoarseness, and inspiratory stridor with or without low-grade fever.

An increasing severity of obstruction is evident with increasing heart and respiratory rate, flaring of alar nasi, and indrawing, especially suprasternal, intercostal, and sternal, in the younger child or infant. Increasing chest wall retractions occur as the intrathoracic pressure becomes increasingly negative and correlates with the severity of the upper airway obstruction.[169] Ribcage and abdominal asynchrony occurs as the condition deteriorates.[170]

Obstruction to airflow through the upper airway results in stridor and difficulty breathing and progresses to hypoxia when the obstruction is severe. Hypoxia with mild obstruction indicates lower airway involvement and ventilation-perfusion mismatch resulting from lower airway obstruction

or lung parenchymal infection or even fluid.[171] Hypercapnia occurs as a late change as hypoventilation progresses with obstruction.

As progressive hypoxia develops, the child is anxious or restless or may have depressed consciousness or cyanosis. Death can occur either from asphyxia or from respiratory fatigue.

On auscultation, breath sounds are normal with no added sounds except transmission of the stridor. Occasionally, there may be wheezing, indicating severe narrowing, bronchitis, or possibly coexistent asthma.

Becoming upset or worried may decrease the child's ability to manage the airway obstruction. Therefore, physical examination should be limited to the respiratory tract and reasonable exclusion of other diagnostic possibilities. Investigations are intrusive and should be avoided when possible.

The term *spasmodic croup* has been used to define a sudden onset of symptoms at night in a child who has been well. The symptoms are identical to viral croup but without fever, last for hours rather than days, and are seldom life threatening. The child may be well during the day and have attacks on three or four successive evenings. During the first attack, it is difficult to make an accurate diagnostic distinction from viral croup.

Diagnosis

The differential diagnosis includes any condition that causes obstruction in the region of the larynx. The most important are epiglottitis and laryngeal foreign body aspiration, both of which require emergency treatment. Acute angioedema usually presents with other evidence of swelling of the face and neck. Other conditions to be considered are retropharyngeal and peritonsillar abscess, bacterial tracheitis, subglottic stenosis, infectious mononucleosis, laryngeal diphtheria, and paraquat poisoning.

Investigations are seldom necessary in straightforward viral croup. When there is severe obstruction, neck radiographs or blood tests cause anxiety in the child, which may precipitate critically poor gas exchange. Pulse oximetry may support the clinical suspicion of hypoxia but should not be used as the only means of clinical assessment.

If radiography is deemed necessary to exclude epiglottitis or foreign body inhalation in a child whose airway is severely obstructed, it should be done in the presence of medical staff able to resuscitate and intubate a child with upper airway obstruction. However, epiglottitis is usually diagnosed clinically and confirmed under direct vision in the intensive care unit.

When radiography has been done, specific abnormalities are seen in 40% to 50% of cases (see Chapter 11). Posteroanterior neck radiographs may show a very narrowed subglottic region. In lateral neck radiographs, there may be widening of the hypopharynx and haziness in the subglottic region. Radiographic changes do not reliably reflect the severity of airway obstruction.

Treatment

Airway obstruction in croup can worsen rapidly; hence, repeated careful clinical assessment is a key component of management.[172,173]

Most children with viral croup have only mild airway obstruction that spontaneously settles; therefore, no specific treatment is indicated. Most of these children can be managed at home. By the time medical attention is sought, the airway obstruction often does not progress but usually lasts 4 additional days.

A commonly used home treatment is to sit the child in the bathroom with a parent with a hot shower running, in the belief that the warm mist will help the breathing. Trials of mist therapy have shown no evidence of efficacy. A single-blinded study of blow-by humidity showed it to result in identical changes in croup scores to those seen in children receiving no therapy.[174] A study of children with moderate croup that compared blow-by humidity with either 100% humidity or 40% humidity with smaller water particles generated by a nebulizer showed no significant difference between treatment groups in the change in croup score.[175]

In the child with obvious indrawing, anxiety, or other evidence of moderate or severe airway obstruction, it is vital to use a careful nonintrusive approach. A parent should stay with the child, and all interactions with the child should appear calm and reassuring. Mist treatment in the hospital is no longer recommended, and it may increase the child's anxiety.

Mild hypoxia with a hemoglobin oxygen saturation lower than 93% is common and closely correlated to the respiratory rate. When there are clinical signs of hypoxia such as restlessness, marked tachycardia, and cyanosis, or when there is significant oxygen desaturation ($SaO_2 < 90\%$) as measured by pulse oximetry, oxygen should be administered.[172]

At the same time, treatment to relieve the obstruction is needed. In a minority of children, the airway obstruction progresses to become severe. Admission to the pediatric intensive care unit is indicated for children with signs of hypoxia or progressive severity of obstruction. Among children hospitalized for viral croup, less than 1% require intubation. Rarely, idiopathic pulmonary edema occurs in severe obstruction.[176]

GLUCOCORTICOIDS

The theoretical mechanism of action of the steroids is suppression of local inflammatory reaction, shrinkage of lymphoid swelling, and reduction in capillary permeability. The mechanism by which glucocorticoids exert their effect in croup is unknown.[172] The place of steroids in the management of viral croup has been debated for 30 years. It was subjected to meta-analysis.[177]

In the large number of studies of corticosteroids for croup, treatment efficacy has been measured using clinical symptom severity scores and the need for return visits and hospital admission, length of hospital or emergency department stay, and the need for other additional therapy.[177] The validated scoring system that is most frequently used is the Westley score. This uses a 17-point scale to assess air entry (2 points), stridor (2 points), intercostal retractions (3 points), cyanosis (5 points), and level of consciousness (5 points).[178]

Efficacy of Glucocorticoids

As measured by improvement in Westley symptom scores: In placebo-controlled studies, glucocorticoids have been

shown to result in significant improvement in symptom scores at 6 and 12 hours but not at 24 hours after administration. The lack of significance of the effect at 24 hours may be due to low study power. The effect size seen at 24 hours is similar to that at 12 hours but has been examined in fewer studies. The number needed to treat at 6, 12, and 24 hours was five, with this considered sufficient to support the use of glucocorticoids over placebo.[177]*

As measured by return visits, length of stay, and use of additional therapy: In comparison with placebo, the rates of return visits and hospital admission are both significantly reduced (number needed to treat to prevent one return visit = 17). Length of stay in the emergency department or inpatient ward are both reduced, with the mean difference being approximately 12 hours. Children treated with glucocorticoids are approximately 10% less likely to be also treated with epinephrine.[177]

Different doses and routes of administration of glucocorticoids: Using symptom scores and return visits/readmissions as outcome measures, the efficacy of glucocorticoids versus placebo given by different routes of administration (oral, spray, intramuscular, subcutaneous) does not differ. Combinations of budesonide and dexamethasone versus either alone do not result in any increased effect.[179] Different doses of dexamethasone (0.15, 0.3, or 0.6 mg/kg) have similar efficacy.[177,180] The onset of action of nebulized budesonide is faster than that of oral or intramuscular glucocorticoids but slower than that of nebulized epinephrine.[172]

Efficacy of glucocorticoids for croup of varying severity: A single dose of glucocorticoid has been shown to be effective in croup of all grades of severity including mild croup defined as a score of 2 or less (of 17) on the Westley scoring system.[181]

Comparison with epinephrine: There is no significant difference in improvement in croup scores in studies that have compared glucocorticoids (dexamethasone or budesonide) with epinephrine.

Adverse effects of glucocorticoids: There is no evidence of any ill effects of a single dose of glucocorticoids given to a child with viral croup. The efficacy and safety of repeated doses of glucocorticoids in children with severe croup have not been established. However, there may be complications with steroids used inadvertently for diagnoses mimicking viral croup, such as epiglottitis or bacterial tracheitis, so the clinician must be certain of the diagnosis before administering them.[167] Both bacterial tracheitis and *Candida* laryngotracheitis have been reported to occur in children with croup being treated with glucocorticoids.[182,183]

EPINEPHRINE

Epinephrine (Adrenalin) was first introduced for viral croup in 1971. It is thought to stimulate α-adrenergic receptors in subglottic mucosa, producing vasoconstriction, resulting in less hyperemia and edema of the larynx and subglottic region. This results in increased airway diameter within 30 minutes. However, the effect is short lived, lasting about 2 hours because of dispersion of the epinephrine.[184] The first use of this treatment was with racemic epinephrine hydrochloride (Vaponefrin, equivalent to 2.25% epinephrine base), a mixture of equal parts of the inactive D-isomer and the active L-isomer. In some early studies,[185] this treatment was given with intermittent positive-pressure breathing, but a similar effect is seen without it.[186] Racemic epinephrine is not readily available in some countries, and it has been replaced by the use of L-epinephrine solution, which is cheaper.[184]

Epinephrine does not alter the natural history of the airway obstruction. Therefore, when the effects wear off, rebound may occur. The obstruction may be either as bad as before or worse if the overall condition is deteriorating. It is dangerous to discharge a child with croup who has been given nebulized epinephrine before ensuring that there is no rebound. The child should be observed for 6 hours after the dose. Epinephrine is used to provide immediate symptomatic relief in patients with moderate and severe croup and in those admitted to the intensive care unit in an attempt to avert the need for intubation.

Epinephrine is given via a nebulizer with a face mask and is driven with oxygen. The usual dose in infants weighing 10 kg is 5 mg, which may be given as 5 mL of 1 : 1000 solution of L-epinephrine or as 0.5 mL of 2.25% solution (22.5 mg/mL) of racemic epinephrine solution, which contains 5 mg of L-isomer. The latter is diluted with isotonic saline to a 3- to 5-mL volume. In young infants, graded doses based on body weight are appropriate: 0.5 mL/kg concentration of 1 : 1000 L-epinephrine to a maximum of 5 mL or 0.05 mL/kg of 2.25% solution to a maximum of 0.5 mL of racemic epinephrine. Doses may be repeated every 2 hours or even more often. Adverse reactions have not been reported. Nebulized epinephrine is relatively contraindicated in children with ventricular outflow tract obstruction, for example, tetralogy of Fallot.[172]

OTHER TREATMENTS

Intravenous fluids are not usually required in viral croup, but if a child is unable to drink, they may become necessary.

Admission to the intensive care unit is indicated when there is restlessness, anxiety, marked tachycardia, or cyanosis or when the child is tiring. In this situation, epinephrine and corticosteroids should be administered.

Helium and oxygen mixtures (helium : oxygen 80 : 20 or 70 : 30) improve gas flow when there is turbulent flow through high-resistance airways. This is because helium is one seventh the density of air, thereby increasing flow as well as allowing carbon dioxide to diffuse through it 4 to 5 times faster than it does through air.[187] Helium is an inert, nonflammable gas with no known pharmacologic effects.[172] Heliox (helium : oxygen 70 : 30) has been shown to be of similar efficacy to nebulized epinephrine in one small double-blind, randomized trial of children with croup who were receiving oxygen and glucocorticoids.[188]

Despite vigorous treatment with epinephrine and steroids, a child occasionally progresses to critical airway obstruction necessitating endotracheal intubation. This should be performed by a pediatric anesthetist or intensive care pediatri-

*In the studies included in the meta-analysis, improvement in the Westley score was defined in a number of ways.

cian experienced in endotracheal intubation using inhalational anesthesia. Intubation should be maintained until an air leak develops, indicating a reduction of airway edema, or until a maximum of 5 days passes, at which time a trial of extubation is attempted. Rarely, tracheostomy may be the only method of providing an alternative airway.

Clinical Course and Prognosis

About half the cases of croup progress to recurrent croup (at least two episodes). In a few individuals, numerous episodes occur. More of these children are boys; more have asthma, hay fever, eczema, and positive allergy prick tests; and more come from families with a history of atopy or croup than do children with nonrecurrent croup.[189] Pulmonary function studies have demonstrated lower expiratory flow rates, and increased airway responsiveness to histamine has been documented on inspiratory and expiratory flow-volume loops (Box 32-20).

EPIGLOTTITIS

Epiglottitis is a very serious infection of the epiglottis and supraglottic structures that results in acute airway obstruction and high risk of death if untreated. It is rare but must be considered in a child with dyspnea and stridor. If suspected, management must be initially focused on securing the airway.

BOX 32-20 Viral Croup Teaching Points

- Viral croup includes acute laryngotracheitis and spasmodic croup.
- Parainfluenza virus infections are the most frequent cause. Seasonal variability in croup reflects the epidemiology of the different etiologic viruses.
- Viral croup is common, affecting 15% of children, most commonly between 6 months and 5 years of age.
- Viral croup is uncommon in the first 6 months of life. Presentation in this age group necessitates consideration of alternative diagnoses such as congenital or vascular airway abnormalities.
- Characteristic clinical features are a barking cough, hoarseness, and inspiratory stridor with an absence of symptoms and signs of systemic toxicity.
- Investigations are seldom necessary in straightforward viral croup.
- Airway obstruction can progress rapidly; therefore, it is necessary to clinically reassess at frequent intervals.
- A single dose of a glucocorticoid has been shown to reduce clinical severity and decrease the need for hospital or emergency department care. Inhaled, oral, and parenteral routes of administration are all effective but do not have an additive effect. Beneficial effect has been shown for mild, moderate, and severe croup.
- Epinephrine provides rapid-onset, short-term relief of airway obstruction but does not alter the natural history of the disease.
- Some children get recurrent croup. Most of them are atopic.

Epidemiology, Risk Factors, and Pathogenesis

Since the introduction of vaccines that protect against *H. influenzae* type B (Hib) infection, epiglottitis has become a rare disease. Most cases now occur in adolescents and adults.[190,191] However, cases of epiglottitis due to Hib continue to be reported.[192] Other causative organisms include nontypable *H. influenzae*, *H. parainfluenzae*, *S. aureus*, and *S. pneumoniae*.[74] Occasionally, viruses[193-195] or *Candida* organisms are also causative.[196]

Direct bacterial invasion causes cellulitis with marked edema of the epiglottis, aryepiglottic folds, ventricular bands, and arytenoids. There is a large potential space for the accumulation of inflammatory cells and edema fluid where the stratified squamous epithelium is loosely adherent to the anterior surface and the superior third of the posterior portion of the epiglottis. There is diffuse infiltration with polymorphonuclear leukocytes, hemorrhage, edema, and fibrin deposition, and microabscesses may form. Infection of the supraglottic larynx may extend but does not usually reach the subglottis or the laryngeal lymphatic system.

Clinical Features

Up to half of the children have preceding upper respiratory tract symptoms. The onset of epiglottitis is typically abrupt, with early toxicity. The duration of symptoms before presentation to the hospital is usually less than 24 hours. Localizing symptoms are caused by supraglottic swelling and airway obstruction.

There is a very sore throat, difficulty swallowing because of pain, respiratory distress, drooling, a choking sensation, irritability, restlessness, and anxiety. The temperature is high, usually between 38.8° and 40° C (101.8° to 104° F). Sighing respirations, mild stridor, retractions, and mild tachypnea occur. Less common symptoms and signs are cough, which may be harsh, and occasionally barking, delirium, lethargy, hoarseness or aphonia, vomiting, chills, anorexia, cervical adenopathy, wheezing, and hypotonia.

The child naturally assumes a posture that maximizes the diameter of the obstructed airway: sitting and leaning forward with hyperextension of the neck and protrusion of the chin. A few may have shock with cyanosis, prostration, and loss of consciousness.

Children with epiglottitis are at risk for total airway obstruction. The enlarged, inflamed supraglottic ring can progress to respiratory obstruction with unexpected suddenness. Epiglottitis progresses to death in about 7% of children who do not have a secured airway. With accurate early recognition and elective intubation, the mortality rate should approach zero. Most deaths occur in the community, during transit to hospital or in the first few hours after arrival.

Chronic epiglottic enlargement may be seen with neck radiotherapy for cancer, granulomatous lymphangitis, or lymphangiectasis and in infection with the human immunodeficiency virus.[197] The chronicity of symptoms makes these conditions easily distinguishable from acute epiglottitis.

Similarly, congenital anomalies of the airway and laryngeal papillomatosis are usually quite distinct.

Diagnosis

Investigations should be left until the airway is secured. The diagnosis is confirmed under direct visualization. Detection of the responsible organism is important for guiding antibiotic management. Direct culture of supraglottic tissues reveals the causative organism in the majority of patients. The blood culture may also be positive. Blood leukocyte counts, mainly polymorphonuclear leukocytes, are increased. The numbers of immature neutrophils are increased in most cases. The level of C-reactive protein is usually raised.

The diagnosis is often clear from the specific clinical signs. However, it is sometimes difficult to differentiate epiglottitis from severe viral croup of a more rapid onset. Distinguishing features include the absence of spontaneous cough and the presence of drooling and agitation.[198] Toxicity, high fever, and sore throat may also occur with bacterial tracheitis, uvulitis, and retropharyngeal or parapharyngeal abscess. Nasopharyngeal diphtheria is now rare but may mimic acute epiglottitis and is associated with serosanguineous discharge. Noninfectious causes mimicking epiglottitis include angioedema, a pharyngeal burn, and a foreign body that is in the valleculae or larynx or that penetrates the posterior pharyngeal tissues.

Lateral radiographic views of the soft tissues of the neck may be needed if a laryngeal foreign body is suspected, but the patient's airway must be carefully monitored throughout the procedure. The best view of the anatomic structures of the upper airway is obtained with the patient upright. The hypopharynx is dilated, and the normal cervical lordosis may be replaced by a straight or kyphotic contour. The valleculae are narrowed and may be obliterated. A thickened mass of tissue extends from the valleculae to the arytenoid muscles (Fig. 32-9).

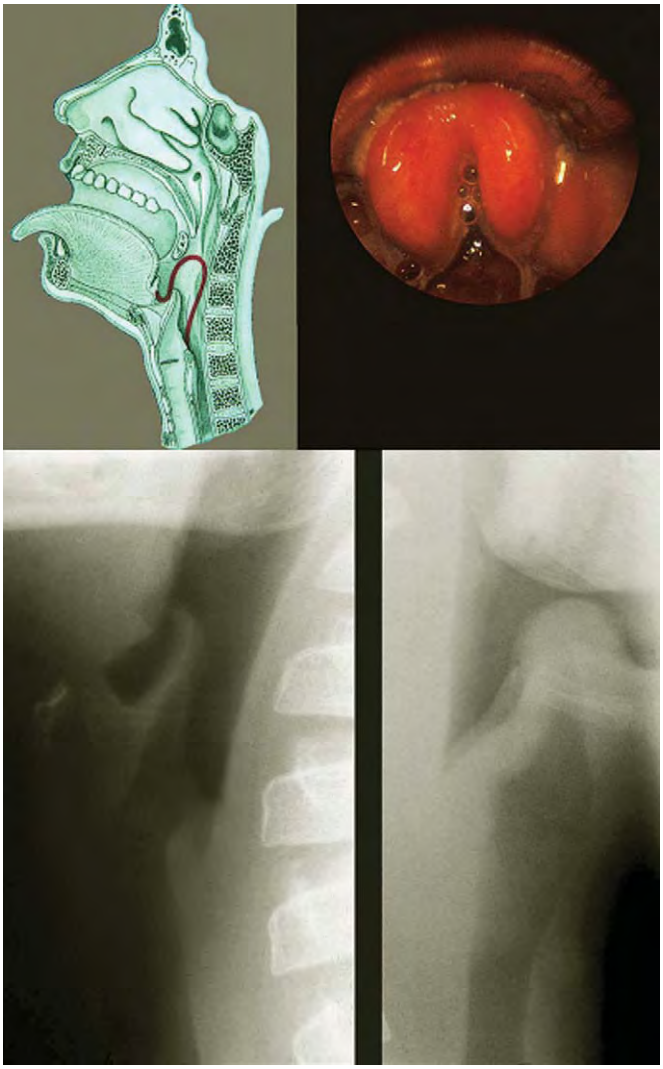

Figure 32-9 Schematic (*top left*) and endoscopic (*top right*) views of epiglottis. *Bottom,* Lateral neck radiographs of a normal child (*left*) and a child with the typical thumb sign (*right*). (From Hammer J: Acquired upper airway obstruction. Paediatr Respir Rev 5:25-33, 2004.)

Treatment

Because of the high risk of complete airway obstruction, great care should be taken in treating epiglottitis. Once a physician suspects this diagnosis, the child should be constantly attended by an individual skilled in resuscitation using the appropriate equipment for airway stabilization and ventilatory support. Delays of 2 to 3 hours have proved fatal. Every effort should be made to reduce the time needed to secure a patient's airway and initiate antibiotic therapy. During this waiting interval, unnecessary stress for the child should be prevented; the throat should not be examined. Extensive clinical assessment, transport delay, and blood tests should be avoided.

The airways should be secured as early as possible after diagnosis. A large body of literature attests to the safety and efficacy of elective nasotracheal intubation, which is the treatment of choice. A short period of airway maintenance is usually all that is required. A nasotracheal tube that is 0.5 mm smaller than that predicted by the patient's age is recommended. Expert nursing care is essential to prevent inadvertent extubation, particularly in the first 12 to 18 hours. The criteria for extubation include being afebrile and swallowing comfortably. Repeat examination of the epiglottis and supraglottic structures by direct laryngoscopy or fiberoptic bronchoscopy is not normally necessary.

Until the results of sensitivity tests are known, the child should be treated with a broad-spectrum intravenous antibiotic to cover the majority of possible isolates. Initial treatment is usually a second-generation cephalosporin such as cefuroxime (if meningitis is not present) or a third-generation cephalosporin such as cefotaxime or ceftriaxone. If the isolate is proved to be susceptible, ampicillin, a cheaper agent, may be substituted. If *S. pyogenes* is isolated from the airway, penicillin is the drug of choice. When *S. aureus* is isolated, a semisynthetic penicillinase-resistant penicillin or glycopeptide such as vancomycin should be used depending on sensitivity patterns. Erythromycin should be used for *C. diphtheriae*.

No controlled studies address the duration of antibiotic treatment, but a course of 7 days of intravenous administration (until the child is afebrile for 48 hours) followed by oral

therapy is commonly used. Ceftriaxone in a single daily dose of 100 mg/kg for 5 days is effective.[199]

Although there have been some recommendations to use corticosteroids, no controlled data support their use; in fact, they may be hazardous because of the side effects. Therapy with inhaled epinephrine is of no benefit.

Clinical Course and Prognosis

Complications are uncommon.[200] Evidence of pneumonia or atelectasis is sometimes seen on the chest radiograph. Other findings may include exudative tonsillitis, cervical lymphadenitis, and otitis media. Meningitis, septic arthritis, and pericarditis occurring with epiglottitis are rare; routine lumbar puncture is unnecessary.

In about 10% of children with epiglottitis in whom there is severe airway obstruction, idiopathic pulmonary edema may occur before or after insertion of endotracheal tubes.[176] The hypothetical mechanism is an increased pulmonary blood flow secondary to airway obstruction, causing markedly negative intrapleural pressure with increased venous return to the right side of the heart and decreased left ventricular output. These changes increase the pulmonary microvascular pressure and produce pulmonary hyperemia and edema. Endotoxemia may play a role in altering vascular permeability, but it is not a necessary prerequisite. Continuous positive airway pressure in intubated patients may decrease the occurrence of pulmonary edema.

Complications occurring after extubation include laryngeal edema and subglottic granulations. Long-term complications of nasotracheal intubation are rare. Tracheostomy is lifesaving but has been replaced by safer nasotracheal intubation.

Secondary disease can occur in household contacts of epiglottitis due to Hib. Epiglottitis has also occurred in household contacts of meningitis resulting from Hib. Rifampin (Rifampicin) prophylaxis eradicates nasopharyngeal carriage and is recommended as follows: a dosage of 20 mg/kg/day (600 mg maximum per dose) for 4 days for all members of a patient contact group when the index case has invasive Hib and there is at least one contact who is 4 years of age or younger. For patients younger than 2 years of age, prophylaxis is required for the child and all household contacts.[201]

Prevention of invasive Hib infection is now universally recommended using one of the approved polysaccharide conjugate vaccine regimens for children up to 5 years of age. These vaccines are highly effective in lowering the incidence of invasive epiglottitis resulting from Hib[202,203] (Box 32-21).

BACTERIAL TRACHEITIS

Bacterial tracheitis is uncommon but potentially life threatening. It is characterized by thick membranous tracheal secretions. These do not clear with coughing and can occlude the airway and cause death.[204]

Epidemiology, Risk Factors, and Pathogenesis

The age group most commonly affected is similar to that for viral croup with a mean age of 4 years.[204]

BOX 32-21 Epiglottitis Teaching Points

- Since the introduction of vaccines that protect against *H. influenzae* type B infection, epiglottitis has become a rare disease.
- Most cases now occur in adolescents and adults.
- The onset is typically abrupt, with duration of symptoms before presentation to the hospital usually less than 24 hours.
- Children with epiglottitis are at risk of total airway obstruction and can progress to respiratory obstruction with unexpected suddenness.
- The diagnosis is confirmed under direct visualization. Other investigations are deferred until the airway is secured.

Direct bacterial infection of the tracheal mucosa is caused by the organisms listed in Box 32-22. *S. aureus* is the most common bacteria reported.[205] A significant proportion of infections are polymicrobial.[204] *Moraxella catarrhalis* is described to be more frequent in younger children and to be associated with a more severe course, although this may be due to its association with younger age.[204]

Influenza virus, parainfluenza virus, and enterovirus have been isolated in children with bacterial tracheitis, suggesting that bacterial invasion may occur in an airway already inflamed by viral infection. Bacterial tracheitis is a recognized complication of measles.[206]

The bacterial infection causes a diffuse inflammatory process of the larynx, trachea, and bronchi with mucopurulent exudate and semiadherent "membranes" within the trachea. These membranes contain numerous neutrophils and cellular debris and cause major obstruction.

Clinical Features

In most children, there are prodromal upper respiratory tract symptoms. Bacterial tracheitis usually presents as severe upper airway obstruction, most often in a child who has had viral croup for several days. Not all children present with high fever, systemic toxicity, and severe airway obstruction. In some, particularly those who are older, the illness can remain localized to the trachea.[204]

BOX 32-22 Causes of Bacterial Tracheitis

Common Causes

Haemophilus influenzae type b and nontypable *Haemophilus influenzae*
Klebsiella pneumoniae
Staphylococcus aureus
Streptococcus pneumoniae
Streptococcus pyogenes group A

Rare Causes

Moraxella catarrhalis
Pseudomonas spp.

The differential diagnosis includes severe viral croup, laryngeal or tracheal foreign body aspiration, or epiglottitis. Bacterial tracheitis has a longer duration, a more typical barking cough than epiglottitis, and no drooling. Diphtheria was once a serious consideration as the most common cause of "membranous croup" that produced severe airway obstruction because of adherent membranes that separate from the airway wall with difficulty, causing bleeding.

Diagnosis

The definitive diagnosis requires direct laryngoscopy and tracheoscopy.[207] Bacterial cultures of tracheal secretions are required to isolate causative organisms. The results from blood cultures are usually negative. White blood cell counts may be high or normal.

Endoscopy reveals thick mucopus and sloughed epithelium. The epithelium forms a sheet-like pseudomembrane that separates easily from the airway wall without hemorrhage and sometimes extends from the trachea to the major bronchi.

A lateral neck radiograph shows subglottic narrowing and often reveals findings of radiopaque material in the airway lumen (pseudomembrane) and tracheal irregularities.[204,208] Plain radiographic abnormalities can be confused with those due to a foreign body.

Treatment

Specific diagnosis and treatment are secondary to definitive treatment of impending airway obstruction.[207] In a child suspected of having bacterial tracheitis, management should occur in a pediatric intensive care unit. At least half of children with bacterial tracheitis will need to be intubated.[204] Intermittent positive-pressure breathing is sometimes needed. Repeated suctioning is usually required because of the thick secretions and their tendency to form crusts, with intubation lasting 3 to 11 days. Sometimes, repeat endoscopic removal of the pseudomembrane is required. Occasionally, tracheostomy is needed if endotracheal tube management of secretions proves too difficult.

Empirical antibiotic choice should provide broad-spectrum gram-positive and gram-negative cover. Appropriate first-line choices include amoxicillin/clavulanic acid, cefuroxime, and ampicillin + sulbactam.

Nebulized epinephrine or corticosteroids do not relieve the acute airway obstruction.

Clinical Course and Prognosis

With effective early management, children should make a complete recovery from this severe illness. Reported complications include toxic shock syndrome, septic shock, pulmonary edema, and acute respiratory distress syndrome (Box 32-23).

BOX 32-23 Bacterial Tracheitis Teaching Points

- Bacterial tracheitis is characterized by thick tracheal membranes, which can occlude the airway and cause death.
- It occurs in both the preschool- and school-age groups and can present either with fever and systemic toxicity or as more localized disease.
- Definitive diagnosis requires laryngoscopy and tracheoscopy.
- The etiology can be polymicrobial.
- At least half of children with bacterial tracheitis will need to be intubated.
- Children with this condition should be managed initially in the intensive care unit.
- Broad-spectrum intravenous antibiotics are required.

RECURRENT RESPIRATORY PAPILLOMATOSIS

Juvenile recurrent respiratory papillomatosis (RRP; also known as laryngeal papillomatosis) is a rare condition with benign, wart-like tumors in the respiratory tract, especially the larynx, usually associated with upper airway obstruction, which can become life threatening.[209]

Epidemiology, Risk Factors, and Pathogenesis

The incidence of recurrent respiratory papillomatosis has been estimated as 4.3 per 100,000 children.[210] It occurs at all ages, with about half of all cases appearing in children and the youngest reported patient being 1 month of age.[211]

Human papillomavirus (HPV) types 6 and 11 cause about 90% of cases of recurrent respiratory papillomatosis.[212,213] Type II is more virulent, associated with earlier presentation and more surgical procedures.[212] Occasional coinfection with other viruses has been demonstrated (e.g., herpes simplex, cytomegalovirus, Epstein-Barr virus) and is associated with a more aggressive course.[214] The replicating virus may cause overgrowth of squamous epithelial cells. The papillomata are multiple projections, each with a connective tissue stalk covered by well-differentiated stratified squamous epithelium. The viral antigen is localized in the nuclei of cells in the very superficial layers. Papilloma occur in the larynx, trachea, bronchi, and lung parenchyma.

There is debate about the mechanism of infection with HPV. The same types of HPV that cause perineal condylomata in women also cause juvenile recurrent respiratory papillomatosis. Children can acquire the infection during the birth process from the mother with perineal condylomata.[215-217] However, there are many children in whom there is no evidence of maternal HPV infection in whom the source of infection remains obscure. Host susceptibility has been investigated in a limited number of patients, and only one child has been found to have IgG_2 subclass deficiency.[218]

Clinical Features

In the pediatric age group, about half of patients have symptoms within the first year of life, although clinical recognition of the disease is often delayed. Patients usually come to medical attention late, with respiratory distress due to airway obstruction and stridor, together with hoarseness or a weak cry. Life-threatening upper airway obstruction may occur

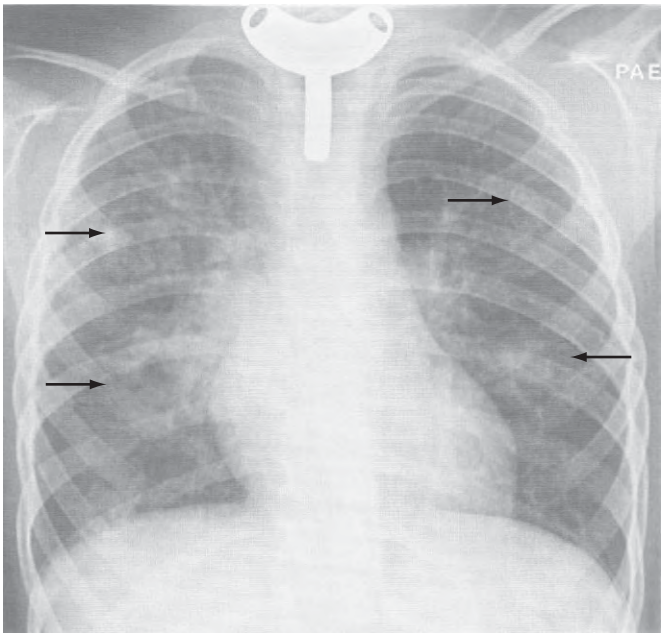

Figure 32-10 In a 13-year-old boy with a tracheostomy tube placed due to laryngeal papillomatosis, chest radiograph shows multiple nodular processes (*arrows*), some of which are cavitating, caused by parenchymal dissemination of the papillomatosis. (From Diagnostic imaging of the respiratory tract. In Chernick V, Boat TF, Wilmott RW, Bush A [eds]: Kendig's Disorders of the Respiratory Tract. Philadelphia, WB Saunders, 2006.)

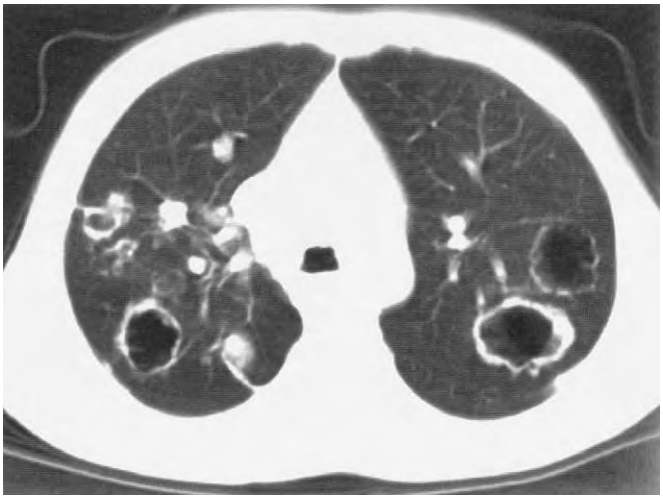

Figure 32-11 Chest computed tomography scan of an 8-year-old girl with laryngotracheal papillomatosis shows multiple peripheral nodules and cavities with posterior dominance, in keeping with pulmonary dissemination. (From Diagnostic imaging of the respiratory tract. In Chernick V, Boat TF, Wilmott RW, Bush A [eds]: Kendig's Disorders of the Respiratory Tract. Philadelphia, WB Saunders, 2006.)

and, less commonly, chronic cough, recurrent pneumonia, failure to thrive, dyspnea, and dysphagia.[209] Although the lesions are usually localized within the larynx, spread to other areas (pharynx, esophagus, trachea, and lung parenchyma) may occur and indicates a more pessimistic outlook.[211] When the lung parenchyma is involved, lung tissue may be destroyed with multiple nodular and cystic lesions (Figs. 32-10 and 32-11). Pneumothorax can occur after the development of cystic pneumatoceles, presumably from the ball-valve effect of a nodular lesion.[219]

The tumors are benign but present obstructive problems because of their localization in the vocal cords or other sites. At presentation, papillomas are usually present on one or both vocal cords with the anterior commissure, supraglottis, or subglottis also commonly affected.

Diagnosis

The condition is diagnosed by inspection of the larynx, either by indirect means such as fiberoptic laryngoscopy or by formal laryngoscopy and bronchoscopy when tissue biopsy samples can be taken for histologic confirmation. The virus signal can be identified in the tissue biopsy, but its intensity does not generally correlate with the clinical behavior of the disease.

Multiple endoscopies are usually required for further investigation and management, and flexible bronchoscopy is the method of choice for surveillance.

A staging system has been developed by Derkay and colleagues[209] with good interobserver reliability.[220] It includes area and severity of involvement, characteristics of voice, and respiratory distress.

Treatment

PREVENTION

Vaccines against HPV types 6, 11, 16, and 18 have been developed to prevent cervical cancer. Vaccination against HPV is likely to be recommended for use in 11- to 12-year-olds.[213] Because of the timing of the vaccination, it is unlikely that it will have an impact on the prevalence of RRP in childhood but could potentially reduce early childhood disease in the next generation.

TREATMENT OF DISEASE

The goals of treatment are to relieve airway obstruction, improve voice quality, and minimize the risk of recurrence. Recurrent respiratory papillomatosis is frustrating to treat because lesions are often recurrent after excision and sometimes locally aggressive. The focus of management is to debulk the papilloma and ensure a safe airway without causing irreversible long-term scarring, especially affecting the voice. Total surgical removal of the disease is impossible in most cases because subclinical viral infection occurs in apparently normal adjacent areas and the degree of destruction necessary to clear the field would require too great a degree of tissue damage.

The carbon dioxide laser is the most widely used surgical tool for removing recurrent respiratory papilloma, vaporizing the papilloma. However, it does not prevent regrowth any better than the older surgical methods, such as direct removal or suction diathermy. Photodynamic therapy has been used, pretreating the patient with a hematoporphyrin derivative and then subjecting the lesion to an argon dye laser beam at a 630-nm wavelength.[221] If possible, tracheotomy should be avoided because of seeding of the disease to the tracheotomy site.

Historically, clinicians have used numerous other therapeutic modalities, including cryotherapy, painting of the

lesions with podophyllin, indole-3-carbinol, photodynamic therapy and antimetabolites, vaccines, and immunotherapy, but the results have been generally poor.

Adjuvant antiviral therapy with acyclovir or ribavirin, or cidovir injected into the lesions has been considered, but there are no controlled clinical trials.[222]

Interferon-α used with surgery has disappointing results. Although most studies have shown a dramatic decrease in the frequency of regrowth immediately after beginning such treatment, regrowth gradually occurs. In one large multicenter, randomized study,[223] interferon was neither of curative nor of substantial value as an adjunctive agent after 1 year of treatment. In another study of 66 patients,[224] there was a 33% sustained complex remission rate, leading the authors to suggest a 6-month trial of interferon-α in children requiring surgery at 2- to 3-month intervals. Although this agent is moderately well tolerated, the almost universal side effects of mild influenza-like symptoms are unpleasant, and the frequent parenteral mode of delivery is disliked, particularly in the younger age group. Interferon therapy may be used in particularly aggressive disease, but it should not be continued beyond 12 months unless the disease responds.[225] In less severe cases, the indication is not absolute.

Clinical Course and Prognosis

The most usual course of the disease is for the papilloma to continue to grow locally despite surgical removal and without significant spread. Over time, the majority of cases in children undergo spontaneous remission (analogous to skin warts). Death is rare. Malignant change to squamous cell carcinoma has been reported in 3% to 5%, mainly in adults.[226] The now-abandoned treatment of these lesions with radiotherapy has been implicated in ensuing malignancies in the pediatric age group (Box 32-24).

BOX 32-24 Recurrent Respiratory Papillomatosis Teaching Points

- Papillomas are projections with squamous epithelium infected with human papillomavirus on a connective tissue stalk.
- They cause airway obstruction, especially around the larynx.
- Diagnosis is often delayed.
- Interferon is considered for aggressive cases.

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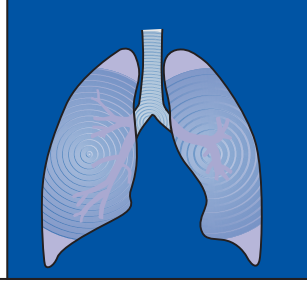

CHAPTER 33 Viral Infections of the Lower Respiratory Tract

Sean P. Elliott and C. George Ray

TEACHING POINTS

- The majority of all childhood lower respiratory illnesses are caused by viral agents.
- In healthy patients, the course of viral respiratory infections is usually relatively predictable in terms of both the nature of onset and the duration of the acute phase.
- When abrupt deviations in the course of an acute viral illness occur, the possibility of bacterial superinfection must be considered.
- Of the more recently recognized viral agents, human metapneumovirus stands out as an important cause of respiratory syncytial virus–like illness.

Worldwide, it is estimated that 3 to 5 million children die annually as a result of acute respiratory disease. In the United States, respiratory diseases account for 75% to 80% of all acute morbidity. Viral infections are the greatest contributors to this morbidity rate, causing approximately 80% of respiratory illness. Many of these infections produce mild, self-limited symptoms of the upper respiratory tract. Lower respiratory tract illness (LRI), particularly that associated with the presence of crackles or wheezes on physical examination or as parenchymal disease on a chest radiograph, accounts for the majority of severe disease. One third of children develop LRI in the first year of life.[1] Childhood asthma may be initially difficult to discriminate from LRI in some patients; indeed, both conditions can be present simultaneously.

Although 60% or more of LRIs are primarily viral[2] (Table 33-1), the concern often remains as to whether bacterial infection is present, as either a primary problem or a complication of viral infection. Of the bacteria, *Streptococcus pneumoniae* is by far the most common, followed by *Haemophilus influenzae* and *Staphylococcus aureus*. Clinical features that suggest these causes include an abrupt onset or a change in symptoms over a few to several hours, toxicity, and radiographic findings of parenchymal consolidation, pleural effusions, or both. White blood cell counts are of variable help, but extreme leukocytosis (>20,000 cells/mm^3) or increased neutrophil band counts (>1500 cells/mm^3) suggest possible bacterial involvement. However, such findings are not absolute; severe viral infections can produce leukocytosis and variable shifts to the left. Conversely, overwhelming bacterial pneumonia can present with ominous leukopenia. The magnitude of fever is thought by some to be helpful in determining the possible presence of a bacterial infection, but viral LRI can also provoke high fevers, which may persist for several days or longer. Serum levels of procalcitonin and C-reactive protein have shown the most promise to date in distinguishing serious bacterial infection from virus-caused disease, but these findings remain untested in respiratory diseases.[3,4]

Other nonviral agents include *Chlamydia trachomatis*, *Chlamydia pneumoniae*, *Mycoplasma pneumoniae*, *Mycobacterium tuberculosis*, deep mycoses, and *Pneumocystis jirovecii*. C. *trachomatis* pneumonia is most common among infants between 2 weeks and 6 months. Characteristically, the onset of respiratory symptoms is insidious over several days, the infant is usually afebrile, and air trapping with interstitial infiltrates is often apparent on chest radiographs. Symptomatic *M. pneumoniae* infections are uncommon in children younger than 5 years; however, they frequently cause pneumonia among children in the 5- to 19-year age group.[5] C. *pneumoniae* infections appear to follow clinical and age-specific patterns similar to those of *M. pneumonia* infections, but more data are needed before such a comparison can be confirmed.[6] Tuberculosis and deep mycoses should be considered when the symptoms and radiographic abnormalities insidiously progress over days to weeks. Finally, *P. jirovecii* infections are suggested in patients who have progressive hypoxemia (often without significant hypercarbia), alveolar infiltrates, and significant risk factors such as congenital or acquired immunodeficiency, malignancy, and severe protein malnutrition.

A common clinical dilemma occurs in reliably discerning treatable causes, such as bacteria, from viral agents that may not be susceptible to specific therapies. Often, the choice is made to treat nearly all young patients who have an acute LRI with an antibiotic in case a bacterial agent is involved. Such therapy is useless in viral disease and has not been shown to alter the risk of bacterial superinfection; furthermore, such a practice can result in the selection of more resistant organisms if secondary infection does occur. With the emergence of molecular diagnostic methods, a timely, specific diagnosis of many viral LRIs is possible. In addition, specific antiviral therapy is available for some viral

Table 33-1
Major Causes of Acute Lower Respiratory Tract Illnesses

Syndrome	Viruses	Nonviral Agents	Estimated Percentage Caused by Viruses
Epiglottitis	Rare	*Haemophilus influenzae, Streptococcus pyogenes, Streptococcus pneumoniae, Neisseria meningitidis, Corynebacterium diphtheriae*	5-10
Laryngitis and croup	Parainfluenza viruses, influenza viruses, adenoviruses, respiratory syncytical virus, human metapneumovirus, rhinoviruses, coronaviruses, echoviruses	Rare	90
Laryngotracheitis and laryngotracheobronchitis	Same as for laryngitis and croup	*H. influenzae, Staphylococcus aureus*	90
Bronchitis	Parainfluenza viruses, influenza viruses, respiratory syncytial virus, human metapneumovirus, adenoviruses, coronaviruses	*Bordetella pertussis, Bordetella parapertussis, H. influenzae, Mycoplasma pneumoniae, Chlamydia pneumoniae*	80
Bronchiolitis	Respiratory syncytial virus, parainfluenza viruses, human metapneumovirus, influenza viruses, adenoviruses	*Chlamydia trachomatis, C. pneumoniae, M. pneumoniae*	90
Pneumonia	Same as for bronchiolitis	*M. pneumoniae, C. trachomatis, C. pneumoniae, S. pneumoniae, H. influenzae, S. aureus, Legionella* species, *N. meningitidis,* mixed aerobic and anaerobic flora*	70-80

*Aspiration-related and lung abscess.

infections and may reduce both the morbidity and the mortality rates.

Despite the concern of bacterial coinfection, viral infections remain the most common causes of pediatric LRIs, especially among children younger than 5 years.[7,8] Of these, respiratory syncytial virus (RSV); human metapneumovirus (hMPV); parainfluenza virus types 1, 2, and 3; influenza virus types A and B; and adenoviruses comprise the majority.[7] Rhinoviruses, human coronaviruses (HCVs), influenza virus type C, and parainfluenza virus type 4 are known to have roles in upper respiratory disease, but relatively little is known about their contribution to LRI. Other viruses, such as Epstein-Barr virus (EBV), cytomegalovirus (CMV), and human herpesvirus-6 (HHV-6), have been associated occasionally with LRI, either as primary pathogens or as possible cofactors with other agents. All three increase in overall importance in the setting of immunocompromise; this is especially true for CMV.[9] Measles virus has a long history as a significant cause of LRI. Although eradication of this virus seems possible, it remains a significant problem in underdeveloped nations.

RESPIRATORY SYNCYTIAL VIRUS

RSV is the most common cause of lower respiratory infection in infants and young children, although infants younger than 2 years are most frequently and severely affected. RSV causes a range of illnesses, including croup, tracheobronchitis, bronchiolitis, pneumonia, or some combination thereof, and is associated with such complications as progressive pulmonary failure, cor pulmonale, and a risk of bacterial superinfection. Some evidence suggests there may be a strong association between severe RSV LRI in infancy and asthma or allergic airways disease in childhood. RSV is discussed thoroughly in Chapter 34.

HUMAN METAPNEUMOVIRUS

Human metapneumovirus (hMPV) is an infectious agent that apparently has existed for a long time but only recently (2001) has been recognized as a major cause of LRI. Initially described in patients with LRI in the Netherlands,[10] hMPV has now been identified in pediatric and adult patients with LRI worldwide. hMPV is in the same subfamily of Paramyxoviruses as RSV and displays the same syncytial formation in cell culture. Although comparative prevalence studies are difficult to evaluate due to differences in sensitivity of detection methods, hMPV certainly appears to cause a significant portion of LRI worldwide. In one prospective 25-year study, hMPV prevalence was 12% in nasopharyngeal samples from patients with LRI, compared with 15% RSV, 10% parainfluenza virus, and 5% influenza virus.[11] Infection usually occurs during childhood, causing hMPV seropositivity in up to 52% of 24-month-old infants and 100% of 5-year-old children.[12,13] Like RSV, hMPV has a seasonal pattern, causing its greatest impact in the winter months. Coinfection with hMPV and other respiratory viruses occurs and appears to increase the severity of illness.[14]

Clinically, hMPV infection is similar to RSV disease and includes mild upper respiratory tract disease, influenza-like symptoms (including fever, myalgia, and vomiting), croup, pneumonia, and, most commonly, bronchiolitis.[11,13] Patients typically present with symptoms commonly seen with RSV but, in general, have less severe signs of respiratory distress (Table 33-2). However, patients with immunocompromise or extremes of age are at higher risk for more severe LRI.

Table 33-2
Clinical and Radiologic Findings in Patients with Human Metapneumovirus (hMPV) Compared with Those with Respiratory Syncytial Virus (RSV)

	Percent of Patients with hMPV	Percent of Patients with RSV
Clinical findings		
Cough	72-90	76
Rhinitis	80-88	72
Fever	52-61	48
Retractions	60	64
Hypoxemia	47	82
Anorexia	33-36	76
Wheezing	22-24	32
Chest radiograph findings		
Atelectasis	40	19
Hyperinflation	33	44
Infiltrate	33	31
Bronchial thickening	0	13

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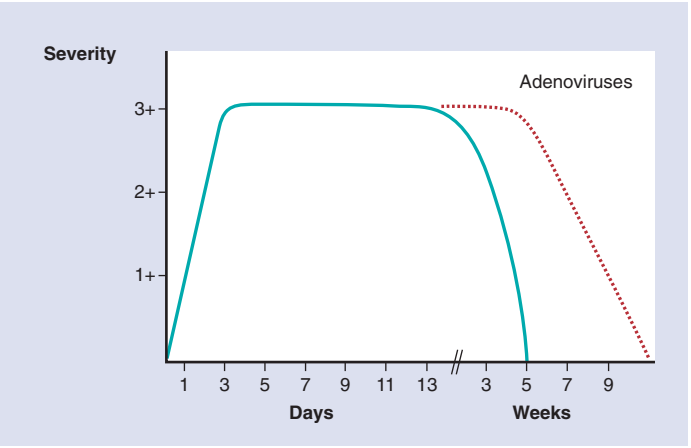

Figure 33-1 Natural history of lower respiratory tract illnesses caused by RSV and parainfluenza viruses, as measured by severity and duration in normal patients (*blue line*). The prodrome with upper respiratory symptoms usually progresses to lower tract involvement over 1 to 3 days. Maximal severity persists as a "plateau" phase for 7 to 21 days (average, 10 days), followed by progressive recovery in the succeeding few weeks. The hatched red line illustrates the similar but more protracted course often seen with severe adenovirus infections.

Patients hospitalized for hMPV-associated LRI require similar length of hospital stays to RSV patients (6 to 7 days[15]). The relationship of hMPV to asthma and reactive airways disease is unclear as studies have demonstrated both positive and negative impacts.

Diagnosis of hMPV is difficult because the virus does not grow readily on routine cell cultures. Reverse transcription–polymerase chain reaction (RT-PCR) assays are the currently available identification methods of choice. Serologic (immunofluorescence and enzyme-linked immunosorbent assays [ELISAs]) testing is not readily available and is compromised by near universal infection in childhood: a ≥4-fold rise in antibody titers must be demonstrated to confirm recent infection.[16] Management of hMPV infection remains supportive, although studies evaluating the effect of ribavirin and intravenous immunoglobulin preparations are in progress. Bronchodilators such as albuterol may benefit those patients with wheezing as part of their symptom complex, but corticosteroids have no demonstrated impact. Prevention of hMPV infection remains the most desirable form of intervention, but no studies on hMPV vaccine products for humans have been reported.[16]

PARAINFLUENZA VIRUSES

The parainfluenza viruses represent the next most common cause of LRI in children younger than 5 years.[8] Parainfluenza virus type 3 is the most common cause of LRI among this group. Such infections can be seen at any time during the year but are most common in the spring and summer.[17] Localized outbreaks of upper respiratory illness, bronchitis, and croup caused by parainfluenza virus types 1 or 2 frequently occur in the autumn and early winter. Parainfluenza virus type 4 is rarely detected and has been associated primarily with upper respiratory symptoms.

The clinical course of parainfluenza virus infection is similar to that described for RSV as depicted in Figure 33-1. Initial symptoms are mild nasal stuffiness and coryza, with variable progression over 1 to 3 days as the infection progresses downward in the respiratory tract causing cough as a predominant manifestation. Parainfluenza 3 often causes bronchitis, pneumonia, and croup in children younger than 1 year. Patients with immunocompromise are at increased risk for serious morbidity and mortality from parainfluenza 3–associated pneumonia.[18] Duration of acute illness can vary from 4 to 21 days but is usually 7 to 10 days.

The basic principles of management for parainfluenza LRIs are the same as those described elsewhere for RSV. When eating and drinking become difficult for the patient, adequate fluids usually need to be provided via an intravenous route. Humidified oxygen is also given when hypoxemia is present, usually beginning at a concentration of 30% to 40%. In severe cases, the oxygen concentration is increased as guided by blood gas determinations. If there is clinical evidence of progressive respiratory failure, endotracheal intubation with mechanical ventilatory assistance is required.

Bronchodilators also may be tried but must be administered cautiously and discontinued if no clear-cut benefit can be demonstrated. Corticosteroids have no demonstrated role in treatment of lower respiratory infection. Their role in upper respiratory infection is discussed elsewhere. Parainfluenza types 1 and 3 are susceptible in vitro to ribavirin, but no controlled clinical trials yet support its use in these infections.

INFLUENZA VIRUSES

The epidemiology of influenza virus types A and B is generally well known: rapidly evolving outbreaks that usually occur during the cooler months of the year. Both types can cause serious, lethal LRI in infants and children.[19] The clinical course contrasts with that of RSV and parainfluenza viruses

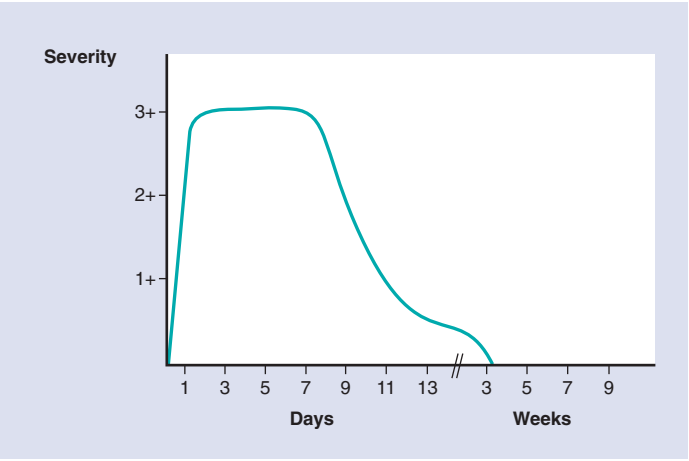

Figure 33-2 Natural history of influenza in normal patients, as measured by severity and duration. Initial symptoms of fever and malaise develop and reach maximal severity over the first 12 to 24 hours and are followed by additional respiratory symptoms. Maximal severity persists for 3 to 7 days (shorter than for RSV and parainfluenza), followed by convalescent period lasting several weeks.

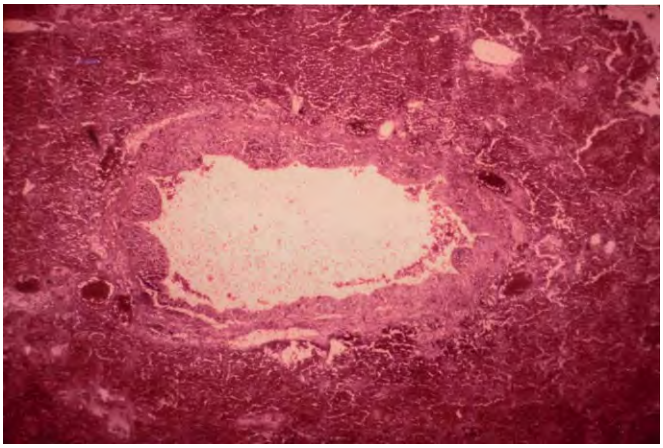

Figure 33-3 Photomicrograph demonstrating bronchiolar necrosis and hemorrhage in a case of overwhelming influenza (original magnification ×100).

in that fever, malaise, and often myalgia usually develop and rapidly become more severe over 12 to 24 hours (Fig. 33-2). Nasal congestion, cough, and subsequent respiratory distress often do not appear until a day or two after the onset of systemic symptoms. Although the mean overall duration of the acute illness (3 to 7 days) is somewhat shorter than with RSV or parainfluenza viruses, the convalescent phase often lasts several weeks, and rapid deterioration as a result of bacterial superinfection can occur at any time in the course. Rarely, patients may develop a rapidly progressive, overwhelming viral pneumonia resulting in death within 2 to 3 days after the initial onset (Fig. 33-3). Pandemic influenza has occurred three times in the past century, causing unusually severe, hemorrhagic pneumonia and millions of deaths. The pathogenicity of these pandemics appears related to a lack of neutralizing serum immunity against the pandemic strain, presumably due to antigenic drift of its hemagglutinin antigen.[20,21]

Diagnosis and basic management are similar to those described for RSV and parainfluenza viruses. Oral amantadine hydrochloride is somewhat effective in treating influenza A but is ineffective against influenza B. If begun within 24 to 48 hours of onset and continued for 5 to 7 days, it may reduce the duration of fever and systemic symptoms and result in a more rapid improvement of peripheral airways function.[22] It also has use as prophylaxis in high-risk children during influenza A outbreaks. A related drug, rimantadine, is also effective and appears to produce fewer adverse effects than amantadine.[22,23] The rapid development of viral resistance to both amantadine and rimantadine has been observed, particularly when either medication is used in households for the simultaneous treatment of symptomatic infection and contact prophylaxis.[24]

The neuraminidase inhibitors (zanamivir and oseltamivir) can also significantly reduce duration and symptom severity of influenza, if begun within 30 hours of onset. Importantly, both agents have efficacy against influenza A and B, are well tolerated, and appear to be associated with viral resistance infrequently.[25]

The combination vaccines for influenza virus types A and B are evaluated annually and reformulated as necessary to antigenically match the strains expected to circulate widely in a subsequent year. Their protective efficacy varies from year to year, ranging between 50% and 95% in immunologically normal individuals older than 6 months. Efficacy in the first 6 months of life is not known, and the influenza vaccine is not recommended for this group; otherwise, annual immunization commencing in the autumn can be used in persons of all ages, except those who have experienced anaphylactic reactions to chickens or eggs. Two doses administered 1 month apart are recommended for children receiving the vaccine for the first time. An intranasal, live attenuated influenza vaccine is also available for children and adults from 5 to 49 years old. This product is highly effective and well tolerated and provides an alternative to further injections. However, it is contraindicated for the high-risk, immunocompromised patient populations, for whom influenza vaccination is recommended.

Children who especially should be immunized annually against influenza include those with chronic pulmonary, cardiac, hematologic, immunologic, and metabolic conditions and those receiving long-term salicylate therapy. In addition, household contacts of these high-risk children and other caregivers (e.g., nurses, physicians, therapists) should be targeted. If an annual immunization is missed and a significant exposure is subsequently suspected (e.g., during a documented outbreak), immunization followed immediately by chemoprophylaxis with amantadine or rimantadine for 2 weeks after the vaccine schedule of one or two doses has been completed can provide "bridging" protection until there is a vaccine response.

Influenza virus type C has been reported to cause outbreaks of febrile respiratory illnesses, especially among pediatric clinic patients and children younger than 3 years. A survey in Los Angeles detected a 64% prevalence of antibodies to this virus among children 5 years and younger.[26] However, longitudinal studies have not supported a significant role for influenza virus type C in LRI, at least among those from birth to 3 years.[17]

Avian influenza A (H5N1) recently has emerged as a highly pathogenic cause of poultry infection in Asian countries that

now has gained the ability to occasionally cause human disease. Influenza A (H5N1) infection in humans is characterized by fever, severe respiratory symptoms, lymphopenia, and a high risk of death.[27] In 2004, at least 44 persons were infected and 32 died; most had direct contact with infected poultry. However, a probable case of person-to-person transmission[28] raises fears of an impending pandemic because few humans will have any immunity against this strain. Chemoprophylaxis with the neuraminidase inhibitors appears to have some benefit, but concerns about emerging viral resistance may limit their use. Thus, such preventive measures as vaccine discovery and prospective poultry screening and culling are critical. Unfortunately, only a few countries have developed influenza pandemic plans and even fewer have the economic and social resources to pursue vaccine development and antiviral stockpiling. Perhaps the greatest impact so far has been the financial reality of domestic poultry destruction in those countries hardest hit by this virus.[29]

ADENOVIRUSES

Adenoviruses are very common causes of fevers, upper respiratory illnesses, and conjunctivitis in young children. Fortunately, they produce LRI only occasionally and sporadically. Adenoviral pneumonia, most commonly caused by types 3, 5, and 7, initially progresses much like the pneumonia described for RSV and parainfluenza viruses (see Fig. 33-1), but the illnesses can be extremely severe and can last for several weeks. Adenovirus types 3 and 7 have been associated with epidemics of LRI.[30] Risk factors for severe, potentially lethal disease include immunocompromise, congenital heart disease, and protein-calorie malnutrition. During the acute phase, chest radiographs often reveal extensive consolidation, particularly in perihilar areas (Fig. 33-4). These findings, along with a frequent occurrence of high fevers, leukocytosis, and multisystem involvement, can make it difficult to discern such infections from bacterial conditions. Other systemic manifestations that sometimes develop are hepatic dysfunction (including Reye's syndrome[31]), encephalopathy, coagulopathies, measles-like exanthems, and diarrhea.[32]

The diagnosis is confirmed best by the detection of the virus in tissues such as lung aspirate or biopsy specimens. Because asymptomatic shedding from the throat or gastrointestinal tract is common in young children, isolation of the virus from the throat must be regarded as diagnostically supportive but not confirmatory, and isolation from stools or rectal swabs needs to be interpreted even more cautiously. Serologic studies of paired acute and convalescent sera obtained at least 2 weeks apart may further aid in confirming the diagnosis. Rapid detection has been used, including immunofluorescence and immunoenzyme assays. Such methods are generally quite specific, but sensitivity ranges between 30% and 60%.

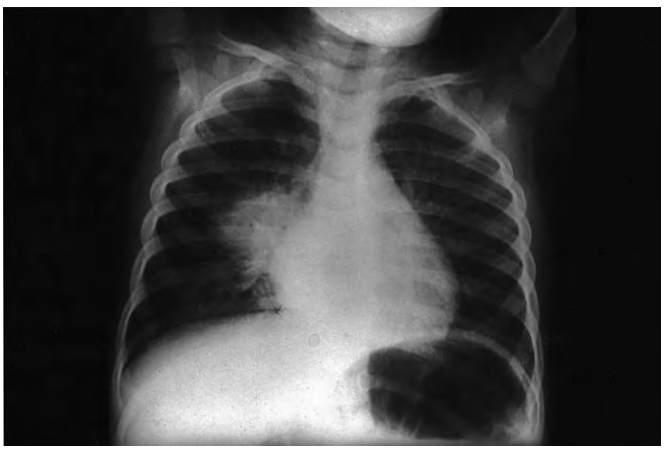

Figure 33-4 Chest radiograph demonstrating extensive perihilar consolidation in a two-year-old patient with adenovirus 3 pneumonia.

Supportive management is all that can be offered at present. These patients must be followed closely because they are at high risk for bacterial superinfection for many weeks. They can also sustain permanent pulmonary sequelae, including pulmonary fibrosis, bronchiolitis obliterans, recurrent wheezing, and bronchiectasis.[33-35] Young age and a previous measles-like illness, as well as nutritional or immunologic deficiencies, have been reported to be risk factors.[34] The persistence of adenoviral antigens and the sustained expression of adenovirus genes in the airway epithelium have been proposed as causes.[35,36]

HUMAN CORONAVIRUSES

Until recently, the role of human coronaviruses (HCoV) in LRIs was not well understood. The two strains most frequently associated with LRI were OC43 and 229E. HCoV OC43 infections produce cough and nasal symptoms in adults and sore throat, cough, coryza, and fever in children.[37] HCoV infections have also been associated with acute attacks of wheezing in children with asthma.[38] In a provocative study of pediatric HCoV LRI,[39] ELISA detected HCoV antigens in 30% of 108 acute respiratory episodes experienced by 30 children younger than 6 years who had a history of at least 10 recurrent respiratory illnesses in the preceding year. In addition, 29% of 51 acute respiratory episodes experienced by the siblings of these patients were also associated with HCoV. Interestingly, 30% of the HCoV infections detected in the former group were associated with LRI symptoms, including wheezy bronchitis, whereas none of the siblings with HCoV had LRI findings. Most infections were due to HCoV 229E, and peaks occurred in the late autumn, early winter, and early summer. Family studies in Seattle have shown that increased levels of antibodies to HCoV strains OC43 and 229E occur more frequently during the winter[40]; children were apparently infected 3 times more often than adults, and serologic evidence suggesting reinfection was frequently observed over 3 years.

Severe Acute Respiratory Syndrome

The 2002 emergence of severe acute respiratory syndrome (SARS) precipitated a new era of international scientific and medical cooperation and led to the discovery of a third coronavirus with human pathogenicity (SARS-CoV).[41,42] The first cases of SARS occurred in China in November 2002 and were followed over the next year by 8098 cases in 26 countries, with 774 deaths.[43] SARS-CoV–like viruses have been detected in raccoon-dogs and Himalayan palm civets in China and also were isolated from such human samples as nasal secretions, serum, feces, and bronchial washings.[42,43] There

is good evidence that bats represent the primary reservoirs of these viruses.[44] Because SARS-CoV has not been demonstrated previously in humans, it appears possible that the virus has crossed the species barrier from animals to humans.[45]

The SARS incubation period ranges from 2 to 10 days, followed by an influenza-like prodrome with such symptoms as fever, myalgias, headache, and watery diarrhea. Respiratory symptoms begin 2 to 7 days after the prodrome and initially include a dry, nonproductive cough and mild dyspnea, accompanied by lung high-resolution CT findings of ground-glass consolidations. Further progression occurs 8 to 12 days later and ranges from a "mild cough variant" with persistent intractable cough to the more common "moderate to severe variant" with hypoxia and dyspnea. Ten percent to 20% of hospitalized patients will require intubation and mechanical ventilation, often heralded by subtle, progressive decreases in oxygen saturation. Recovery begins approximately 14 to 18 days after onset of symptoms.[43,46-48]

Diagnosis of SARS-CoV is available by use of culture and RT-PCR, although the sensitivity of culture is lower than RT-PCR. Specimens obtained 10 days from symptom onset are associated with the highest yield, correlating with the timing of peak virus load. Serologic assays for SARS-CoV include immunofluorescent assays, ELISA, and Western blot assays; however, none is sensitive early enough in the disease course to be useful for rapid diagnosis and thus should be used for paired acute and convalescent-phase serologic diagnosis.[43]

Treatment of SARS remains largely supportive and aimed at those patients who develop respiratory failure. Barotrauma appears to be a frequent complication of SARS-CoV infection, leading to pneumothorax and pneumomediastinum in 20% to 34% of ventilated patients.[49] Thus, a "lung protective" ventilation strategy is recommended for those patients on mechanical ventilation. Other therapeutic interventions have included use of ribavirin, interferon α, lopinavir-ritonavir, and such immunomodulatory therapies as corticosteroids, intravenous immunoglobulin, and plasma exchange.[43] However, no controlled trials have demonstrated benefit in outcome or mortality related to these. Despite the high mortality and devastating impact of SARS-CoV in 2002, the story of its emergence serves to describe a victory due to the worldwide public health measures used successfully to bring the outbreak under control.

A fourth HCoV, NL63, has also been identified and found to cause a significant proportion of acute respiratory disease in humans. Initially described in the Netherlands,[50] HCoV NL63 now has been demonstrated globally, including Australia, Canada, Japan, Belgium, China, Switzerland, and the United States.[51-54] In the United States, the virus currently is named HCoV-New Haven (NH) and most likely represents the same or closely related species as the NL63 described elsewhere. Of 895 children less than 5 years old with acute respiratory illness, 8.8% tested positive for HCoV-NH and negative for other common viral respiratory pathogens.[51] In addition to upper respiratory symptoms, children with HCoV NL63 infection can develop croup, asthma exacerbation, febrile seizures, and such lower respiratory tract findings as tachypnea, abnormal breath sounds, hypoxia, and abnormal chest radiographs.[51,52] HCoV NL63 may demonstrate a variable seasonality, ranging from fall and winter in temperate zones to spring and summer in tropical zones.

Most recently, a fifth HCoV, HKU1, has been described. Initially demonstrated in a 71-year-old man who returned to Hong Kong from an SARS-endemic area of China,[55] a subsequent prospective study of nasopharyngeal aspirates from 418 patients with community-acquired pneumonia demonstrated 10 (2.4%) positive for HCoV-HKU1.[56] All 10 cases occurred in spring and winter; 9 were adults, and 4 had underlying respiratory tract disease. All had symptoms that were indistinguishable from other study participants with community-acquired pneumonia. The global impact of this novel virus remains to be determined.

RHINOVIRUSES

The rhinovirus group is composed of at least 115 unique serotypes that are widely known as the agents responsible for many of the upper respiratory ("common cold") symptoms in adults and older children. Rhinoviruses have been isolated from infants and children hospitalized with LRIs but not at rates that differ significantly from children without respiratory illnesses.[57] The usual incubation period is 2 to 3 days, and the acute symptoms usually last 3 to 7 days. In one retrospective study, the clinical features of 44 rhinovirus culture-positive children with respiratory symptoms, who were either hospitalized or seen in an emergency department, included bronchiolitis or pneumonia; sometimes, both conditions were found (32 patients). The majority of patients were younger than 12 months. Although infrequent, LRIs in children infected with rhinoviruses were indistinguishable from those caused by RSV.[58] Rhinoviruses appears to have a role in triggering episodes of acute asthma.[59,60]

The routine diagnosis of rhinovirus infections depends on tissue culture, although a PCR assay exists that is several times more sensitive than culture. Technical difficulties of identifying rhinoviruses in diagnostic specimens may contribute to an underestimation of their role as causes of LRI. The treatment of rhinovirus infections consists of supportive care; no antiviral medications are recommended at this time. Great attention has been given to possible preventive and therapeutic benefit of such alternatives as zinc and Echinacea, but no controlled studies to date have demonstrated benefit of either.

HERPESVIRUSES

Although uncommon as pulmonary pathogens in healthy children, all members of the herpesvirus family (herpes simplex virus [HSV] types I and II, varicella-zoster virus [VZV], CMV, EBV, HHV-6, HHV-7, and HHV-8) can cause LRI in immunocompromised patients, generally hematogeneously spread as part of a systemic infection. CMV is primarily of concern in the recipients of allogeneic bone marrow transplants, but normal children with lower respiratory tract symptoms can also have positive cultures for CMV. Serologic studies do not generally support a primary role for CMV in LRI among healthy children[17]; however, pneumonia associated with acute, primary, systemic CMV infection in otherwise normal infants has been reported.[61]

CMV pneumonitis in recipients of bone marrow transplantation most frequently results from reactivation of latent virus and less often by transmission via blood products to seronegative patients. Graft-versus-host disease is a significant risk factor for the development of CMV pneumonitis; thus autologous and syngeneic recipients of bone marrow transplant are affected much less often. CMV pneumonitis commonly presents as a primary pulmonary process characterized by fever, tachypnea, and progressive pulmonary distress. Diffuse, bilateral pulmonary infiltrates are generally seen on chest radiographs. The diagnosis can be made by culture of the virus from bronchoalveolar lavage fluid or from lung tissue, although detection of increased viral load by nucleic acid detection methods in the setting of LRI is strongly suggestive. The advent of prophylaxis with intravenous ganciclovir or oral valacyclovir in high-risk patients has greatly reduced the incidence of CMV during the first 3 months after bone marrow transplantation.[62] Ganciclovir is less effective in treating CMV pneumonitis in patients after disease is clinically apparent.

Herpes simplex pneumonitis is most commonly seen as part of perinatally acquired disseminated infections but can also be transmitted during resuscitative efforts. Immunocompromise of any type is also a risk factor for HSV pneumonitis at all ages.

Varicella pneumonitis is a life-threatening complication of primary VZV infection in neonates, immunocompromised patients, and, rarely, healthy children. VZV is spread by aerosolized respiratory secretions, and the initial round of viral replication occurs in the lungs. A primary wave of viremia then occurs and is followed by further viral replication in lymphatic tissue. Characteristic cutaneous lesions erupt after a secondary viremia. Varicella pneumonitis generally develops 2 to 5 days after the outbreak of a rash.[63] The clinical and radiographic manifestations vary. Asymptomatic miliary lung lesions (especially in adult varicella) may later become apparent as calcified foci. In others, a mild interstitial pneumonia is present, which may be overshadowed by a severe bacterial pneumonia caused by such organisms as group A streptococci or *S. aureus*. These are often accompanied by effusions and empyemas and can be extremely difficult to treat. Varicella alone can cause a progressive, lethal pneumonia in immunocompromised patients.

The transmission of VZV to neonates occurs when primary maternal chickenpox occurs within 3 weeks of parturition. Transplacental transfer of maternal antibody specific for VZV is minimal if the onset of illness occurs fewer than 5 days before birth. Thus, if maternal varicella develops within 5 days before to 2 days after delivery, systemic disease and pneumonitis can develop in the neonate, with an estimated case-fatality rate of 5%.[64]

The diagnosis of varicella in normal hosts is generally made by clinical observation. Culture or immunofluorescence staining of vesicular lesions is important in immunocompromised hosts to rule out disseminated herpes simplex infections. Serologic antibody tests are useful for assessing immune status. γ-Globulin preparations containing high titers of anti-VZV activity are effective in preventing varicella if given soon after exposure. Neonates and immunocompromised children are candidates for this treatment.[64] Acyclovir and other related agents are the drugs of choice in treating high-risk patients and reduce the severity of illness if administered within 2 days of the outbreak of a rash. Fortunately, a live VZV vaccine has resulted in a significant reduction of primary varicella and its complications.[65]

Like the other herpesviruses, EBV produces life-long infections and causes a variety of clinical syndromes, including infectious mononucleosis, central nervous system illnesses, malignant lymphoproliferative diseases, and nasopharyngeal carcinoma. Pneumonitis, pneumonia and pleural effusion can occur as part of primary EBV infection but are uncommon, although perhaps underdiagnosed. In a group of 113 normal children with documented EBV-induced mononucleosis, 6 children, all younger than 4 years, developed pneumonia during the illness.[66] Pneumonia was self-limited in all cases. The diagnosis of primary EBV infection is made on clinical grounds in conjunction with serologic tests for heterophil antibody or IgM anti-VCA antibody.

HHV-6, the usual causative agent of roseola infantum, has been suggested as a possible cause of some cases of interstitial pneumonitis in recipients of bone marrow transplants.[67] This virus is one of the most ubiquitous of human viruses: More than 90% of the population becomes infected by 2 years of age. Detection of HHV-6 by culture is not routinely available, but the diagnosis of primary infection can be made by evidence of serologic conversion. Reactivation is difficult to document because a majority of healthy individuals have evidence of continuous viral replication in the salivary glands and blood. HHV-7, more recently described, appears to have similar epidemiology and pathogenicity as HHV-6, whereas HHV-8 has a well-known association with Kaposi sarcoma in immunocompromised and, rarely, immunocompetent patients. Both HHV-7 and HHV-8 appear to cause interstitial pneumonitis in bone marrow transplant patients.[68,69] HHV-6, HHV-7, and HHV-8 are not thought to cause pneumonia in normal persons, and no specific therapy is available.

MEASLES VIRUS

Otitis media and pharyngitis are normal components of the early phase of measles infection. Bronchitis is common, and severe laryngitis may occur occasionally. Pneumonia caused by the measles virus probably occurs in at least 50% of children. In most cases, it is a mild bronchopneumonia and is recognized only by nonspecific lower respiratory signs and hyperinflation on chest radiograph. In other cases the inflammation is more extensive, leading to diffuse infiltrates or even segmental or lobar consolidation on chest radiographs.

Children with measles are prone to secondary bacterial infection with organisms such as pneumococci, *H. influenzae*, *S. aureus*, and *Streptococcus pyogenes*. This is particularly important in developing countries, where infection secondary to measles is a major cause of death in young children. Measles may also have a deleterious effect on the course of tuberculosis in malnourished infants.

The immunodeficient child is prone to develop a progressive and fatal infection that evolves about 3 weeks after exposure. The clinical manifestations start with a fever, and there may be an atypical rash. Nonspecific respiratory symptoms and signs evolve over 2 to 3 days. The chest radiograph generally shows coarse nodular infiltrates, and air leaks are common.

The diagnosis is usually made on culture from nasopharyngeal secretions or bronchoalveolar lavage fluid. Occasionally, a lung biopsy may be necessary. The histopathologic picture is most often that of giant cell pneumonia with inflammatory cell exudate and thickening of the alveolar walls with inflammatory cells. The alveolar lining cells are transformed and contain intranuclear and intracytoplasmic inclusions.[70] Rapid diagnosis by immunofluorescence and serologic diagnosis are also possible.

Treatment of measles involves supportive measures and close observation for signs of bacterial superinfection. Prevention is available via a live, attenuated vaccine that is highly immunogenic but contraindicated in pregnant and immunocompromised individuals. Measles pneumonia can be prevented in the immunodeficient host by active community immunization. Those exposed should have immunoglobulin as soon as possible after exposure.

Modified measles does occur in the partially immune host and presents with fever and an itchy maculopapular rash, particularly over the wrists and ankles. Respiratory involvement is relatively common in this type of measles, presenting with dyspnea and widespread crackles heard on auscultation. The chest radiograph shows hilar adenopathy with nodular infiltrates and frequently a pleural effusion.[71]

HANTAVIRUS

In 1993, an outbreak of acute febrile illness progressing within 3 to 5 days to respiratory failure and shock was noted in the southwestern United States. The hallmark of this syndrome, the hantavirus pulmonary syndrome, is unexplained severe noncardiogenic pulmonary edema occurring in previously healthy persons. Subsequent studies have implicated at least three different hantaviruses, which are primarily maintained as zoonotic agents in rodent reservoirs.[72] As of November 2004, more than 379 cases of hantavirus pulmonary syndrome had been reported from 31 states in the United States, with a case-fatality rate of greater than 50%.[73-75] Hantavirus pulmonary syndrome has also been documented in Canada, Brazil, Argentina, and Paraguay. Few cases have been reported in people 16 years or younger, but the disease spectrum and mortality are similar to those reported in adults.[75,76] The diagnosis can be made by serologic tests, PCR study of frozen tissues, immunochemistry, or paraffin-embedded tissues. No specific therapy has proved efficacious; however, intravenous ribavirin has been suggested based on in vitro data and experience with other hantaviruses.

SIMULTANEOUS INVOLVEMENT BY MULTIPLE PATHOGENS

Other viruses, *C. trachomatis*, *M. pneumoniae*, and *B. pertussis*, can also be detected in a significant number of young children with infections caused by RSV. In the Tucson Childrens' Respiratory Study,[77] 10.9% of previously healthy patients with RSV infection were coinfected with another potential pathogen as documented by culture or antigen detection, and the proportion became even greater when serologic results were also extensively used for diagnosis. The clinical diagnosis and outcomes were no different among patients with RSV alone compared with those already coinfected with additional agents. Routine searches for coinfecting agents when a primary pathogen such as RSV is identified are not recommended for otherwise healthy infants and children. Such extensions of a diagnostic workup are best reserved for patients who are known to have significant underlying illnesses or patients whose clinical course is not congruent with that expected for the pathogen detected.

PROSPECTS FOR PREVENTION AND TREATMENT

Current knowledge concerning the major causes of viral LRIs and their epidemiology and diagnosis has matured remarkably. Exciting advances are now being made in the critical areas of immunopathogenesis, molecular virology, and antiviral therapy. Future discoveries will surely provide even more rational approaches to prevention and treatment, including specifically designed peptide vaccines that can more appropriately recruit specific T-cell populations as allies in long-lasting protection. Other emerging strategies include enhancement of host defenses by cytokine manipulation and novel applications of older concepts, such as specific antibodies for prophylaxis and treatment. There is considerable cause for optimism, in contrast to the state of affairs described by Andrewes more than 4 decades ago, when he suggested that clinicians should perhaps accept these infections as "one of the stimulating risks of being mortal.[78]"

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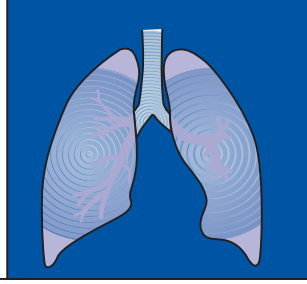

CHAPTER 34 Respiratory Syncytial Virus–Associated Lower Respiratory Tract Disease

Mark L. Everard

TEACHING POINTS

- The respiratory syncytial virus (RSV) causes annual epidemics of respiratory disease that particularly affect infants and the elderly. It remains the most common cause of hospitalization and death among infants outside the neonatal period.
- Phenotypes of lower respiratory tract infection (LRI) caused by the virus in early childhood include acute bronchitis, croup, bronchiolitis, wheeze-associated viral illness (wheezy bronchitis), and virus-induced exacerbations of asthma. The clinical consequences of infection are likely to reflect host factors.
- The only proved therapy for RSV infection in the first 2 years of life is good supportive care including oxygen when patients are hypoxic. Some older subjects with predominant wheeze may respond to bronchodilators. It is likely, but unproved, that these individuals have a viral exacerbation of asthma.
- RSV LRI in early childhood is associated with increased recurrent respiratory morbidity during the first year of life. The patterns of symptoms are likely to be heavily influenced by host factors. Those with "acute bronchiolitis" (characterized by widespread crepitation on auscultation) have relatively mild symptoms most prominent in the first year or two after the initial illness.
- RSV LRI in infancy does not increase the incidence of atopy or atopic asthma.

The respiratory syncytial virus (RSV) is an extraordinarily successful respiratory virus that causes annual epidemics of respiratory disease.[1-7] Although the virus is able to reinfect individuals throughout life, its greatest impact is in the very young[1-7] and the elderly.[8-12] It is the most important infectious agent affecting infants and young children, being responsible for the majority of cases of acute viral bronchiolitis and pneumonia in patients admitted to hospital in this age group. Over the past decade, it has become clear that the virus also has a major impact on the elderly and those with chronic obstructive airways disease. During most years, it rivals influenza in terms of being associated with both the increased respiratory morbidity and mortality in this age group.

The RSV is an RNA virus belonging to the pneumovirus family. It is closely related to the paramyxoviruses but differs in a number of important respects.[13] It is most closely related to the bovine RSV that causes a illness similar to bronchiolitis in young calves. The virus was first isolated from a chimpanzee in 1956 and was originally called the "chimpanzee coryza virus." It was not long before it became clear that this virus was responsible for outbreaks of respiratory disease in infants, and it was renamed because of its predilection for the respiratory system and its tendency to produce syncytia when inoculated into human cell lines.

The virus has been shown to cause respiratory disease in all parts of the world. The virus, without fail, produces yearly outbreaks of respiratory disease. In temperate climates, these commence in late autumn/early winter, rising rapidly to a peak and then falling away by late spring. Isolation of the virus in the summer is uncommon. In tropical and subtropical climates, epidemics tend to occur during the rainy season.[14-17] It is still unclear why the epidemics follow such a regular pattern, and the trigger for each epidemic remains to be defined.[14] It has recently been demonstrated that the virus appears to be able to productively infect human dendritic cells during the RSV season but that out of the season it appears to lie dormant within these cells.[18] Viral replication can be triggered by exogenous nitric oxide (NO),[18] which may be relevant to the seasonality of the epidemics and the observation that the severity of illness is greatest in industrialized areas because NO levels, in contrast to other pollutants, peak in the winter and are highest in industrialized areas. It is also of note that exposure to postnatal cigarette smoke is associated with more severe disease.[19]

The incubation period before the onset of symptoms appears to be in the range of 3 to 8 days. Spread of infection appears to be via large droplets or fomites.[20-23] These droplets are transmitted to hands and fingers, and self-inoculation then occurs with transmission of virus into the eyes or nose, which act as portals to the respiratory tract. Small droplet aerosols appear not to be an important form of transmission. Survival of the virus on hands is variable but generally less than 1 hour. Survival on other surfaces is also generally short, but it can survive for as long as 30 hours on hard, nonporous surfaces in the presence of high humidity. Shedding of virus by hospitalized infants continues even after significant clinical improvement, and the infants generally continue to shed virus for many days after discharge from hospital.[24] Thus, infants, and probably older individuals,

remain a potential source of infection for a period after resolution of the acute symptoms. Within pediatric units, infected members of staff are an important source of nosocomial infection.

During any particular epidemic, a large proportion of the population will develop an RSV respiratory tract infection, but in infancy, the risk of infection is significantly greater, with in excess of 60% of infants being infected.[1,25-27] Almost all infants will have been infected by the virus by the end of their second winter, and half will have experienced two infections during their first two winters. For most infants, symptoms will be relatively mild with upper respiratory tract symptoms alone. However, up to 25% will develop lower respiratory tract symptoms. In most cases, these lower respiratory tract symptoms can be managed in the community, but between 0.5% and 1.5% of all infants are admitted to hospital during the winter epidemic following their birth with RSV lower respiratory tract symptoms. Those aged 1 to 4 months are at particular risk of severe infection and hospitalization. Risk factors for severe disease include postnatal age, preterm birth, chronic lung disease of prematurity, cardiac disease with pulmonary hypertension, neurologic disease, and immunodeficiency.[27-35] Other factors increasing the likelihood of severe disease include attendance at day care, exposure to tobacco smoke, overcrowding, and having older siblings.

RSV infections in infancy are of considerable importance for a number of reasons. Although the mortality rate in hospitalized, previously healthy, infants is very low,[15,16] the acute morbidity is significant. Despite improved outcome with improved supportive care, the virus still poses a threat to those with certain at-risk conditions, which include immunodeficiencies, chronic lung disease of prematurity, and congenital heart disease associated with pulmonary hypertension. However, even in these groups, mortality is low due to advances in supportive care.[31-35] The annual epidemics of RSV lower respiratory tract disease in infancy place great strains on pediatric services every winter. In 2000, it was estimated that in the United States alone, there were approximately 86,000 hospitalizations, 1.7 million office visits, 402,000 emergency department visits, and 236,000 hospital outpatient visits for children younger than 5 years that were attributable to RSV infection. In the United States, total annual direct medical costs for all RSV infection–related illnesses in children less than 5 years of age during 2000 were estimated to be approximately $652 million, with 60% being accounted for by hospitalization and 40% attributable to the medical care of nonhospitalized patients. RSV infection–related hospitalizations increased from 1993 to 2000, but average costs per hospitalization were relatively stable.[36] The trend for increasing admissions has been noted in other countries through the 1980s and 1990s, but more recent data suggest that rates have reached a plateau and indeed are probably falling.

In addition to the acute morbidity, it is clear that RSV LRIs in infancy are associated with an increase in the prevalence of respiratory symptoms in early childhood. This has been observed in cohorts recruited from both hospitalized infants[37-49] and infants managed in the community with RSV LRIs.[50] The nature of these symptoms is unclear but do not appear to be related to an increased prevalence in atopic asthma induced by RSV LRIs. As discussed later, it is likely that it is the host response rather than the virus per se that determines the nature of acute illness and subsequent symptoms. The phenotype of the acute illness probably reflects host factors that impinge on both the acute illness and subsequent symptoms.[51]

The large number of infants being admitted to hospital each winter as a result of RSV infections probably reflects the virus's ability to infect huge numbers of very young infants. This in turn probably reflects poor herd immunity as evidenced by the observation that more than a third of the population are infected every winter. As noted earlier, infection rates in infants are in excess of 60%, and this presumably reflects the ineffectiveness of prenatally acquired passive immunity, a factor that will be even more important in preterm infants. With so many very young infants being infected and having relatively poor protection against extension of virus to the lower respiratory tract, it is inevitable that a significant number will develop respiratory difficulties. Anatomical and physiologic factors such as poor collateral ventilation will further increase the severity of the lower respiratory tract symptoms in those aged less than 6 months. It appears clear that a similar proportion of infants aged 6 to 12 months are infected and probably experience lower respiratory tract symptoms at similar rates, but a far smaller proportion are admitted to hospital because they have the ability to more effectively cope with the effects of airways inflammation.

The poor herd immunity is probably attributable to the ability of the virus to inhibit the production of an effective long-term immune response in infected individuals through direct effects on the immune response or through hiding the important epitopes. Alternatively, antigenic variation may be more important than is currently appreciated.[52-55] If so, this has important implications for the production of vaccines. Unfortunately, there is currently no immediate prospect of preventing these annual epidemics.

PHENOTYPES OF DISEASE

Over the past 30 years, researchers have been trying to identify possible specific immunopathologies that may explain the association of RSV with acute bronchiolitis and/or the association between RSV LRI in early childhood and subsequent respiratory tract infections. As noted, the virus almost certainly influences the host response in order to minimize the effectiveness of memory responses to the virus, and as a consequence, certain aspects of the host viral interaction may differ from that observed with other respiratory viruses. This does not mean that the basic immunopathology is significantly different from that observed with other viruses, and indeed any of the respiratory viruses may induce any of the clinical phenotypes of disease associated with RSV infection.[54] As with other viruses, RSV may cause a simple coryzal illness, acute otitis media, bronchitis, laryngotracheobronchitis, bronchiolitis, pneumonia, virus-associated wheezing, and viral exacerbations of asthma. It is likely that there are differences in both the distribution of virus and host response to the virus in these different phenotypes of disease.

In the past, many studies focused on the presence of RSV itself rather than the phenotype of the illness. More recently, studies have again tended to focus on the phenotype of

disease experienced by an infant rather then the causative organism, and this approach has consistently led to data that suggest that aspects of the host response rather than the particular virus are largely responsible for the phenotype of the acute illness and subsequent respiratory morbidity associated with that phenotype. Lack of precision in defining clinical phenotypes of illness has probably played a major role in perpetuating a number of the controversies that surround this virus.

Acute Bronchiolitis

Surprisingly, despite the frequency and importance of this condition, there are still a number of controversies surrounding the diagnosis and optimal management of infants with "acute bronchiolitis." This appears largely attributable to a failure to agree on the clinical features that characterize patients with acute bronchiolitis. In the United Kingdom, Australia, and parts of Europe, the term *acute bronchiolitis* is limited to infants who present with the following clinical pattern.[58,59] Upper respiratory tract symptoms with coryza and cough precede the relatively abrupt onset of lower respiratory symptoms after 2 to 3 days. Fever is common but frequently settles early in the course of the illness and may be absent when the patient presents to the hospital. The onset of lower respiratory symptoms is frequently acute, and at presentation, the infant is dyspneic with a moist irritating cough. Difficulty feeding and agitation due to hypoxia are not uncommon. Wheeze may be present intermittently but is not characteristic. Tachypnea, hyperinflation of the chest with downward displacement of the liver, and subcostal recession are typically present. However, the defining and characteristic clinical feature is that auscultation reveals widespread bilateral fine inspiratory crackles.

The diagnosis is essentially a clinical diagnosis, and most guidelines recommend that chest radiographs are not indicated unless there are atypical features[60] because clinicians are frequently tempted to use antibiotics when there is evidence of apparent lobar consolidation or bronchopneumonia.[61,62] These radiographic appearances may also encourage clinicians to inappropriately use the term *pneumonia* for such patients even though they have widespread crackles bilaterally. Most infants admitted to hospital with the typical phenotypic illness of acute bronchiolitis characterized by widespread crackles on auscultation will be less than 6 months old. Although older infants will also develop the same clinical picture, far fewer require admission to hospital as hypoxia and significantly impaired fluid intake are less common.

The acute inflammatory response in the airways of infants with this phenotype is dominated by an intense neutrophilia.[63,64] Such a response also characterizes the response to other respiratory viruses such as rhinovirus.[65] Inflammatory mediators such as human neutrophil elastate, myeloperoxidase, and metalloproteases will induce mucus secretion, airways edema, coughing, and sneezing and hence are likely to play a major role in the induction of symptoms and dissemination of the virus.[66,67] Indeed, there is some evidence that the peak of symptoms appears to correlate with the peak in neutrophil numbers, which lags behind the peak in viral titers. The support for the suggestion that neutrophils rather than virus-induced cytopathology are responsible for the generation of symptoms comes from experimental rhinovirus infection in adults in whom symptoms only occurred if there was significant neutrophilia within the airway and did not appear to correlate to evidence of viral replication.[65] If symptoms are peaking as viral titers are falling, then it is perhaps not surprising that antiviral agents have not been shown to have a significant effect in this disease. It is probable that approaches that might reduce the intensity of the neutrophil response may prove to be more effective. There is evidence that neutrophils do have a role in reducing viral titers within the airways, although the mechanism remains to be elucidated.

There are overwhelming data indicating that there is no increase in atopy associated with this phenotype and that the pattern of subsequent respiratory morbidity does not appear to be asthmatic, in that it has yet to be shown that these symptoms respond to inhaled steroids or bronchodilators.[39-42,46-50] The excess of respiratory symptoms experienced by hospitalized infants exhibiting this phenotype is most marked in the preschool years, is associated predominantly with subsequent intercurrent viral infections, and is rarely severe enough to cause further hospitalization.[48] The excess in respiratory morbidity declines rapidly through the early years of life with cohort studies suggesting that this excess has resolved by the beginning of the second decade of life.

Viral Pneumonia

Viral pneumonia in infancy is significantly less common than acute bronchiolitis, although viruses account for the majority of pneumonic illnesses in infancy. Infants with viral pneumonia, including those caused by RSV, typically exhibit a cough, are febrile, and develop significant respiratory distress. They are often more severely affected than those with acute bronchiolitis with a greater need for supportive and intensive care but, somewhat surprisingly, there generally is little to hear on auscultation. Typically, there are widespread nonlobar chest radiograph changes that often change and evolve over relatively short periods of time. There are no specific follow-up data in this group of patients

"Wheeze-Associated Viral Infections" and Exacerbations of Asthma

In much of North America and parts of Europe, the term *acute bronchiolitis* is frequently applied to infants experiencing their first wheezing illness associated with an apparent respiratory viral infection characterized by symptoms such as rhinorrhea and cough.[68] Some would limit the diagnosis to those less than 1 year of age, but many would include children up to 2 years of age or even older. In many countries, including the United Kingdom and Australia, these patients would be described as having "wheezy bronchitis" or an "acute virus-associated wheezing episode." In contrast to those admitted with acute bronchiolitis as defined earlier, those patients admitted to hospital with this phenotype of illness characterized by wheezing without crepitations are generally older than 6 months. Such episodes may recur, and it is likely that this phenotype contains both those with virus-associated wheezing illness (which may be a single episode or

the first of a number of episodes) and those experiencing an early virus-induced exacerbation of asthma.[60,69]

This suggestion has been supported by a number of studies following up infants and young children with virus-associated wheezing episodes attributable to a number of respiratory viruses.[45,70-74] These studies have suggested that wheezing with rhinovirus is more strongly linked with subsequent asthma than is wheezing with RSV. However, even among those with rhinovirus-induced wheeze in early childhood, asthma develops in only a minority. The one study in which patients hospitalized with RSV infection were categorized as "acute bronchiolitis" (based on finding of widespread crepitations) or "wheeze-associated viral illness" at admission[49] found at 3 years of age that there was a predictable increase in cough and wheeze with intercurrent viral infections but no increase in atopy in those admitted with acute bronchiolitis. Despite the increased burden of episodic symptoms, there was no increase in the use of preventive therapy such as inhaled corticosteroids. These findings were in marked contrast to those among the patients with RSV-induced wheezing. In these subjects, there was a significant excess of atopy, and this was accompanied by a significant increase in use of inhaled corticosteroids and health care utilization at 3 years of age, suggesting that the phenotype of the initial illness was associated with different outcomes even though all subjects had been infected with RSV. One recent small study also highlighted the different inflammatory responses in infants with RSV bronchiolitis and those with virus-induced exacerbations of asthma.[75]

Other Presentations

It is well known that the virus can induce severe life-threatening apneas in young infants with or without other evidence of lower respiratory tract involvement.[31,76-81] Apneas are more common in those born preterm and in young infants. The infants infected with the virus can also present with the clinical picture of acute septicemia.

Immunologic Factors

High circulating antibody titers have been shown to be associated with protection from recurrent infection,[82] although it has been claimed that protection correlates more closely with levels of mucosal IgA.[83] High maternal and cord antibody levels are associated with protection against developing bronchiolitis,[84,85] but it is likely that the level of protection is related to the titer of passively acquired neutralizing antibody rather than the total titer of antibodies directed against RSV, because much of this will be nonprotective antibody. These observations led to the development of monoclonal antibodies directed toward conserved epitopes on the relatively stable F surface glycoprotein. It appears clear that the current preparations cannot achieve concentrations sufficient to prevent infection of the upper respiratory tract[85] but are able to provide incomplete protection against significant lower respiratory tract disease.[85-87] The use of an effective monoclonal agent might be expected to result in the emergence of resistant strains,[88] but as yet this does not appear to be a problem in clinical practice. This may well be due to inability of the current preparation to prevent infection of the upper airway, and hence it will exert less evolutionary pressure than a more effective preparation. To date, no other aspect of the host response has been clearly shown to provide protection.

It is clear that elimination of virus is necessary for recovery from infection, but it is of interest that clinical symptoms often peak after the titer of virus starts to fall, suggesting that the host's inflammatory response rather than viral cytopathology is the principal cause of the symptoms.[90] One study has suggested a link between viral titers and disease severity,[89] but if such a link exists, it is unclear whether this reflects infecting load or a relative failure to limit viral replication after inoculation. Immunocompromised patients, especially those with defects of cell-mediated immunity, have difficulty in eliminating the virus and have a high mortality rate.[92-94] Hence, it seems likely that cell-mediated immunity is important in recovery from RSV infections. As noted earlier, antibodies appear to be important in protection from infection, and it is possible that they may have a role in eliminating virus after infection has occurred. Animal[95] and in vitro studies have also suggested that neutrophils play a role in clearing virus from the airway lumen and are not just responsible for generating symptoms, as outlined earlier.

Immunopathology

More than 30 years ago, it was suggested that there may be a specific immunopathology operating in those infants admitted to hospital with RSV bronchiolitis. This was based on the observation that the illness occurred at an age when passively acquired antibody levels are still generally high and on the results of the trials using a formalin-inactivated vaccine in which infants receiving the vaccine had increased morbidity and mortality on subsequent natural exposure to the virus.[96] The first hypothesis proposed that the condition results from an immune complex reaction between nonneutralizing antibody and virus.[97] Subseqeunt theories have included the suggestion that there is a specific IgE response[98] during the acute illness and the suggestions that the pathology is due to excessive cytotoxic[99] T-cell activity, excessive Th2 activity, or impaired macrophage activity due to infection of these cells.[100] Despite intense efforts, it has not been possible to show that any of these proposed mechanisms are fundamental in the causation of the symptoms experienced by infants with RSV-induced lower respiratory tract disease. This is perhaps not surprising when one reflects that identical clinical illnesses can be induced by a wide range of respiratory viruses.

A number of studies have sought to identify genetically determined risk factors such as polymorphisms in certain genes controlling cytokines and Toll receptors. Many potential associations have been reported, but further work is required to determine which, if any, have a significant impact.

Over the past three decades, there have been numerous studies that have used infected rodents such as the cotton rat in an attempt to unravel the immune processes contributing to acute RSV bronchiolitis. The results obtained in such studies must be interpreted with considerable caution because not only have apparently contradictory results been obtained but, perhaps more importantly, these animals are not the natural host for the virus and they do not develop a clinically

significant illness resembling acute bronchiolitis when infected experimentally.[99] Most proposed immunopathologic mechanisms have been supported by at least one rodent model, but these generally involve significant manipulation of the animal model in order to obtain the desired result. Rodent models may prove to be more valuable in assessing the potential role of therapeutic interventions such as immunoglobulin preparations.

A better animal model for determining immunologic responses may prove to be the acute respiratory illness observed in calves and sheep caused by the bovine RSV.[95,102,103] There are a number of similarities in the clinical picture in that they develop upper and lower respiratory signs, the youngest calves experience the most severe illness at a time when passively acquired antibodies are present, and only a small proportion of infected calves experience severe disease. Again, neutrophils are the most prominent inflammatory cell in the airway.

Management of Respiratory Syncytial Virus Infection in Infancy

Although the morbidity associated with RSV infections in infancy is high, the mortality is fortunately low. While the virus is able to cause a variety of phenotypic illnesses, including acute bronchiolitis, pneumonia, and wheeze-associated viral illness, management is essentially the same for each group of patients and has essentially remained unchanged for more than 40 years. Good supportive care remains the cornerstone of therapy, with oxygen being vital in those with hypoxia. There is no convincing evidence that pharmacologic agents have any role in treatment of infants with RSV infection, but despite this, agents such as bronchodilators are still widely used.[104] It is possible that patients less than 2 years of age with an RSV-induced viral exacerbation of asthma will benefit from traditional asthma therapies. However, it is difficult to differentiate those with their first significant exacerbation of asthma from those with wheeze-associated viral illness (bronchiolitis [wheezy bronchitis]) who represent the majority of patients in whom wheeze is a major feature. This difficulty probably underlies some of the apparent discrepancies in outcomes of trials assessing the role of bronchodilators in the treatment of bronchiolitis and is reflected in the American Academy of Pediatric (AAP) bronchiolitis (diagnosis based on presence of wheeze) guidelines,[105] which recommend that bronchodilators not be used routinely in the management of bronchiolitis. They suggest that a carefully monitored trial of α- or β-adrenergic medication is an option, but the inhaled bronchodilators should be continued only if there is a documented positive clinical response to the trial, using an objective means of evaluation.

A small percentage requires more aggressive supportive care, which might include ventilation and even extracorporeal membrane oxygenation (ECMO), but most infants admitted with RSV infections have a brief, self-limiting illness. In North America, the United Kingdom, and northern Europe, the mean duration of hospitalization is 3 days, compared with approximately 9 days in continental Europe.[104] This may reflect differences in severity of patients admitted, differences in criteria for discharge, or availability of hospital beds.

Differential Diagnosis

In the majority of infants admitted with the clinical syndrome of acute bronchiolitis as defined earlier, the causative organism will be the RSV. However, in the midst of an epidemic, it is important to continually consider possible alternative diagnoses that may masquerade as acute bronchiolitis such as cystic fibrosis, recurrent aspiration, congenital lung abnormalities, perinatally acquired *Chlamydia* infection, immunodeficiencies, and congenital heart disease (particularly total anomalous pulmonary venous drainage), all of which can present with many of the features characteristic of acute bronchiolitis. Similarly, disorders such as interstitial pneumonitis and bronchiolitis obliterans due to adenovirus can present with an illness initially suggestive of acute viral bronchiolitis.

Diagnosis

RSV infection and other respiratory viruses can be identified using rapid diagnostic approaches such as immunofluorescent antibody method, enzyme-linked immunosorbent assays (ELISAs), or polymerase chain reaction (PCR). Reliable commercial kits are now readily available and widely used, and indeed some are designed for use by the clinician at the bedside. Samples are generally obtained by means of nasopharyngeal aspirates, nasal lavage, or nasal swabs. A positive result is valuable in supporting the diagnosis and in isolating infants with the virus. However, it should be remembered that all these methods require good-quality samples and a negative result does not exclude RSV infection because the sample may be of poor quality and contain few epithelial cells. Significant rises in RSV antibody titers are uncommon in young infants, and although ELISA techniques appear more sensitive, serologic diagnosis is of little value clinically because convalescent sera are required and hence results are not available for many weeks.

ACUTE BRONCHIOLITIS AND PNEUMONIA

Clinical Assessment

At present, there is no way of predicting which of the many infants presenting with an upper respiratory tract infection during an RSV epidemic will develop acute bronchiolitis. However, as outlined earlier, there are certain groups of children who are at risk of severe disease should they develop bronchiolitis. In previously healthy infants, the peak incidence of admissions is in those aged 1 to 4 months, which is probably due to the low incidence of the condition in younger infants and relatively mild disease in older children, possibly due to growth in the airways and development of collateral ventilation that reduce the impact of occlusion of airways with mucus and secretions. For those admitted to hospital the severity, as judged by the degree of hypoxia, duration of admission, and the need for ventilation are increased in younger and smaller infants.

Certain infants are at increased risk of severe disease, which may lead to respiratory failure, requiring ventilatory support and, in a small proportion, death. This includes those with congenital cardiac disease, particularly those with pulmonary hypertension, chronic lung disease with oxygen

dependency, immunodeficiencies, or cystic fibrosis and those born prematurely. However, the mortality rate even in these groups is now very low.

During RSV respiratory infections in very young infants, the two most serious complications are respiratory failure and apnea. Apnea is most common in the youngest patients, those born preterm, and those with chronic lung disease. Infants may present with apneas and progress to bronchiolitis, show signs of bronchiolitis and develop apneas, or have apnea as the sole sign of RSV infection. Again RSV is not unique in its ability to induce apnea. RSV infection has been implicated in a number of cases of "cot [or crib] death,"[81,106] and its ability to precipitate apnea may be relevant to this observation. A significant proportion of infants with RSV infection requiring assisted ventilation do so because of severe recurrent apneas rather than respiratory failure.[107,108] The mechanisms leading to these apneas are unclear, but they tend to resolve within a few days. The use of apnea monitors is therefore important in young infants, those born preterm, and those with preexisting lung disease.

It is well recognized that the clinical assessment of hypoxia is poor.[109,110] Perhaps the most reliable clinical sign of respiratory failure is agitation, which, if not relieved by supplemental oxygen, can contribute to exhaustion and respiratory failure. Hypercapnia is uncommon in all but the most severely affected infants; hence, with the widespread use of pulse oximetry, blood gas monitoring is rarely required unless mechanical ventilation is being considered. Although these monitors have certain limitations, they play a central role in the assessment of hypoxia and subsequent management of oxygen therapy. Two studies found that an infant's oxygen saturation, as judged by pulse oximetry, was the best objective predictor of disease severity.[111,112]

Decisions regarding hospital admission are therefore based on age, risk factors, clinical assessment, and oxygen saturation. Most infants in at-risk groups will be admitted unless symptoms are very mild, and similarly the threshold for admitting infants less than 6 months of age is relatively low because of the risk of progression to more severe disease and their increased risk of apnea. However, for many infants, the illness is mild and can be managed at home. For those not admitted, it is important to alert parents to signs suggestive of deterioration such as poor feeding and agitation.

During each annual epidemic, it is inevitable that a number of infants will be infected with RSV at the same time as they develop another major problem such as meningitis, osteomyelitis, or urinary tract infection.[113,114] Therefore, every child with evidence of acute bronchiolitis should be thoroughly evaluated to ensure that there is no coexisting acute pathology. However, serious coinfection outside the respiratory tract is uncommon and coexisting bacterial infection of the lower respiratory tract is rare in all but those requiring ventilation.[113,114]

Investigations

Other than obtaining samples for viral identification, no other investigations are required routinely. Chest radiographs are commonly requested, although there is no evidence that they are of any value in most infants admitted with a clinical diagnosis of RSV bronchiolitis and indeed, as noted above, most guidelines state that they should not be obtained unless the child is particularly unwell. It has been suggested that most areas of shadowing suggesting subsegmental consolidation are in fact small areas of collapse, and the authors concluded that this appearance should not alter a pediatrician's decision to withhold antibiotics.[115] A further study found no correlation between the changes on the chest radiograph and clinical severity, leading the authors to suggest that this investigation should be limited to those in whom intensive care was being considered, in those who deteriorate unexpectedly, and in those with an underlying cardiac or pulmonary disorder.[61]

Although inappropriate antidiuretic hormone secretion can occur,[116,117] electrolyte disturbances are uncommon except in the most severely ill babies, and hence there is no indication for the routine assessment of serum electrolytes. Neutrophilia with an excess of immature neutrophils is a frequent finding during RSV infections,[117] and full blood counts are also of little value.

Management

Careful monitoring and good supportive care remain the cornerstones of management. For those without an underlying immunodeficiency, RSV infections are self-limiting, and management is aimed at providing adequate support until the illness resolves. Monitoring is principally directed toward the detection of apnea, hypoxia, and exhaustion. Supportive care is directed at alleviating hypoxia, providing adequate fluids, and preventing exhaustion by relieving hypoxia and minimal handling.

OXYGEN

In the early 1960s, Reynolds and Cook noted that "oxygen is vitally important in bronchiolitis and there is little evidence that any other treatment is useful,"[119] and this is essentially true today with improved supportive care allowing correction of hypoxia in those in whom supplemental oxygen alone is not sufficient. Hypoxia due to ventilation-perfusion mismatch is frequent,[120] although, as noted earlier, it is difficult to detect clinically. Oxygen at 30% to 40%, warmed and humidified and delivered via a headbox or nasal cannula, is sufficient to correct the hypoxia in most cases and rapidly relieves the distress and agitation observed in hypoxic infants. The AAP guidelines recommend the use of supplemental oxygen for those infants whose saturation falls below 90%,[105] although some centers would commence supplemental oxygen at higher levels.

FLUIDS

If uncorrected, the poor intake of fluid due to the respiratory distress and cough can lead to dehydration, and this tendency may be compounded by vomiting associated with the bouts of coughing. Hyponatremia due to inappropriate antidiuretic hormone can occur,[116,117] and hence it is sensible to restrict fluids to about two thirds of maintenance.

The route of administration varies between units. Some argue that the risks and disadvantages associated with nasogastric feeding are such that any infant requiring supplemen-

tal oxygen requires intravenous fluids. The potential problems include increased work of breathing due to obstruction of the upper airway, increased work of breathing due to fluid within the stomach, and an increased risk of gastroesophageal reflux and aspiration. Other units find that those with mild to moderate illness tolerate a nasogastric tube very well and appear more comfortable with frequent small-volume feeds. However, intravenous fluids are recommended in those more severely affected. Occasionally, infants suddenly deteriorate due to aspiration.

ANTIVIRAL AGENTS

Ribavirin is a broad-spectrum virustatic drug first synthesized in 1972 whose exact mode of action is unclear. Since the initial enthusiasm that greeted its launch in 1986, concerns have been raised about its cost, safety, and efficacy. A systematic review[121] concluded that further large studies were required if a role for the drug were to be established. Most studies are now almost 20 years old, contained very few subjects, and had remarkably high death rates compared with current practice. The drug is administered as an aerosol generated by a small-particle aerosol generator (SPAG). The aerosol is usually delivered into a headbox for 12 to 18 hours. No study to date has clearly demonstrated a significant impact on the course of the disease, and few units currently use the drug in previously healthy individuals or indeed those at risk of severe disease such as those with cardiac or pulmonary disease. Anecdotal reports suggest it is valuable in treating those with immunodeficiencies.[122]

ANTIBIOTICS

Secondary bacterial infection appears uncommon in infants with RSV bronchiolitis,[113,114,123] and hence antibiotics are rarely indicated even in those with patchy changes suggesting pneumonia. The clinical picture together with the rapid confirmation of RSV infection provides reassurance in most mild to moderately unwell infants. A large prospective study, covering a period of 9 years, found that secondary bacterial infection was more common in those given antibiotics than in those who did not receive them.[113] However, dual infections with viruses and bacteria do occur, and it is not unreasonable to start antibiotics in those who are particularly ill or in those with atypical features, and possibly in some disadvantaged populations. Even in those ventilated, bacterial coinfection is relatively uncommon but is probably sufficiently frequent to justify the use of antibiotics in those requiring ventilatory support while awaiting the results of bacterial cultures on samples obtained from the lower airway.[124,125]

Although uncommon, it is also important to bear in mind that coincidental infections, such as urinary tract infections or meningitis, do occur in infants with RSV infections including bronchiolitis.

BRONCHODILATORS

One of the greatest areas for contention in the management of acute bronchiolitis is in the role of bronchodilators. This probably stems in part from the desire of clinicians to have some form of therapy that they can offer beyond simple supportive therapy. Some of the differences may also be influenced by the types of clinical illness included in studies under the label of acute bronchiolitis. Published data suggest that bronchodilators such as selective β–agonists and nonselective agents such as epinephrine and theophylline are widely used, particularly in North America,[104] but to date there is no evidence that any of these interventions has a significant impact in those with acute bronchiolitis.[105,126,127] These findings are perhaps not surprising in view of the marked mucus production and mucosal inflammation that are contributing to the airways obstruction. It should be borne in mind that one potential problem with studies in the age group is that it is extremely difficult to assess symptomatic improvement. For example, it would be inappropriate to assess the impact of a bronchodilator on a child with moderately severe exacerbation of asthma by recording the time to discharge. The modest symptomatic relief obtained while awaiting the impact of systemic steroids clearly needs to be assessed using a different outcome measure. In infants, it is more difficult to objectively document symptomatic benefit as the patient cannot give his or her opinion.

OTHER THERAPIES

Published studies have consistently failed to show any benefit from the use of systemic[128] or inhaled corticosteroids. Despite this, steroids are used extensively in North America to treat these patients. There is also no evidence that mist therapy or physiotherapy has any role in the treatment of acute bronchiolitis,[129] and indeed the excessive handling associated with physiotherapy can be detrimental.

MORE INTENSIVE SUPPORTIVE CARE

Although the number of infants with acute bronchiolitis requiring ventilation can be minimized by good supportive care, a small proportion of infants admitted to the hospital may require ventilation for either recurrent apnea or respiratory failure. The majority of those admitted to intensive care are previously healthy individuals.[130] Indications for intubation vary from unit to unit, but in general, infants are intubated for either recurrent apnea with significant oxygen desaturations or respiratory failure with persistent acidosis or hypoxia despite high oxygen requirements. Rising CO_2 levels of greater than 7 to 8 kPa would be viewed by some as an indication for intubation, but others would tolerate significantly higher levels in the absence of overt exhaustion, acidosis, or uncorrected hypoxia. Patients should be weaned from the ventilator as rapidly as possible. Occasionally, these infants develop a picture consistent with adult respiratory distress syndrome.

A number of units have reported a reduction in the need for assisted ventilation following the introduction of nasal continuous pressure ventilation (CPAP). Some infants who continued to deteriorate despite mechanical ventilation have been treated with extracorporeal membrane oxygenation (ECMO) and preliminary reports are encouraging. The role of NO, high-frequency ventilation, heliox, and other agents such as surfactant continue to be debated, and the role of these interventions has still to be clearly determined.

Advances in supportive care have ensured that the prognosis for the vast majority of infants who develop acute bronchiolitis is very good, with an overall mortality rate significantly less than 1%.[131,132] Mortality in previously well

infants is extremely low, but the mortality rates in high-risk groups has historically been much higher with figures as high as 37% reported in infants with congenital heart disease.[133] With improved supportive care, the mortality in infants from high-risk groups who develop severe bronchiolitis is now generally below 4%

Post Bronchiolitic Symptoms

As noted earlier, there is increased respiratory morbidity in subsequent years among infants admitted to the hospital with RSV bronchiolitis, the nature of which has not been fully explained. It is possible that it reflects a preexisting predisposition to experience significant LRIs when infected with a virus.[134] It may also be attributable to changes induced in the airways by the intense inflammation during the acute event. This may be due to an increase in airways responsiveness or structural changes such as mucus gland and goblet cell hyperplasia, either of which may be responsible for heightened symptoms during subsequent viral infections. The evidence to date would argue strongly that neither inhaled[135,136] nor oral steroids administered during or immediately after the acute illness significantly alter the frequency or severity of such symptoms, although the topic remains a subject of debate, with a minority of studies suggesting that there may be some benefit from the use of inhaled steroids during and/or immediately after the acute illness.[137]

In addition to these symptoms, it is clear that infants can experience ongoing symptoms in the weeks immediately following the acute illness and discharge from hospital. One pilot study has suggested that a leukotriene antagonist administered after discharge does have an impact on the level of morbidity in the weeks immediately after the acute illness,[138] but no such benefits were identified in a second study.[139] The results of a much larger study are awaited, but interpretation of the results may be difficult if RSV infection in those under the age of 2 years is used as the criterion for entry, as patients experiencing a number of phenotypes of disease will be included.

WHEEZING ASSOCIATED WITH RESPIRATORY SYNCYTIAL VIRUS INFECTION

As noted, many of those admitted to the hospital with an acute LRI during the later part of the first year of life will have this phenotype of illness. Within this group, the majority are likely to have a pattern of illness variously labeled as "wheezy bronchitis" or "wheeze-associated viral illness" (or "acute bronchiolitis" in North America and parts of Europe if it is the first episode) and will likely outgrow this tendency to wheeze with viruses in the preschool years. A minority will be experiencing their first episode of asthma, but clearly it is very difficult to distinguish these two entities on clinical grounds. In those with true asthma, that is a condition defined by a clear and unequivocal response to asthma therapy; there may be benefit from using inhaled β-agonists and indeed oral steroids, but at present, we are unable to reliably identify those who will respond to therapy. As a result of this inability, there is ongoing debate as to the value of conventional therapy in those with an apparent viral infection and wheeze.[105,140-142] This may be resolved only if a definitive test for "asthma" (other than response to therapy) is devised.

Prevention

Attempts to produce an effective vaccine have continued for more than four decades without success. As yet, the only widely applicable effective measures available are those designed to prevent nosocomial spread within pediatric wards.

Cross-Infection

It has been known for many years that the virus rapidly spreads through infants on pediatric wards if precautions are not taken,[143-147] and fatalities among infants acquiring the virus while they are inpatients are well recorded. Inhalation of small-droplet aerosols generated by coughing and sneezing does not appear to be an important method of transmission. Infection of staff is common through self-inoculation of virus from hands into eyes or the nose[18]; indeed, infection in members of staff appears to be a major source of nosocomial spread. The virus is transmitted to infants on the hands of attendant staff or relatives, and hence simply isolating infants is inadequate in preventing spread. Careful attention to hand washing appears to be the most important aspect in the prevention[143,144] of cross-infection because it will help to reduce both self-inoculation of staff and transmission of virus directly to other patients. More extensive precautions have been advocated by some authors who argue that simple isolation and hand washing are ineffective; these include the use of gowns, gloves, and even goggles. Most of these measures will serve principally to reduce the infection rate among staff and so prevent them from passing it on to other children, but they will also heighten appreciation of the need for infection control measures.

Although severe disease is unusual in neonatal units, it is still very important to try to prevent nosocomial spread in these units, as the virus can cause significant respiratory disease, can mimic other forms of sepsis with nonspecific symptoms, and may induce significant apneas.[146] During epidemics, it is important to devise strategies designed specifically to avoid spread to inpatients at highest risk.[145]

Vaccines

For over two decades, much effort has been devoted to producing a vaccine able to prevent much of the respiratory morbidity associated with RSV bronchiolitis. The 1960s trials of a formalin-inactivated alum precipitated vaccine produced alarming results in that not only did the vaccine fail to protect infants but also there was excess morbidity and mortality in the immunized children when they subsequently were infected with the virus. Whether the enhanced disease severity noted on subsequent exposure to the virus was due to an abnormal response or represented an exaggeration of the natural response is unclear, although animal data suggest an aberrant response was induced.

Subsequent approaches have been to try to develop live attenuated strains, the generation of subunit vaccine, expression of viral glycoprotein genes on the surface of carrier viruses using recombinant gene technology, and the use of purified F protein obtained from tissue cultures.[147,148] Debate continues as to whether injection, inoculation into the respiratory tract to produce local immunity, or even administra-

tion to the mother[149] would be the most appropriate route if an effective vaccine could be developed.

Specific Immunoglobulin

Studies have demonstrated that a humanized synthetic anti-F antibody preparation (Palivizumab) administered intramuscularly at monthly intervals does reduce hospitalization in certain at-risk groups, including preterm infants, those with chronic lung disease,[87,150] and those with hemodynamically important cardiac disease.[88] The protection is incomplete, and despite large numbers of subjects, the use of this preparation was not shown to have an impact on intensive care unit days or mortality, which is low even in these high-risk groups due to improved supportive care. As noted earlier, these high-risk groups represent a minority of those reaching the intensive care unit, and therefore this approach is unlikely to have a major impact on the workload of pediatric units during the winter. The cost effectiveness of this approach is the subject of considerable debate in many countries.[150-153] Work is ongoing to produce better preparations while other non-vaccine approaches to preventing infection are also being pursued.

CONCLUSIONS

The prevention of acute RSV bronchiolitis in infancy remains a major challenge. The morbidity associated with this condition is considerable, and the financial strain placed on health services is enormous. With improved supportive care, the mortality is now low even in at-risk groups, but the condition still poses a major threat to the health of infants with underlying disease. A phenotypic approach to the management of infants infected with the virus appears to be important both clinically and when assessing the outcomes in clinical trials. The basis of treatment for those with acute bronchiolitis remains good supportive care.

Despite an enormous amount of work aimed at preventing the annual influx of infants with acute bronchiolitis, it seems likely that the annual epidemics of RSV will continue to be the cause of season-affective disorder among pediatricians for the foreseeable future.

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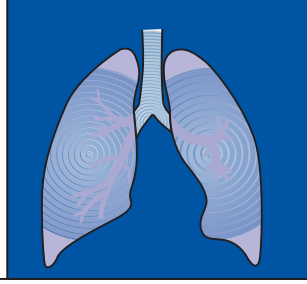


CHAPTER 35 Bacterial Pneumonia, Lung Abscess, and Empyema

Susan E. Crawford and Robert S. Daum

TEACHING POINTS

- The etiology of pneumonia varies based on patient age, vaccination status, relevant exposures, immunologic status, and clinical setting in which the causative agent was acquired.
- Determining the etiology of pneumonia is difficult and the choice of antimicrobial therapy is often empirical.
- *Streptococcus pneumoniae* is the most common bacterial etiology of community-acquired pneumonia in all age groups including children.
- Immunization practices have influenced the incidence of *Haemophilus influenzae* type b and *S. pneumoniae* pneumonia.
- The incidence of pneumonia with empyema appears to be increasing in many geographic locales across the world; the optimal treatment strategies remain to be defined.

GENERAL ASPECTS OF BACTERIAL PNEUMONIA

History

The importance of pneumonia has been known at least since the time of Hippocrates, who described *peripneumony* as an acute, febrile illness characterized by unilateral or bilateral pain, painful breathing, cough, scanty "high-colored" urine, and improvement usually by about the seventh day. It was not until around 200 AD, however, that Aretaeus provided a clinical description of this syndrome. In the early 1700s, De Konilfeld offered the first distinction between pleurisy and pneumonia. Later, in 1728, Boerhaave distinguished lobar pneumonia from other syndromes. After the introduction of percussion by Auenbrugger in 1761, Laennec described the signs and symptoms of pleurisy and pneumonia in 1819 and, further, detailed the histopathologic changes for the first time. In 1837, Seiffert introduced the term *bronchopneumonia*, and in 1850, Barthez and Rilliet called attention to the fact that this syndrome also occurred in children.

The modern era of clinical observation regarding pneumonia began in 1880 when Sternberg recognized *Pneumococcus* organisms in the saliva of healthy adults and continued in 1881 with Pasteur's observation of *Pneumococcus* organisms in the saliva of a child with pneumonia. However, not until 1884 did Fraenkel suggest that the organism found by Sternberg and Pasteur (known as the *coccus of sputum septicemia*) was the most common cause of pneumonia. In the early twentieth century, the term *Captain of the Men of Death* was applied to bacterial pneumonia in recognition of its high mortality rate, the term having originally been coined by Bunyan in reference to tuberculosis.[1]

Epidemiology

The World Health Organization (WHO) estimated that in 2000 to 2003, pneumonia was responsible for 2 million deaths each year, or 19% of the 10.6 million yearly deaths in children younger than 5 years of age.[2] Results from several studies in the United States indicated that children younger than 5 years of age have an incidence rate of three to four lower respiratory tract infections per 100 children per year.[3,4] Overall, the highest rates of pneumonia have been documented in young children; the rates gradually decline with increasing age, a trend continuing until adolescence.[5,6] Most mortality occurs in developing countries, where a child younger than 5 years of age dies every 7 seconds of an acute respiratory infection. The WHO reports that 46% of worldwide pneumonia deaths occur in Africa, where undernutrition is a large contributor to this mortality rate. Even in developed countries, however, childhood pneumonia is an important cause of morbidity and remains an important reason for the hospitalization of young children.[7,8]

Thus lower respiratory tract infections, particularly pneumonia, constitute a major health problem throughout the world. Bacterial pneumonias make up only a small number of lower respiratory tract infections but have the highest mortality rates. Overall, the mortality rate from bacterial pneumonia is 2.7 times higher than that from presumed viral pneumonia.[9]

Several factors have been associated with an increased incidence or severity of pneumonia, particularly in developing countries.[10] These include young age, increasing birth order, low birth weight,[11,12] young maternal age, limited parental education, day-care attendance, exposure to passive tobacco smoke,[13] industrial pollution,[14] urban residence,[15] previous history of pneumonia, chronic heart and lung disease, male gender,[4] and asthma.

In addition, malnutrition has been identified as a risk factor for the incidence and severity of pneumonia. The results of one study found that although the incidence of

respiratory infections was similar in nourished and malnourished Costa Rican children, the likelihood of pneumonia was 12 times higher in the malnourished group.[16] A possible explanation for this predisposition is vitamin A deficiency.[17] However, data conflict on this point.[18]

Environmental factors may also affect the incidence of pneumonia. For example, up to 30% of urban households in developing countries use biomass fuels, such as wood, agricultural waste, and manure for cooking and heating, and, although a resulting increase in bacterial pneumonia has not been documented, their use has the potential to disrupt physiologic protective mechanisms of the lung. Household crowding may also be a risk factor, presumably because it facilitates the spread of droplets containing relevant pathogens.[19]

Many pathogens that cause bacterial pneumonia, such as *S. pneumoniae*, *H. influenzae* type b, and, occasionally, *S. aureus*, can be transmitted from person to person by the spread of contaminated droplets during breathing, coughing, or sneezing. Contaminated water and aerosols have been implicated in the spread of some pathogenic bacteria, such as *Legionella pneumophila*. In hospitals and other health care facilities, contaminated equipment used for respiratory support may be involved in outbreaks of nosocomial pneumonia caused by pathogens such as *Klebsiella pneumoniae* or *Pseudomonas aeruginosa*. Some pathogens associated with bacterial pneumonia in children, such as *Francisella tularensis* and *Yersinia pestis*, are zoonoses, animal pathogens that occasionally infect humans.

On contact with a pathogenic organism, many individuals become asymptomatic carriers, whereas others become ill, some in a very short time. Similarly, the time of communicability of the offending pathogen after antibacterial therapy has been initiated is uncertain; this is probably pathogen specific and aided by case-specific clinical features, such as the presence of cough. As a rule of thumb, many experts consider that communicability is greatly decreased 24 hours after the initiation of therapy, although few explicit data support this view.

Cases of bacterial pneumonia are sporadic and may occur any time throughout the year. However, most studies indicate a peak incidence in winter, which may extend into early spring.[5] This seasonal distribution may partly reflect an association between bacterial pneumonia and certain preceding viral illnesses that have a peak winter incidence. For example, *S. aureus* pneumonia has been associated with influenza epidemics.

Epidemics of community-acquired bacterial pneumonia are relatively unusual. In nosocomial settings, such as intensive care units or nurseries, outbreaks of pneumonia caused by *K. pneumoniae*,[20,21] *P. aeruginosa*,[22] and other microorganisms have been described. Typically, the spread of the organism in these settings has implicated contaminated health care delivery materials or local environmental contaminations.

Many cases of bacterial pneumonia in children are preventable by the current universal vaccination programs. For example, invasive *H. influenzae* type b infection, including pneumonia, has decreased by more than 95% with the implementation of universal immunization programs in infants. Additionally, a 7-valent protein-polysaccharide pneumococcal conjugate vaccine licensed for use in infants and young children in the United States in 2000 has decreased the incidence of pneumococcal pneumonia.[23,24] Importantly, deploying these vaccines in developing countries has been problematic because of their high cost.

Certain underlying conditions render a host more susceptible to bacterial pneumonia (Box 35-1).[25,26] These may be divided into those likely to produce pneumonia in a single region of the lung and those likely to produce diffuse or multifocal pneumonia.

Etiology

The etiology of any pneumonia (Box 35-2), including that caused by bacteria, differs according to age of the patient, the clinical setting in which the pneumonia was acquired (e.g., community versus hospital), relevant local epidemiology (e.g., annual respiratory syncytial virus epidemics and influenza activity), the vaccination status of the child (e.g., *H. influenzae* type b), relevant exposures (e.g., to contaminated water or infected animals), host factors (e.g., the presence of underlying diseases that predispose to pneumonia), and immunologic status. Even with all relevant clinical information, determining the etiology of uncomplicated pneumonia is difficult and infrequently attempted in practice; with the exception of blood cultures, culture material suitable for definitive diagnosis requires invasive procedures not justifiable for mild to moderately ill children. Thus, in most cases, the precise etiology is never determined, and the therapeutic approach to the patient is based on generalizations regarding etiology in the relevant clinical setting.[4,27,28] This is particularly true for community-acquired pneumonias, many of which are self-limited diseases for which no specific therapy is available or needed.

In the neonate, the most common causes of bacterial pneumonia are the group B β-hemolytic streptococci (GBS) and gram-negative enteric bacilli, such as *E. coli* and *K. pneumoniae*, the same organisms that cause bacteremia and sepsis. Less frequent etiologic agents include *S. aureus*, *P. aeruginosa*, *H. influenzae* (often not serotype b), *S. marcescens*, and *Flavobacterium* species.

In children past the neonatal period, viruses are the most frequent etiologic agents in community-acquired pneumonia, although a viral and bacterial etiology may occur concomitantly.[29-31] In addition, *Chlamydia trachomatis* is an important pathogen in infants who are 3 to 19 weeks of age.

Among the bacterial etiologies, *S. pneumoniae* is most frequent.[30,32,33] *H. influenzae* type b was an important cause in the prevaccination era but is now rare. *S. aureus* pneumonia is also infrequent but requires special consideration because it may rapidly progress and because the usually prescribed antimicrobial therapies may not provide satisfactory coverage against this pathogen. The group A β-hemolytic streptococci are an uncommon cause of pneumonia, although their necrotizing nature may prolong its course. In children who chronically aspirate, anaerobic bacteria are important pathogens implicated in pulmonary infections.[34]

Viruses are also the most common etiologic agents in school-age children and adolescents. Bacterial causes are similar to those causing disease among preschoolers. *S. pneumoniae* is the most frequent cause. *S. aureus*, *H. influenzae*, and *Neisseria meningitidis* are rare causes. *Mycoplasma pneumoniae* is an important etiologic consideration among school age children.

BOX 35-1 Conditions Predisposing to Bacterial Pneumonia

Abnormalities Usually Resulting in Pneumonia in a Single Lung Region

- Abnormalities within the airway lumen
  - Foreign body
  - Bronchial tumor
    - Adenomas
    - Mucoepithelial dysplasia
    - Lipoma
    - Papilloma
  - Broncholithiasis
- Abnormalities producing external compression of the airway
  - Lymphadenopathy associated with infections
    - Tuberculosis
    - Histoplasmosis
    - Coccidioidomycosis
    - Blastomycosis
    - Other conditions
  - Lymphadenopathy associated with tumors
  - Structural abnormalities that cause decreased mucus clearance
    - Tracheal bronchus
    - Bronchial stenosis or atresia
    - Localized bronchiectasis
- Right middle lobe syndrome associated with asthma
- Bronchogenic cyst
- Pulmonary sequestration syndrome

Abnormalities Usually Resulting in Pneumonia in One or More Contiguous Lung Regions

- Microaspiration
  - Impaired swallowing
    - Cranial nerve injury
    - Drug-induced injury
    - Seizures
    - Cricopharyngeal incoordination
      - Maturational incoordination
      - Familial dysautonomia
      - Myasthenia gravis
      - Sydenham's chorea
      - Multiple sclerosis
    - Neuromuscular disorders
      - Idiopathic cricopharyngeal achalasia
      - Myotonic dystrophy
      - Muscular dystrophy
      - Other conditions
  - Laryngeal cleft
  - Submucosal cleft
  - Obstructive lesions of the tongue or larynx
  - Esophageal obstruction or dysmotility
    - Vascular rings
    - Mediastinal cysts
    - Enteric duplications
    - Esophageal web
    - Esophageal stricture
    - Achalasia
    - Tracheoesophageal fistula before and after repair
  - Gastroesophageal reflux
- Asthma
- Immunodeficiency syndromes
  - Severe combined immunodeficiencies
  - Immunoglobulin deficiencies
  - Wiskott-Aldrich syndrome
  - Ataxia-telangiectasia
  - DiGeorge syndrome
  - Immunodeficiency secondary to other diseases or cytotoxic treatment
  - Complement deficiencies
  - Phagocyte defects
- Acquired immunodeficiency syndrome (AIDS)
- Mucociliary dysfunction
  - Cystic fibrosis
  - Ciliary dyskinesias
  - Tracheobronchomegaly
  - Cartilage deficiency
  - Williams-Campbell syndrome
- Segmental bronchomalacia
- Congenital heart disease
- Bronchopulmonary dysplasia
- Pneumotoxic gases, drugs, and radiation
- Miscellaneous
  - Sickle cell disease
  - Alveolar proteinosis
  - Langerhans' cell histiocytosis
  - Idiopathic pulmonary fibrosis

In hospital-acquired pneumonia, consideration of the possible etiology requires knowledge of the institution-specific epidemiology of nosocomial infections.[35] Most published data defining the etiology of nosocomially acquired bacterial pneumonia have been gathered from adult populations, and it is likely that the etiologies in children are similar.[36] Gram-negative organisms, such as *K. pneumoniae*, *Pseudomonas* and *Serratia* species, and gram-positive organisms such as *S. aureus*, occur most frequently. Water-associated organisms such as *Acinetobacter* and *Flavobacterium* species, are occasionally implicated as well. Nosocomially acquired *Legionella* pneumonia is rare in pediatric populations[37] and has been linked to contaminated aerosols, typically from the water supply or air-conditioning cooling towers.[38]

In developing countries, the bacterial agents frequently responsible for community-acquired pneumonia are not unlike those causing similar disease in developed countries.[39] Exceptions include the important role ascribed to nontypeable and non-type b *H. influenzae* isolates in Papua New Guinea, The Gambia, and Pakistan as well as an observation of uncertain importance regarding the serologic diagnosis of

BOX 35-2 Bacterial Etiology of Pneumonia in Children

Causes of Frequent Clinical Concern

Streptococcus pneumoniae
Streptococcus aureus
Group B streptococci*
*Escherichia coli**

Causes of Occasional Clinical Concern

Group A streptococci
Anaerobic organisms
Haemophilus influenzae†
*Klebsiella pneumoniae**

Causes of Rare Clinical Concern

Acinetobacter species
Actinomycosis species
Arcanobacterium haemolyticum
Bacillus anthracis
Bacillus cereus
Bordetella henselae
Bordetella pertussis‡
Brucellosis species
Citrobacter species
Coxiella burnetii
Enterobacteriaceae
Filaria tularensis
Kingella kingae
Legionella pneumophila
Leptospira interrogans
Listeria monocytogenes
Moraxella catarrhalis
Neisseria meningitidis
Nocardia species
Non–group A and non–group B streptococci
Pasteurella multocida
Proteus species
Pseudomonas aeruginosa
Pseudomonas cepacia
Pseudomonas pseudomallei
Streptobacillus moniliformis
Salmonella species
Serratia marcescens
Yersinia enterocolitica
Yersinia pestis

*Designations of *frequent* or *occasional* apply to pneumonia in the neonatal period.

†*H. influenzae* type b vaccine has greatly decreased the number of cases of childhood bacterial pneumonia caused by *H. influenzae.*

‡Pertussis is discussed in Chapter 38.

putative *Moraxella catarrhalis* infection in children with pneumonia in The Gambia.[40,41]

Pathophysiology

Most bacterial pneumonia results from inhalation of contaminated air. Bacteria, including pulmonary pathogens, can be found in ambient air. Droplets can be transmitted from person to person, and pharyngeal secretions may contain up to 10^8 bacteria per milliliter of saliva. Bacteria may gain access to the respiratory tract by inhalation or microaspiration, events occurring daily even in normal children.[42] Whether pneumonia results from such bacterial entry depends on the outcome of interactions between the bacterium and the host respiratory defense system (Fig. 35-1).

Droplet size plays a major role in determining the level of the respiratory system reached by inhaled bacteria. Most inhaled bacteria are enveloped in moisture and therefore acquire aerodynamic and dimensional characteristics that determine their destination. For example, particles larger than 10 μ do not usually traverse the pharynx, whereas those 3 to 10 μ may lodge in the larger airways, and those 0.5 to 3 μ can reach the alveolar surface.[43]

Certain medical interventions or anatomic abnormalities can facilitate bacterial transit toward the alveolus. Examples include tracheostomy, endotracheal intubation, and respiratory therapy. Similarly, direct extension to the pulmonary parenchyma through a bronchopleural fistula also facilitates bacterial access to the alveolar epithelial surfaces.[44] Bacteria may also reach the lungs via metastatic hematogenous spread from a distant site.

Because the usual interaction between bacteria and the host limits bacterial access to the lowest regions of the respiratory tract, it is generally believed that the respiratory tract below the major bronchi is sterile or nearly so. However, when a bacterium does gain access to the alveolus, additional host defense mechanisms are called into action. The bacterium makes initial contact with the alveolar wall and is enmeshed in the epithelial lining fluid that contains opsonins and, depending on the immunologic experience of the host, specific immunoglobulin G (IgG) antibody. The usual outcome of this interaction is ingestion by alveolar macrophages (alveolar type II cells); an alternative, less common outcome is complement-mediated bacterial lysis. The former mechanism is especially important in dealing with encapsulated bacteria such as *S. pneumoniae*. The process is rapid; in an animal exposed to a bacterial inoculum, whether aerosolized or instilled onto the alveolar surface, bacteria remain free for only 30 minutes before being internalized by a macrophage.[45,46]

When these mechanisms fail to destroy alveolar bacteria, polymorphonuclear leukocytes with their phagocytic capability are recruited, and an inflammatory response, presumably mediated by cytokine release, occurs. If continued, this process results in pneumonia with attendant vascular congestion and exuberant edema, best characterized for pneumonia caused by pneumococci. In this instance, sheets of pneumococci ride waves of edematous fluid from alveolus to alveolus through the pores of Kohn. This edematous zone of engorgement progresses centrifugally and leaves behind clusters of erythrocytes and purulent exudate consisting of fibrin, polymorphonuclear leukocytes, and bacteria. This stage is histologically termed *red hepatization*. The pneumococcal cell wall is probably the bacterial component that initiates these events.[47] Pneumococci do not produce a known toxin, and it is thought that bacterial growth and the exudative response to their presence cause consolidation.[47]

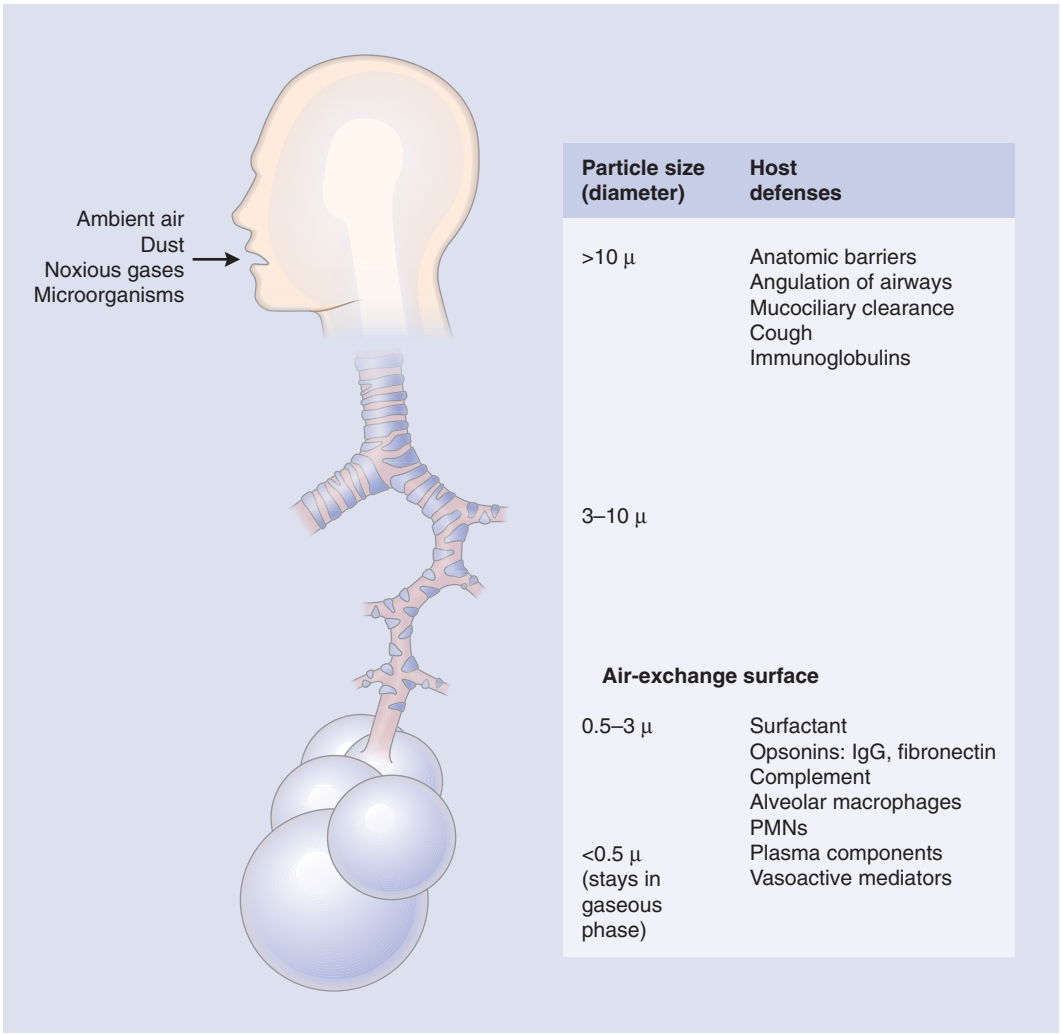


Figure 35-1 Lung defense system. IgG, immunoglobulin G; PMNs, polymorphonuclear neutrophils [leukocytes].

The next stage in pathogenesis is termed *gray hepatization*. Events characterizing this stage include the active phagocytosis of pneumococci by polymorphonuclear leukocytes. The release of bacterial cell wall components and pneumolysin by enzymatic degradation leads to increased inflammation and cytotoxic effects on all pulmonary cells. The result is the blurring of cellular elements and the loss of cellular architecture.

Resolution of pneumonic consolidation begins when anticapsular antibody appears. Polymorphonuclear leukocytes continue to phagocytose the pneumococci; monocytic cells clean up the debris. The term *zone of resolution* is sometimes applied to such an area. As long as the reticular structure of the lung remains intact (i.e., involvement of the interstitium is absent), complete parenchymal restoration and healing of the alveolar epithelium occur after successful treatment. Scarring is minimal.[47,48]

Death from bacterial pneumonia is due to respiratory failure, which occurs when the airspaces are filled with edematous fluid or exudate. The residual volume of the lung is markedly expanded by this fluid, which precludes air exchange at the alveolar level. The clinical picture of sepsis may be concomitant; shock may further complicate end-organ perfusion, and a mixed metabolic and respiratory acidosis therefore typically precedes death.[48] The pathogenesis of pneumonia caused by other bacteria may vary. For example, tissue necrosis and rapid bacterial spread throughout the alveolar spaces characterize pneumonia caused by *S. aureus* and make full recovery less likely when extensive necrosis occurs.

Clinical Manifestations

In children who are no longer neonates and who have acute pneumonia, no reliable clinical symptoms or signs distinguish the pneumonia caused by bacteria from that caused by other infectious agents. Children with bacterial pneumonia are more likely to appear ill, anxious, or distressed; have a higher incidence of and more severe fever; and have physical signs attributable to respiratory tract infection. However, there is sufficient overlap in the clinical picture to recommend caution in inferring etiology. For bacterial pneumonia of any etiology, cough is usual but not invariable. Sputum production by children younger than about 8 years of age is rare because any sputum produced is swallowed. Abdominal pain and emesis are variable complaints and may be sufficiently severe

to misdirect the diagnostic evaluation toward an acute abdominal condition.

Signs localized to the respiratory tract may provide important clues to the diagnosis. Audible expiratory noise or grunting may be present in young children or infants. Cyanosis and hypoxia, flaring of the alae nasi, subcostal and intercostal retractions, and nonspecific signs of dyspnea may also be present. Shallow breathing, splinting, and tachypnea (≥50 to 60 breaths/min in children younger than 12 months of age and ≥40 breaths/min in older children) suggest pneumonia. Pain during respiration, often called *pleuritic pain,* may be present, as may pain appearing to originate from an abdominal process. On auscultation, crackles, evidence of pulmonary consolidation, decreased breath sounds, bronchophony, increased fremitus, and dullness to percussion are often present. A friction rub suggests pleuritis, a common concomitant condition of bacterial pneumonia.

In the neonate, the clinical picture of bacterial pneumonia may resemble that found in the older child. However, apnea and signs suggestive of generalized sepsis may be the dominant clinical features instead. Auscultation of the chest may produce normal results; fever and cough are usually absent.

Diagnosis

Guidelines for the diagnosis of pediatric pneumonia were formulated by a group of Canadian pediatricians.[49] Most pediatric patients who are no longer neonates and who have bacterial pneumonia have symptoms and signs suggesting an abnormality of the respiratory system; in their absence, bacterial pneumonia is an unlikely diagnostic consideration. An exception may be some children with very high temperature (≥41.1° C) who may have radiographic evidence of pneumonia in the absence of findings attributable to respiratory system infection.[50] In developing countries, where sophisticated diagnostic tools may not be available, it has been suggested by the World Health Organization that tachypnea with indrawing of the respiratory muscles should alert the clinician to a presumptive diagnosis of pneumonia. Although the reliability of this superficial approach is obviously less than optimal, respiratory rates higher than 50 and 40 breaths/min have been used as diagnostic criteria in children younger than 12 months and between 13 months and 5 years of age, respectively,[51-55] particularly when more sophisticated tests are unavailable.

Once a determination is made that pneumonia is likely, defining its etiology poses a clinical challenge. Indeed, for many children with pneumonia, particularly when it is community acquired and mild, clinicians often take an empirical approach and perform little more than a blood culture in the way of investigation. Occasionally, there is no investigation at all; this approach is justified because the procedure required to obtain a specimen is invasive and examination of the specimen is unlikely to accurately provide the etiology. A result of this clinical dilemma is that more than 80% of patients who have "nonbacterial" pneumonia may receive antimicrobial therapy.[56]

In cases of suspected bacterial pneumonia in which precise microbiological diagnosis is deemed clinically important, a variety of techniques are available to sample respiratory secretions at various levels of the respiratory tract. Many of these procedures use instrumentation, such as a bronchoscope or another suction device, that traverses the pharynx or upper airway.[57] Generally, the easier the specimen is to obtain, the less likely it is useful in providing diagnostic help.

Moffet[58] has divided acute pneumonia culture sources in children into the following categories: conclusive, occasionally conclusive, and dubious. Examples of conclusive culture sources include blood, pleural fluid, and material obtained by open lung biopsy or lung puncture. Occasionally conclusive sources include cultures obtained at bronchoscopy, cultures of tracheostomy secretions, and, in older children, cultures of fluid obtained by transtracheal aspiration. Cultures of dubious importance for bacterial pneumonia include nasotracheal aspirates and throat cultures. Potential pathogens may be present as flora at these sites, which may create ambiguity in interpretation. For example, the leading cause of bacterial pneumonia, *S. pneumoniae,* may colonize the nasopharynx in up to 40% of healthy children in the winter.[56]

Therefore the clinician must consider which various diagnostic tests should be used in the evaluation of a patient in whom bacterial pneumonia is likely. Consideration is given as to how the microorganisms obtained from a given site may reflect the theoretical gold standard, the demonstration of etiologic bacterium in the infected lung.[59]

In a patient presumed to have pneumonia, isolation of a bacterium from the blood,[60] pleural fluid, or lung tissue is considered etiologic. However, bacteremia occurs in only 3% to 12% of cases[56] of presumed bacterial pneumonia, and at least 1 day is required to obtain results from tests. Because phlebotomy is relatively noninvasive and inexpensive, a blood culture is recommended for routine performance when the clinician is evaluating children for possible bacterial pneumonia. When pleural fluid is present, whether ascertained by physical examination or radiography of the chest, sampling it (e.g., by ultrasound-guided needle aspiration) provides a valuable specimen for Gram staining and culture. Depending on the clinical situation, culture for *Mycobacteria* species, fungi, or bacteria requiring special media may also be relevant. Additional studies commonly performed in the evaluation of such pleural effusions include a leukocyte count (including cytologic analysis when relevant) and measurement of the pH, protein, glucose, and lactate dehydrogenase concentrations. Attempted detection of relevant bacterial antigens (e.g., by latex agglutination) is sometimes performed. In practice, diagnostic pleurocentesis is performed in patients sufficiently ill to require hospitalization for putative bacterial pneumonia, in patients who nosocomially acquire presumed bacterial pneumonia (particularly during a course of antiinfective therapy), or in patients with presumed bacterial pneumonia and pleural effusion who do not respond to initial, empirically chosen therapy.

In children, the examination of sputum by Gram stain and culture is limited by the difficulty in obtaining a satisfactory specimen, especially in children younger than 8 years of age. The quality of the specimen can be inferred from a paucity of epithelial cells. Material that is produced by cough and that contains excess squamous rather than epithelial cells testifies to an upper tract origin. Clinical laboratories generally do not process specimens submitted as "sputum" with more than 25 squamous cells per low-power field on micro-

scopic examination. Other useful parameters are the presence of polymorphonuclear leukocytes and a monotonous or relatively monotonous morphology of the bacteria in the specimen. (Upper respiratory tract flora consists of bacteria of diverse morphologic structure.)

Even if a satisfactory specimen can be obtained, its usefulness in the diagnosis of bacterial pneumonia is questionable. Although once considered helpful in defining the etiology, it is now widely accepted that the diagnosis made from organisms recovered from sputum correlates poorly with that made from organisms recovered from more reliable sites, such as blood or pleural fluid, because of contamination of the sputum by the flora in the upper respiratory tract. In adults, these secretions may contain 10^8 to 10^9 bacteria per milliliter. Nevertheless, in the presence of many polymorphonuclear leukocytes and bacteria of a single morphology, Gram stain and culture of properly collected sputum may provide useful information regarding the etiology of bacterial pneumonia.[61] Identification of acid-fast bacilli or fungi by examination of sputum provides valuable diagnostic information because such microbes are infrequent constituents of the normal flora.

A variety of clinical situations require a more aggressive approach for defining the etiology of a putative bacterial pneumonia. Examples include acute pneumonia when a patient is severely ill or has respiratory failure, the condition fails to respond to therapy, the condition worsens despite initial empirical antimicrobial therapy, or it occurs in a patient with compromised immunologic integrity. In these instances, determining the etiology may be necessary so that more precise therapy can be prescribed and the toxicity of unnecessary agents can be avoided.

Bronchoscopic techniques are sometimes used in the diagnosis of bacterial pneumonia, particularly when there is local expertise in performing the procedure and when the child is sufficiently stable to allow the 1- to 2-day interval required for specimen handling. Bronchoalveolar lavage (BAL) fluid obtained during bronchoscopy should be submitted to the appropriate laboratories for histopathologic and microbiologic evaluation. Interpretation of the data is limited by the nonspecificity of the inflammatory cells present (even in large quantities) and the uncertainty regarding the importance of bacteria and yeast present in the specimen, which may represent airway flora or organisms infecting the lung. Aubas and coworkers[62] suggested that two indexes, the simplified bacterial index and the predominant species index obtained from quantitative BAL fluid cultures, were useful in defining the presence and etiology of bacterial pneumonia in adults. However, these indexes are not widely used, and the observations have not yet been extended to children.

To solve the problem of airway contamination, clinicians have used devices such as a protected catheter brush or a telescope-plugged catheter. Cultures obtained by the brush technique correlated well with the isolate obtained from blood in a small number of bacteremic adults with pneumonia.[63] However, the telescope-plugged catheter does not add much to the results obtained from lavage.[64] Few assessments of these bronchoscopy-based techniques have been performed in children, but the available data in adults suggest that quantitative BAL bacterial culture may help in the accurate diagnosis of bacterial pneumonia, particularly when a single or limited number of bacterial species is present in excess of 10^3 colony-forming units per milliliter.

Transtracheal aspirations are generally not performed in young children because of the high rate of complications, particularly in small infants, uncooperative children, and children with bleeding diatheses, severe coughing, severe hypoxemia, and dyspnea. It is uncertain whether the procedure is useful in the accurate diagnosis of bacterial pneumonia.[65] The correlation with organisms obtained by lung puncture[66] is only fair.

Obtaining lung tissue for culture can be accomplished by percutaneous lung puncture,[66] transthoracic needle aspiration biopsy (TNAB),[67-69] or open lung biopsy.[70] These procedures are normally considered in an immunocompromised host and in patients with severe pneumonia, particularly when the condition is nosocomially acquired or when empirical therapy has not produced a clinical response. They are more likely to yield important information regarding etiology when performed early in the clinical course. Percutaneous lung puncture and TNAB are usually performed under radiologic guidance[68] and should be done by an experienced person.[66] In both procedures, the pleural space is aspirated to detect an inapparent effusion before entry of the parenchyma proper. The clinician may choose not to continue into the parenchyma when pleural fluid is encountered, reasoning that the pleural fluid may provide sufficient opportunity to recover the pathogen without the increased morbidity of the lung puncture itself. Important complications of these two procedures are hemoptysis and pneumothorax,[66] although a review of 32 lung puncture studies reported in the last 70 years found that treatment for a complication was needed in less than 0.5% of cases.[67] TNAB has the advantage of providing a core of tissue for histologic examination when a large-bore needle is used, although the results may occasionally be misleading.[71] Dorca and associates[68] compared the results of TNAB performed with an ultrathin needle to other microbiologic and serologic criteria frequently used in the diagnosis of nosocomial pneumonia in adults. TNAB results were specific and had a high positive predictive value in this population. However, the relatively low sensitivity (60.9%) and low negative predictive value precluded reliance on this single diagnostic modality.[68] Vuori-Holopainen and colleagues[69] also compared the results of TNAB with microbiologic criteria used in the diagnosis of community acquired pneumonia in children; they found a similar sensitivity rate of 59% in determining the etiology of pneumonia.

Open lung biopsy is often considered the standard but requires general anesthesia and a skilled support staff. It is usually performed when a variety of microbiologic diagnoses are being considered but seldom performed when bacterial pneumonia is the most likely consideration. Pneumothorax may complicate the postoperative recovery and prolong the ventilator-dependent recovery phase.

A variety of nonspecific laboratory evaluations have been used to support the likelihood of bacterial pneumonia; these include an increased serum concentration of C-reactive protein, an increased erythrocyte sedimentation rate, and an increased blood leukocyte count with a predominance of polymorphonuclear leukocytes.[56] However, all these techniques suffer from poor sensitivity and positive predictive value.[32,72,73]

Bacterial antigen detection in blood and urine has a limited role in the diagnosis of bacterial pneumonia. Several available techniques include counterimmunoelectrophoresis, latex particle agglutination, and staphylococcal coagglutination; the last two are more widely used. Only a limited number of bacterial antigens theoretically useful for the diagnosis of bacterial pneumonia (e.g., *S. pneumoniae*, *H. influenzae* type b, *N. meningitidis*, group B streptococci) can be detected by commercially available methods; however, false-positive and false-negative results are frequent.[30,32,56,74,75] Furthermore, the meaning of *antigenemia* or *antigenuria* may be difficult to interpret because the patient may have an infection such as pneumonia, be an asymptomatic carrier of an organism such as a pneumococcus, or be colonized by a "cross-reacting" microorganism, such as *S. pneumoniae* type 14, which cross reacts with *H. influenzae* type b. Bacterial antigen detection in pleural effusions was recently evaluated and found to have a sensitivity of 90% and specificity of 95% when compared with the test standard of culture or polymerase chain reaction (PCR).[76]

The serologic diagnosis of bacterial pneumonia has received some attention, but is rarely used in clinical practice. Reasons include the delayed time frame inherent in the process of gathering sera and performing assays, the paucity of bacterial agents for which reliable antibody assays are available, and the immature immune response often present at the time of infection (e.g., with *H. influenzae* type b) that results in a modest or absent antibody response to infection. Investigators from Finland claimed success in diagnosing pneumonia by performing enzyme immunoassays on "convalescent" sera (obtained as early as 5 days after hospitalization) to detect antibodies directed against *S. pneumoniae* (pneumolysin), *H. influenzae* type b (whole cell), *M. catarrhalis* (whole cell), and *M. pneumoniae* (whole cell).[73] For the reasons already noted, it seems unlikely that this approach will become a widely available, clinically useful tool.

Highly sensitive techniques that detect bacterial nucleic acid sequences, such as in situ hybridization, PCR, and ligation-mediated PCR, have shown some promise in determining the etiology of bacterial pneumonia. Their value will likely be limited when performed on specimens such as sputum, in which discrimination between a colonizing and an infecting isolate has proved problematic. However, PCR may be a useful diagnostic tool when performed on a normally sterile fluid, such as blood or pleural fluid. For example, streptococcal sequences from the autolysin gene *lyt* were found in the blood of patients with presumed pneumococcal pneumonia in The Gambia.[77] Perhaps the greatest promise of these techniques lies in the relatively rapid diagnosis of infections caused by *Chlamydia*, *Mycoplasma* and *Mycobacterium* species, *Bordetella pertussis*, and a variety of viruses. In many of these instances, PCR may be useful on specimens obtained from airway secretions because these microorganisms are not typically among the denizens of the respiratory tract, and culturing them requires extra effort and time.

Many patients require evaluation for a variety of pathogens not amenable to detection by standard culture techniques. For example, evaluation of a patient, particularly when severely ill or immunocompromised, includes tests for important viral pathogens. It is important to remember that multiple pathogens may be responsible for pneumonia in a given instance (e.g., when influenza is complicated by bacterial pneumonia). In addition, evaluation of a patient with pneumonia may involve an etiologic search for fungi, *P. jiroveci*, mycobacteria, and *Chlamydia* and *Mycoplasma* species.

Imaging Modalities

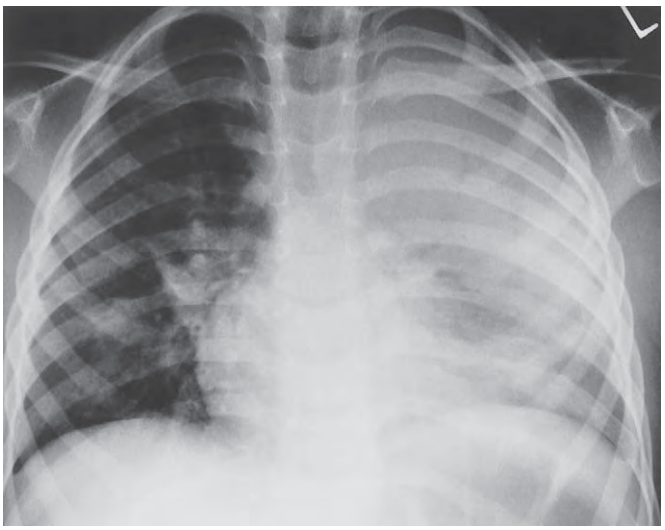
In the absence of respiratory signs, the detection of pneumonia by radiography in otherwise healthy young children is unlikely[78]; thus, the use of a radiograph as a screening tool should generally be avoided and carefully individualized. In older children, a chest radiograph is usually not indicated in the absence of respiratory signs except as part of an evaluation for prolonged, unexplained fever.

Interpretation of a chest radiograph is seldom performed without clinical data regarding the patient's illness. Even experienced radiologists are biased by this clinical information and incorporate it into the assessment of a radiograph.[79] Indeed, the rate of pneumonia diagnosed when radiologists were aware of the clinical impression was higher than that when radiologists were unaware of the clinical data.[79] Thus, despite a tendency to accord a standard to the chest radiograph, this potential for "overcall" bias should be kept in mind. Conversely, a negative radiograph does not exclude the diagnosis of bacterial pneumonia, particularly when the illness has been of short duration.

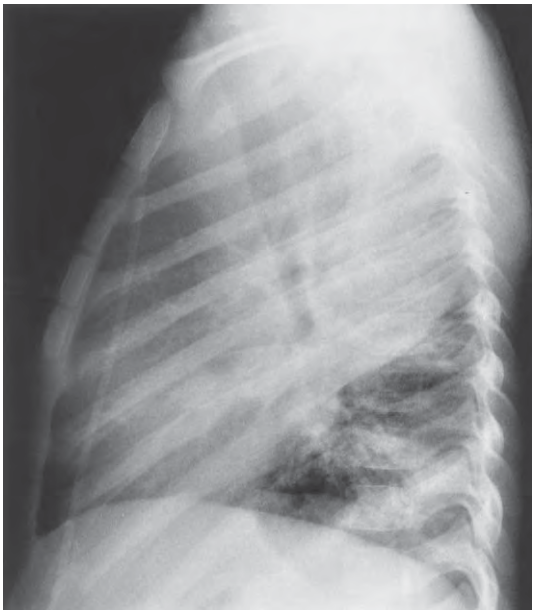
Despite these concerns, the radiograph of the chest remains an important diagnostic tool in the evaluation of a child for bacterial pneumonia.[80] The frontal posteroanterior upright chest view is generally preferred to an anteroposterior view to minimize the cardiac shadow, except in the young child in whom there is no difference in the cardiothoracic ratio between the two positions.[81] In this instance, an anteroposterior supine film is preferred because of the increased likelihood of better inspiration and ease of immobilization. It has been suggested that the frontal posteroanterior chest view (anteroposterior in young children) may often suffice for initial radiographic evaluation. However, the possibility that pneumonia may "hide" behind the dome of the diaphragm or the cardiac silhouette has resulted in the lateral film being routinely obtained at the initial evaluation.

Radiographic findings in children with pneumonia are traditionally divided into interstitial and alveolar/airspace patterns. Bacterial pneumonias are usually alveolar/airspace processes, and interstitial patterns usually reflect other etiologies; however, there is substantial overlap as well as the possibility that one pattern may progress to the other with ongoing disease.[56] Highly suggestive of bacterial pneumonia are a large lobar or diffuse consolidation, a bulging fissure (Fig. 35-2) implying extensive exudate or occult abscess in a lobar pneumonia, and associated pleural effusion[56] in the setting of a clinical pneumonia. Such pleural effusions may occur in about 20%, 40%, and 60% to 80% of children with pneumonia caused by *S. pneumoniae*, *H. influenzae* type b, and *S. aureus*, respectively.

Swischuk and Hayden[82] suggested that several radiologic patterns help differentiate among possible etiologies of an infective pulmonary infiltrate. A so-called *lobar consolidation*, whether homogeneous or fluffy, suggests a bacterial or *M. pneumoniae* pneumonia. A diffuse, bilateral, fluffy infiltrate extending into the periphery suggests a bacterial process,

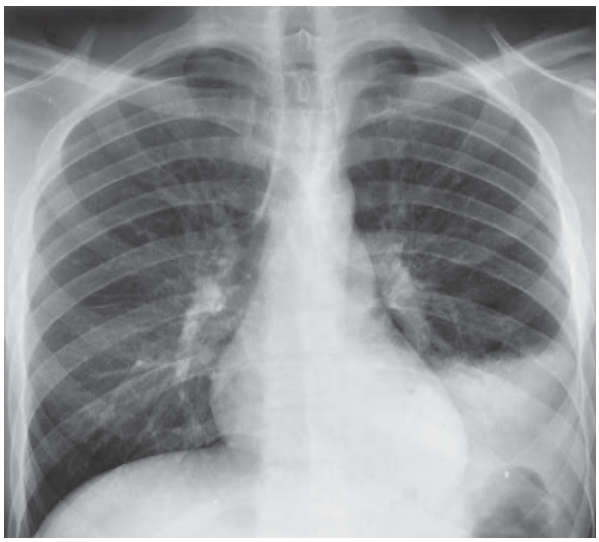


A

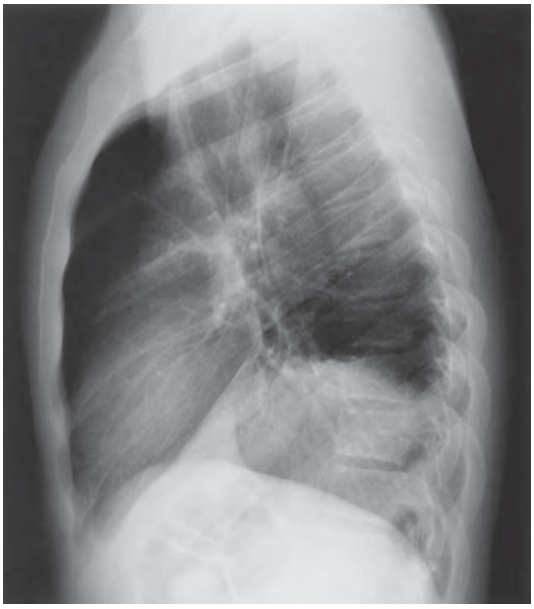


B

Figure 35-2 Bulging fissure in a 3-year-old boy with group A streptococcal pneumonia. The chest radiograph demonstrates consolidation in the left upper lobe with expansion of the lobe. The increased volume is manifested as a larger-than-expected infiltrate in the anteroposterior view **(A)** and posterior bulging of the upper portion of the oblique fissure on the lateral view **(B).** Sonography of the same patient on the same day demonstrated areas of early cavitation.



A



B

Figure 35-3 Alveolar pneumonia in the left lower lobe in a 16-year-old boy with fever, chest pain, and cough. Posteroanterior **(A)** and lateral **(B)** radiographs demonstrate the typical characteristics of an alveolar process involving the left lower lobe. The infiltrate stands out against the preserved left cardiac silhouette in the posteroanterior projection. (It is posterior to the heart.) It silhouettes the diaphragm in both the posteroanterior and lateral views.

whereas a central peribronchial infiltrate with or without atelectasis suggests a viral or *Mycoplasma* infection. A peribronchial infiltrate with peripheral consolidation suggests a viral process but is not inconsistent with a superimposed bacterial infection; a reticulonodular infiltrate restricted to one lobe suggests *Mycoplasma* pneumonia.[82] Although these criteria are helpful in distinguishing bacterial from viral and mycoplasmal pneumonia, the etiology cannot be inferred solely from the chest radiograph because substantial overlap among the observed patterns exists.[56,79,83,84]

Bacterial pneumonia is commonly manifested radiographically as an alveolar consolidation whose pattern corresponds to its pathologic characteristics. The basic radiographic unit of the alveolar consolidation is the acinar shadow, which corresponds to a secondary pulmonary lobule in which the air is replaced by fluid. It is 2 to 5 mm in size with an ill-defined margin caused by extension of the exudate into adjacent acini via the canals of Lambert and pores of Kohn. When confluent, acinar nodules produce the typical continuous, homogeneous alveolar infiltrate. The borders are unclear at the interface with uninvolved lung; however, the margins are sharp at the interface with pleural surfaces, such as interlobar fissures. When an alveolar process abuts an adjacent organ (e.g., the heart, another mediastinal structure, the diaphragm), the loss of definition of the margin is called the *silhouette sign* (Fig. 35-3). The larger bronchi frequently remain aerated when

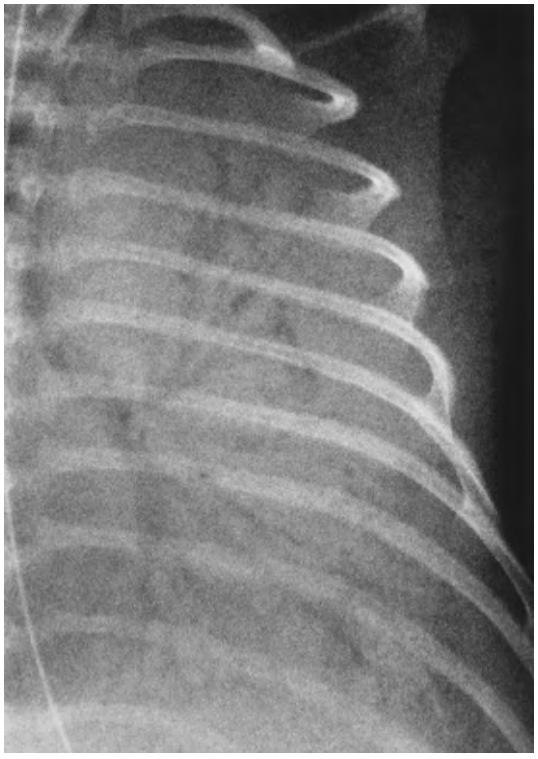


Figure 35-4 Air bronchogram. The air-filled bronchial tree stands out against the background of consolidated lung in fatal staphylococcal pneumonia in a 1-month-old infant. Rapid evolution of complete pulmonary consolidation within a few hours caused the entire bronchial tree to be visible on this plain radiograph of the left hemithorax.

the surrounding pulmonary lobules are consolidated. Those bronchi stand out against the opaque background, producing an air bronchogram (Fig. 35-4).

Alveolar consolidative pneumonias have been subclassified into two groups—airspace pneumonia and bronchopneumonia—according to the pattern of distribution of the infiltrate at diagnosis; however, the distinction between them may blur if the process is extensive. Airspace pneumonia is acquired by the inhalation of small particles and starts in the peripheral parenchyma. Typical examples are *S. pneumoniae*, *Legionella*, and *K. pneumoniae* pneumonia. Consolidation spreads concentrically because of the production of exudate and typically results in a spherical infiltrate (so-called *round pneumonia* [Fig. 35-5]), the most common "mass" lesion of the lung in children. In most patients, this kind of infiltrate has a single focus; however, multiple or bilateral foci also occur, particularly in children with predisposition to pneumococcal infection, such as patients with sickle cell disease. The round configuration may rapidly form a more extensive alveolar infiltrate.

Because bronchopneumonia (Fig. 35-6) is acquired by the aspiration of infective particles, it tends to start adjacent to centrally located bronchi. The multiple central segmental infiltrates that are typically produced may become confluent and diffuse. This sequence is typical of pneumonia caused by *Streptococcus aureus*, *Streptococcus pyogenes*, *H. influenzae*, and enteric gram-negative bacilli. Pathogens associated with bronchopneumonia are more commonly associated with lung necrosis, cavitation, pneumatoceles, and abscesses than those producing airspace pneumonia.

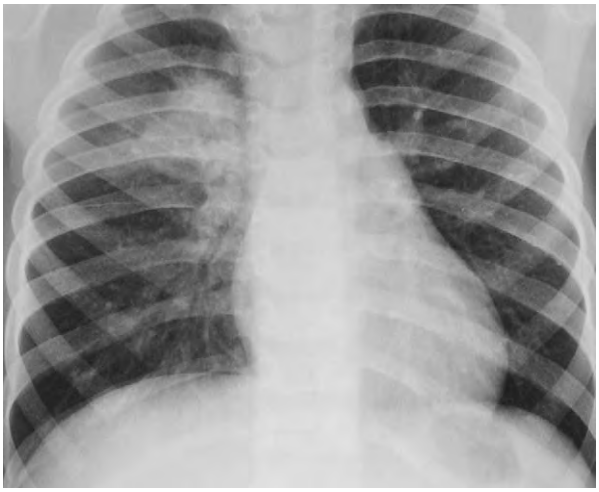


Figure 35-5 *Streptococcus pneumoniae* pneumonia in a 6-year-old boy. A round, mass-like infiltrate is present in the right upper lobe. It disappeared at follow-up after treatment.

Certain situations (e.g., complete opacification of a hemithorax, differentiation of pleural and parenchymal components of a complex suppurative process) may require resolution between pulmonary and other intrathoracic processes and may exceed the resolution capabilities of a chest radiograph. In these instances, other cross-sectional modalities such as computed tomography (CT) and sonography are useful.

CT has the advantage of imaging all of the chest anatomic structures, including aerated lung and bony elements. It is not as operator-dependent as ultrasound but is better than other modalities at depicting an associated pneumothorax or osteomyelitis of the rib. It is particularly helpful when there are multiple superimposed chest abnormalities involving large areas and more than one anatomic site, such as the lung parenchyma, pleura, and mediastinum. Air bronchograms are more readily seen in pulmonary opacities by CT than in plain radiographs, an observation enabling more confident differentiation of consolidation associated with bacterial pneumonia or any kind of airspace process from other chest opacities. With the administration of intravenous contrast material, the branching pulmonary blood vessels may be visualized within consolidations; this observation may aid in differentiating consolidation associated with bacterial pneumonia from other pulmonary opacities when an air bronchogram is absent.[85]

The value of ultrasonography of the chest varies with the experience of the operator. Modern sonographic equipment has the advantage of superior tissue characterization, real-time acquisition that permits evaluation of tissue motion and adherence, spectral and color Doppler that allows identification of the blood supply, and portability that allows rapid evaluation of critically ill patients in an intensive care unit or emergency department without the need for sedation.[86] This modality is helpful in identifying early cavitation (Fig. 35-7) and in distinguishing a pneumonic process from other intrathoracic events, such as avascular cavities and fluid collections from vascular consolidations. Ultrasonography of the chest requires an acoustic window. Because bone and air interfere with the sound beam, sonography is optimal for lesions that

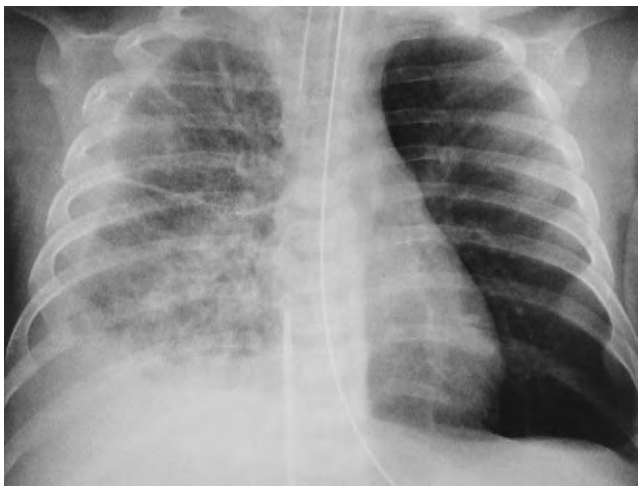


Figure 35-6 Bronchopneumonia. In this 3-month-old girl, *Streptococcus pneumoniae* pneumonia evolves as a typical bronchopneumonia with multiple central patches of segmental and confluent alveolar infiltrates accompanied by a parapneumonic pleural effusion.

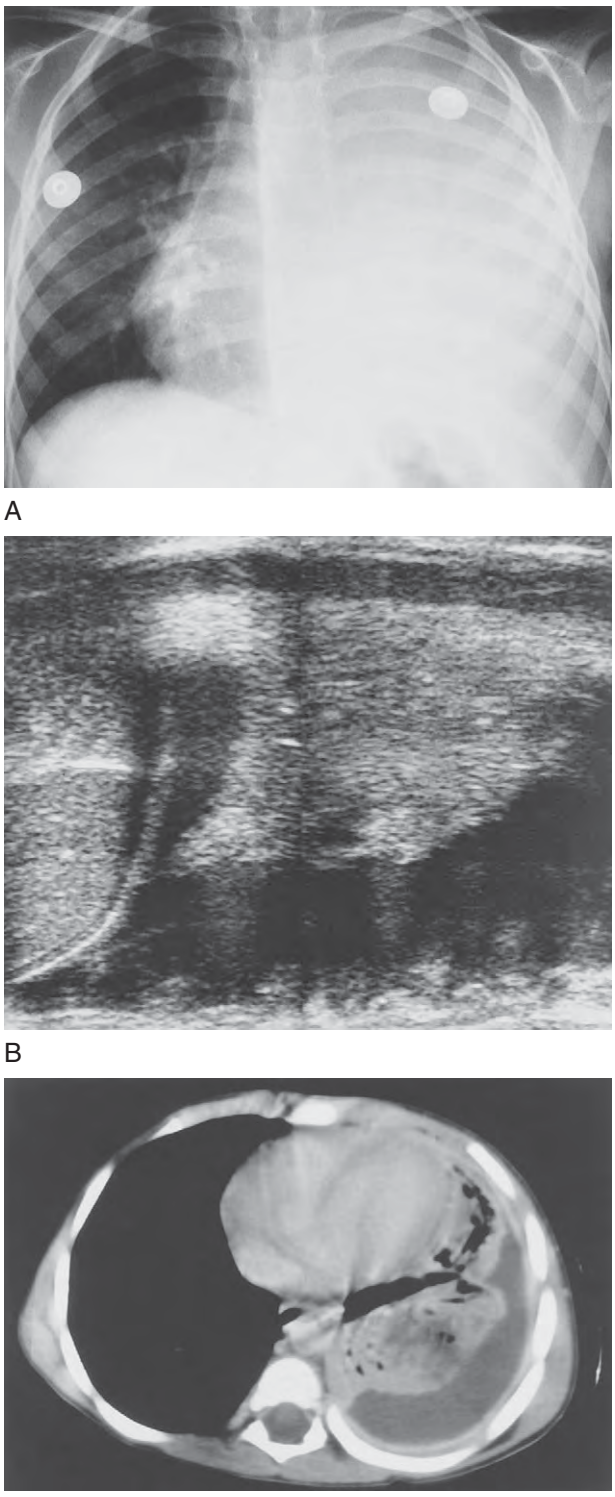
are peripheral without intervening aerated lung (i.e., for processes that abut the chest wall, diaphragm, or both structures). With this modality, the consolidated lung has a liver-like architecture; air bronchograms appear as branching, highly echogenic structures.[87,88] A fluid bronchogram may be seen by sonography but not by CT.[89] In a patient with peripheral lesions, ultrasonography allows differentiation between pulmonary and pleural involvement[90,91] and is also useful for guiding needle aspiration, biopsy, or drainage. Magnetic resonance imaging adds little benefit over CT in the diagnosis of pneumonia and, in young children, requires sedation.

Management

The approach to management is greatly influenced by the age of the child,[56] the clinical setting in which the illness is acquired (e.g., community or nosocomial), and the immunologic status of the host. For community-acquired pneumonia suspected to be bacterial, hospitalization is the rule for children younger than about 4 to 6 months of age. For older children, the decision to hospitalize should depend on the severity of the clinical picture.

The choice of the antimicrobial regimen for childhood pneumonia is often empirical because of the difficulty in defining the etiology. General guidelines for the initiation of therapy in commonly encountered clinical situations may be found in Table 35-1. These recommendations have been affected by changes in the prevalence of β-lactam resistance in *S. pneumoniae* and *S. aureus* and ampicillin resistance in *H. influenzae*.

For nosocomially acquired pneumonia suspected to be bacterial, empirical therapy is guided by knowledge of the clinical setting and the underlying disease prompting the hospitalization. Also, the consideration of possible etiologic agents differs from that of community-acquired pneumonias. For example, gram-negative bacilli and *S. aureus* are important causes of nosocomial pneumonia in infants and children, whereas gram-negative bacilli are not an important consideration if the infection is community-acquired. In community-



A

B

C

Figure 35-7 Pneumonia with an opaque chest. This 4-year-old girl with fever, cough, and shortness of breath had group A streptococcal pneumonia. **A,** Chest radiograph demonstrates an opaque left hemithorax with a mediastinal shift to the right. **B,** Sonography of the chest demonstrates a large pleural effusion with sediment in the fluid. The underlying lung is consolidated with an area of impending cavity. **C,** CT 1 week later demonstrates pulmonary consolidation with multiple cavities—some containing fluid and some containing air. A typical crescent empyema has evolved posterolaterally.

Table 35-1
Approach to Antimicrobial Therapy for Bacterial Pneumonia in Immunocompetent Children

Age	Regimen	
	Inpatient	Outpatient
Birth-4 wk	Ampicillin and gentamicin*†‡	Not applicable
>4-8 wk	ESC and ampicillin§	Not applicable
>8 wk-1 yr	ESC*‡§	Amoxicillin§
>1 yr	ESC*¶	Amoxicillin¶

*Add oxacillin, clindamycin, or vancomycin as appropriate if *Staphylococcus aureus* is suspected.
†ESC (extended-spectrum cephalosporin) and gentamicin if *Klebsiella pneumoniae* or another ampicillin-resistant gram-negative bacillus is suspected.
‡Use erythromycin or another macrolide if *Bordetella pertussis* is suspected.
§Use erythromycin if *Chlamydia trachomatis* is suspected.
¶Use erythromycin or another macrolide if *Mycoplasma pneumoniae* is suspected.

acquired or nosocomially acquired pneumonia, antimicrobial therapy is targeted toward the specific bacterium when the etiology is identified. Guidelines for therapy in this instance are detailed in Table 35-2.

Few data exist regarding the optimal duration of antimicrobial therapy for bacterial pneumonia. A 7-day course is usually sufficient for uncomplicated, community-acquired pneumonia in children who are no longer newborns. Pneumonia in the neonate is typically treated for 14 days by the parenteral route. For nosocomial bacterial pneumonia, the duration of therapy (typically 10 to 14 days) is guided by the clinical course and knowledge of the likely causative microorganism. Staphylococcal pneumonia may require extended treatment.

Guidelines from the World Health Organization for the therapy of children with pneumonia in developing countries reflect uncertainty regarding the etiology of pneumonia in a given child, the increased likelihood that a clinically relevant pneumonia is bacterial, the cost of antimicrobial agents, the necessity for reliance on clinical signs (e.g., tachypnea) to diagnose pneumonia, and the relatively high mortality rate associated with pneumonia. For outpatient therapy of children with nonsevere pneumonia, a 5-day course of cotrimoxazole or amoxicillin, has been recommended. In severe cases of pneumonia, chloramphenicol is often used prior to referral to an inpatient setting. It may be given intramuscularly prior to hospitalization or if hospitalization is not possible, intramuscular injections may be given twice daily for 5 days followed by oral therapy for 5 additional days.[92] Inpatient treatment of pneumonia includes administration of ampicillin or penicillin. For infants younger than 2 months of age, penicillin or ampicillin plus gentamicin may be used; oxacillin may be substituted for penicillin when staphylococcal pneumonia is suspected. These antibiotic regimens may all be given intramuscularly.[31] The increasing recognition of antimicrobial resistance of *S. pneumoniae*, *S. aureus*, and *H. influenzae* will prompt ongoing evaluation of these guidelines that will vary according to local resistance patterns and resources available for the purchase of antimicrobials.

Adjuncts to antibiotic therapy for the child with bacterial pneumonia include supplemental oxygen, if needed, and provision of maintenance fluids. Chest physiotherapy has been widely used; however, the modern view is that its efficacy is poor and that it does not hasten resolution.[93] Vitamin A supplementation has not proved to be definitely efficacious.[94]

Long-Term Management and Prognosis

In uncomplicated, community-acquired pneumonia, documentation of a normal chest radiograph is unnecessary.[95]

Table 35-2
Antimicrobial Therapy When the Etiology is Known

Organism	Regimen of Choice	Alternative Regimens
Streptococcus pneumoniae	Penicillin*	ESC Macrolide† TMP/SMX
Haemophilus influenzae	Ampicillin/amoxicillin*	ESC Doxycycline (for children >8 yr) Chloramphenicol TMP/SMX
Staphylococcus aureus	Oxacillin/nafcillin for MSSA Clindamycin for MRSA	Cefazolin for MSSA Vancomycin, linezolid, or daptomycin for MRSA
Group A streptococci	Penicillin	Macrolide†
Moraxella catarrhalis	ESC	Macrolide† TMP/SMX
Gram-negative enteric bacilli	ESC with or without aminoglycoside	ESC
Pseudomonas aeruginosa	Anti-pseudomonal β-lactam (e.g., ticarcillin/clavulanate, piperacillin/tazobactam) and aminoglycoside	Ceftazidime
Anaerobes	Clindamycin	Metronidazole Chloramphenicol

*When susceptible.
†Erythromycin or azithromycin, for example.
MRSA, methicillin-resistant *Staphylococcus aureus;* MSSA, methicillin-susceptible *Staphylococcus aureus;* TMP/SMX, trimethoprim-sulfamethoxazole.

Indications for serial radiography include neonatal pneumonia, severe symptomatology, suspicion of a complication (such as a lung abscess), pleural involvement (such as an effusion or empyema), or an unsatisfactory response to treatment.

The traditional view is that timely administration of antimicrobial therapy renders an excellent outcome in bacterial pneumonia. In developed countries, the mortality rate from uncomplicated cases of pneumonia is less than 1%; lung structure and tissue almost always return to normal—even in patients with empyema or a lung abscess. Some caution regarding this generally bright outlook has come from a recent study, which suggested that a relation might exist between pneumonia in children younger than 2 years of age and the occurrence of chronic obstructive lung disease later in life[96]; however, no data support this association with bacterial pneumonia.

Recurrent pneumonia, defined as at least two episodes in 1 year or three or more episodes at any age with radiographic clearing between episodes, should prompt further patient evaluation.[26] Components of such an evaluation may be found in Box 35-3, but the evaluation of each patient must be individualized. Many of the disorders listed in Box 35-1 are associated with recurrent bacterial pneumonia in children and young adults and should be considered as predisposing to pneumonia in such a patient. These disorders include cystic fibrosis (CF), pulmonary sequestration, bronchiectasis, disorders of normal pulmonary physiology (e.g., immotile cilia syndrome), and a variety of congenital (e.g., severe combined immunodeficiency, immunoglobulin deficiency disorders, Job's syndrome) and acquired (e.g., human immunodeficiency virus [HIV]) immunodeficiency disorders.

Complications and Outcome

Pneumothorax is an uncommon complication of pneumonia and is usually associated with *S. aureus* pneumonia. An intraparenchymal cavity containing air may sometimes be associated with bacterial pneumonia. This may represent a pneumatocele, a cavitation, an abscess (see separate section), or rarely, a sequela of massive lung necrosis. A pneumatocele, recognized most commonly in staphylococcal pneumonia, is a thin-walled air collection that can become large and occasionally cause a clinically important mass effect. Its pathogenesis remains controversial. Some argue that a pneumatocele is an enlarged airspace whose walls ruptured after air trapping distal to a bronchus that was occluded by inflammatory exudate and mucosal edema. However, others have invoked thin-walled, subpleural interstitial blebs that occasionally coalesce and appear radiographically as a pneumatocele.[97] Although a pneumatocele contains no fluid when it is first formed, an air-fluid level may develop. When this occurs, it may be difficult to differentiate it from a cavity or an abscess, particularly if a surrounding infiltrate prevents accurate evaluation of the lesion wall. A pneumatocele typically appears during convalescence and may either resolve spontaneously within weeks or linger for months before it gradually diminishes and disappears.[98] The earliest radiographic sign of a cavity may be visualized by sonography, before demonstration by CT or plain radiography, as an echolucent focus within the pulmonary consolidation at the hepatization phase. Later, bronchial communication results in air entering the cavities,

BOX 35-3 Evaluation of Children with Recurrent Bacterial Pneumonia

General

A history should be taken, with special attention to high-risk situations for foreign body aspiration, stools consistent with malabsorption, sinusitis, otitis, asthma and atopy, severe pulmonary disease, environmental exposure, prematurity, oxygen exposure, and early deaths in family members.

A physical examination should be done, with special attention to nutritional state, anatomic structures of the upper airway, muscular strength, neurologic functions (such as swallowing and gag reflexes), resting respiratory rate, accessory muscle use, inspiratory to expiratory ratio, wheezes, crackles, and cardiovascular system for suggestion of congenital anomalies of the heart or great vessels and the presence of heart failure.

Specific

- The chest radiograph should be reviewed by a radiologist.
- A complete blood count with differential should be obtained.
- A blood culture should be done.
- Sputum should be examined for a cell morphologic study if the patient is old enough to comply—Gram's stain, fungal smear, acid-fast smear, and culture for aerobes, fungi, and *Mycobacterium* species.
- Fiberoptic bronchoscopy may be needed in some cases to obtain sputum.
- Bronchoalveolar lavage (BAL) fluid should be examined by silver methenamine stain for *Pneumocystis jiroveci,* fungi, *Mycobacterium* species, and cellular elements (e.g., eosinophils, erythrocytes).
- Alveolar macrophages can be stained for hemosiderin for the diagnosis of recurrent pulmonary hemorrhage.
- Purified protein derivative analysis should be done.
- A sweat chloride test should be obtained.
- *Further evaluation should be performed as appropriate:*
  - Chest CT
  - Airway fluoroscopy
  - Laryngoscopy
  - Bronchoscopy
  - Endoscopy
  - Barium swallow
  - Mediastinal magnetic resonance imaging to evaluate vascular structures
  - Lung biopsy
  - Quantitative serum immunoglobulin assay
  - Neutrophil function studies
  - T and B cell enumeration, quantitative of subsets' function
  - Nasal turbinate or tracheal biopsy for electron microscopy for cilia ultrastructure and phase microscopy for function
  - Spirometry without and with β_2-agonist inhalation challenge

rendering them visible first by CT and later by plain radiograph.

Pneumonia in the First Month of Life

Despite having many features in common with pneumonia in older children, certain unique aspects of bacterial pneumonia in the first month of life warrant special consideration. It has been convenient to subdivide neonatal bacterial pneumonia according to the acquisition time of the etiologic microorganism and the onset of clinical manifestations. A classification scheme similar to that proposed by Marks and Klein[99] provides a useful framework. In this scheme, pneumonia occurring in the first month of life is subdivided into congenital or intrauterine pneumonia and neonatal pneumonia.

The term *congenital* or *intrauterine pneumonia* is applied when the bacteria are acquired transplacentally or in utero by the ascending route; the source of the etiologic organism is most often the maternal genitourinary tract. Infants with congenital or intrauterine pneumonia are stillborn or die shortly after birth, usually within 24 hours. The pathogenesis is not completely understood. Identified risk factors, such as prematurity, prolonged rupture of membranes, intrauterine asphyxia, and infection of nonrespiratory tract sites, are similar to those predisposing to neonatal bacteremia. Microorganisms from the maternal genitourinary tract may contaminate the maternal membranes, amniotic fluid, and periumbilical vascular tissues by ascending to them through small, unrecognized defects in the decidua or after premature membrane rupture.

The pulmonary pathology (as defined at autopsy) reflects an inflammatory reaction. Polymorphonuclear leukocytes are evident and are often accompanied by vernix and squamous cells. The interstitial tissue of small bronchioles and the interalveolar septa may be infiltrated by lymphocytes.[100] Alveolar macrophages may also be present and tend to increase in number with the duration of the postnatal illness.[101] The distribution of inflammation is characteristically diffuse. Interestingly, certain features of bacterial pneumonia acquired after birth, such as pleural reaction, alveolar fibrinous exudate, and infiltration or destruction of the bronchopulmonary tissue, rarely occur in congenital or intrauterine pneumonia.

The term *neonatal pneumonia* is used to describe pneumonia in which bacterial acquisition occurs during passage through the maternal genital tract or shortly thereafter; the clinical features are manifested in the first few days to the first month of life.[99] The portal of entry for the etiologic agent may be the lung after the aspiration of infected amniotic fluid and may therefore be a consequence of contact with vaginal or uterine secretions in the birth canal, contaminated water or medical equipment, or contact with caregivers.

The pulmonary pathology in neonatal bacterial pneumonia is similar to that in older children and adults. The lungs may contain regions of exudate with hemorrhage, congestion, and necrosis.[99] Bacteria are often seen in lung sections—a finding absent in the histology of congenital or intrauterine pneumonia. The histopathology depends in part on the microbial etiology. For example, *S. aureus* and *K. pneumoniae* typically cause necrosis of lung tissue, empyema, or microabscesses.[102-104] *S. aureus*, *E. coli*, and *K. pneumoniae* may be associated with pneumatocele formation.[105] GBS pneumonia has been associated with intra-alveolar hyaline membranes in which microorganisms may be visualized.[106] Similar hyaline changes have also been noted with neonatal pneumonia caused by *H. influenzae* and gram-negative enteric bacteria.[107]

The incidence of neonatal pneumonia is difficult to determine because of uncertainty regarding case definitions, rate differences in patient populations, and ascertainment bias. In a study of consecutive live births at a tertiary care center in Oxford, England, pneumonia was defined as respiratory distress associated with changes on the chest radiograph that persisted for more than 48 hours. Early onset pneumonia, which occurs in children younger than 48 hours of age, was found in 1.8 per 1000 live births, whereas late-onset pneumonia, which occurs in children older than 48 hours of age (mean, 35 days of age), was found at a rate of 2.0 per 1000 live births.[108] In a review of nine studies describing autopsy findings in stillborn and live-born neonates, the incidence of pneumonia was 15% to 38% and 20% to 32%, respectively.[99]

Neonates born into low-income families have a significantly greater incidence of pneumonia than those from higher-income families. At comparable economic levels, however, African-American infants have a higher incidence of newborn pneumonia than do Hispanic or white infants, although this racial/ethnicity difference has not yet been reasonably explained.[109,110] Pneumonia in newborns is also found at much higher rates in developing countries.

Epidemics of neonatal pneumonia have occurred. The outbreak is often caused by a single source of infection (e.g., a nursery worker, contaminated equipment or solutions used for patient care). In the 1950s and early 1960s, many nurseries in the United States experienced epidemic *S. aureus* pneumonia. The identification of infants colonized with virulent *S. aureus* phage 80/81 was often accompanied by a sharp increase in the incidence of *S. aureus* neonatal pneumonia. For unclear reasons, the frequency of epidemic *S. aureus* pneumonia has greatly decreased since that time, but sporadic cases still occur.[103]

Recent reports of clusters of methicillin-resistant *S. aureus* (MRSA) skin infections in neonates has again prompted further examination of hygiene and infection control practices in nurseries.[104] Other bacteria, such as *Pseudomonas* species, *Flavobacterium* species, and *S. marcescens*, have also been responsible for nursery epidemics.[99]

When the pathogen is acquired in the maternal genital tract, the most common causes of pneumonia are group B streptococci and gram-negative enteric organisms such as *E. coli*, *K. pneumoniae*, and *Proteus* and *Enterobacter* species. *Chlamydia* organisms are also believed to be acquired in this manner. Occasionally, pathogens normally associated with respiratory tract spread, such as group A streptococci, *H. influenzae*, *S. aureus* and *N. meningitidis*, are found in the maternal genital tract and transmitted vertically to neonates.

After birth, bacteria causing pneumonia are usually acquired from parents, caregivers, or environmental sources. These include *S. aureus* (30% of all cases caused by this organism occur in children younger than 3 months of age)[111] and gram-negative bacilli, such as *Pseudomonas* and *Flavobacterium* species, *Citrobacter diversus*,[112] and *S. marcescens*.

H. influenzae, *M. catarrhalis*, *L. pneumophila*, and *Bacillus cereus*[113] are infrequently recognized etiologic agents. *S. pneumoniae*[114] pneumonia is infrequent in this age group. It usually manifests shortly after birth and has a high mortality rate.

The diagnosis of neonatal pneumonia is usually based on clinical, microbiologic, and diagnostic imaging data. Because the clinical manifestations are usually nonspecific, especially at the onset, the birth history may provide important clues. Important risk factors in neonates are prolonged rupture of the maternal membranes (particularly longer than 24 hours), prolonged maternal labor, the identification of meconium-stained or malodorous amniotic fluid, and meconium-stained laryngeal or tracheal secretions.

If not stillborn, infants with congenital or intrauterine pneumonia are often very ill at birth. There are usually signs of asphyxia, including the presence of meconium, nuchal cord, apnea, and depressed respirations; the mortality rate within the first 24 hours of life is high. Pneumonia occurring during or shortly after birth is manifested by lethargy and anorexia, both of which are nonspecific signs of a generalized illness. Fever is commonly absent. Signs attributable to the respiratory tract, such as dyspnea, tachypnea, grunting, nasal flaring, coughing, cyanosis, and retractions, either may be initially evident or may develop later. The presence of auscultatory findings of crackles and diminished breath sounds also varies.

The most helpful aid in diagnosing neonatal bacterial pneumonia is a chest radiograph. The typical findings include diffuse or patchy bilateral alveolar infiltrates, streaky densities, confluent opacities, and peribronchial thickening. The presence of these findings is inconsistent, however, and the radiologic diagnosis of pneumonia in the newborn may, therefore, be difficult.[115] Other causes of respiratory distress in the newborn, such as hyaline membrane disease, retention of fetal fluid, and pulmonary edema, may also be associated with diffuse, bilateral radiographic opacities. Conversely, the chest radiographs may be normal in some infants with pathologically proven bacterial pneumonia.[116] Further complicating this conundrum are the variable radiographic findings when pneumonia is the certain diagnosis. For example, among infants with histologic evidence of pneumonia at autopsy, 77% had diffuse or patchy bilateral alveolar infiltrates. In 17%, however, the radiograph suggested retained fetal fluid consistent with transient tachypnea of the newborn. In 13%, the radiographic picture closely resembled hyaline membrane disease.[116] Indeed, the radiographic picture of this disease may mimic that of pneumonia, particularly when group B streptococcus is the pathogen (Fig. 35-8). The presence of a pleural effusion may aid in differentiation because this finding is not observed in hyaline membrane disease.

The diagnosis of pneumonia in a neonate in intensive care with underlying chronic lung disease is especially difficult. Infection is suspected in the presence of a suggestive clinical picture (i.e., a sudden increase in the severity of pulmonary abnormalities or another clinical deterioration and a new pleural effusion or an opaque chest radiograph). Pneumonia with pneumatoceles or cavitation may mimic congenital diaphragmatic hernia or a cystic adenomatoid malformation.

CT of the chest with infusion of contrast material is less helpful in the neonate than in the older child but may be of use in localizing a lesion, especially in distinguishing among an abscess, empyema, pneumatoceles, or a bronchopleural fistula. Ultrasonography has been useful in assessing pleural effusions for the presence of loculation or debris, differentiating empyema from lung abscess, and clarifying the components of an opaque chest radiograph. It has also been used to diagnose a case of pneumonia in utero in a fetus of 32 weeks' gestation.[117]

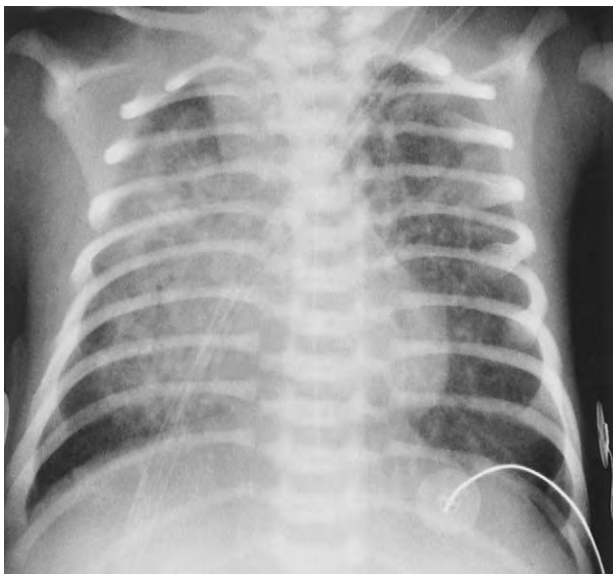


Figure 35-8 Group B streptococcal pneumonia in a neonate. A full-term male newborn with diffuse bilateral infiltrates, both reticular-linear and confluent.

Aspirating pulmonary exudate under radiologic guidance can provide unequivocal information about the causative agent. Bronchoscopy may also be helpful. In addition, open lung biopsy has been useful in newborns when other diagnostic techniques have failed to provide precise information in infants with respiratory failure.[118]

The evaluation of an infant in the first month of life for suspected pneumonia is usually performed in the context of evaluation for a possible systemic infection. Thus, many infants with suspected neonatal pneumonia undergo blood, urine, and cerebrospinal fluid (CSF) cultures at the time of initial evaluation. Because viruses, such as herpes simplex virus and cytomegalovirus, may be responsible for pneumonia and even a clinical picture resembling a systemic infectious illness, evaluation of an infant in the first month of life may include consideration of these nonbacterial agents.

A bacterium recovered from blood, urine, or CSF often provides a valuable clue to the etiology of suspected pneumonia. Some researchers have suggested that a tracheal aspirate performed during the first few hours of life may also provide a clue as to the etiology of pneumonia.[119] Antigen-detection techniques such as latex particle agglutination may also provide clues; however, in the neonate, these are limited to detection of group B streptococcal antigens, which have been found in the serum and urine of patients with group B streptococcal pneumonia.

The selection of antimicrobials for the therapy of neonatal pneumonia is also performed in the context of a possible systemic bacterial infection (see Table 35-1). An empirical

regimen that includes a β-lactam, such as ampicillin, and an aminoglycoside, such as gentamicin, often constitute initial therapy. Once a bacterium is identified, the regimen may be targeted toward it (see Table 35-2). Few explicit data are available to guide the duration of antimicrobial therapy. The decision regarding length of therapy is often guided by treatment response and by the etiology, if identified. For example, a 14-day course may suffice when the clinical response has been prompt; however, a course of at least 21 days is often used for pneumonia caused by gram-positive organisms such as *S. aureus* and group B streptococci or pneumonia of any other etiology when the response has been slow.

Supportive care includes the provision of oxygen and mechanical ventilation (when appropriate), maintenance of fluid, electrolyte, and metabolic balance; and drainage of appropriate pleural effusion or abscesses. Such care is essential to optimize chances for a good outcome.

The outcome of therapy depends on many factors. The availability of state-of-the-art neonatal intensive care greatly improves the likelihood of a good outcome; the mortality rates in developing countries lacking these facilities are often high.[120,121] In developed countries, prematurity, underlying diseases, the host response, the aggressiveness and appropriateness of antimicrobial therapy, and supportive care measures all have a great impact on the mortality rates and prognosis.

SPECIFIC CAUSES OF PEDIATRIC PNEUMONIA

Causes of Frequent Clinical Concern

STREPTOCOCCUS PNEUMONIAE, PNEUMOCOCCUS

The pneumococcus is the most common cause of bacterial pneumonia in children.[32,122] The observation by Pasteur[123] and Pasteur and colleagues[124] that lancet-shaped pairs of cocci found in human saliva could cause disease in rabbits provided the first notion that these bacteria were important human pathogens. In 1886, Fraenkel[125] named these bacteria *pneumococci* because of their tendency to cause pneumonia, but in 1920, the Society of American Bacteriologists assigned the name *Diplococcus pneumoniae*.[126] However, because pneumococci form chains in liquid media, the name *S. pneumoniae* was assigned to the species in 1974.[127]

The organism is a gram-positive coccus that was among the first bacteria described by the then fledgling technique developed by Gram in 1884.[128] The classic Gram stain morphology is so-called lancet-shaped, gram-positive diplococci. The organism grows easily in fresh beef heart infusion broth with whole blood or serum, which provides catalase to break down the accumulating hydrogen peroxide. Incubation at 35° to 37° C and an atmosphere containing 5% carbon dioxide improve growth.

In the United States the epidemiology of pneumococcal disease has been greatly influenced by the introduction of the heptavalent pneumococcal conjugate vaccine in 2000 (Prevnar, Wyeth-Lederle, Madison, NJ). High cost has limited its use in developing countries. Prevnar was licensed for use after it had been demonstrated to have an efficacy of 97.4% against invasive pneumococcal disease caused by serotypes contained in the vaccine in infants and children attending Kaiser Permanente Clinics in Northern California.[129] The vaccine contains purified capsular polysaccharide from serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F linked to a nontoxic mutant of diphtheria toxin (CRM_{197}). The serotypes included in the vaccine accounted for about 84% of cases of invasive disease in United States children.

In the prevaccine era, the incidence (number of children per 100,000 per year) of invasive pneumococcal infections in Northern California peaked at 241 per 100,000 per year in children 12 to 17 months. This compares to an incidence of 150 per 100,000 per year for invasive *H. influenzae* type b disease in the same population in infants younger than 12 months of age and 63 per 100,000 per year in toddlers before the introduction of vaccination. The decline in overall pneumococcal disease after introduction of vaccination has been 69% among those younger than 2 years and 59% among those younger than 5 years.[130] Invasive disease caused by vaccine and vaccine-related serotypes declined by more than 75% in controlled clinical trials done in the United States.[129-131] Disease rates among adults have also declined, presumably reflecting decreased transmission from children to adults.[132] Rates of antibiotic-resistant invasive pneumococcal infections have also decreased by 57% since introduction of the conjugate vaccine, presumably because 5 of 7 serotypes in the vaccine were responsible for most penicillin-resistant infections.[133]

The effectiveness of the pneumococcal conjugate vaccine in prevention of pneumonia has also been evaluated. Rates of clinically diagnosed pneumonia and of pneumonia with a positive radiograph were compared between 37,868 children stratified into vaccinated and nonvaccinated groups. In recipients of the pneumococcal vaccine, first episodes of clinically diagnosed pneumonia declined by 4.3% but all episodes with a positive radiograph decreased by 20%, $P = .02$.[134] When the radiographs were subjected to analysis using World Health Organization standardized interpretive criteria, the efficacy of the vaccine against a first episode of radiograph-confirmed pneumonia was 30%.[135] Ten of the 11 cases of pneumococcal pneumonia with a positive blood culture were in the nonvaccinated group, suggesting greater efficacy for the vaccine against bacteremic pneumonia. Additionally, a Texas study evaluating the epidemiology of pleural empyema in children found that the number of children hospitalized with empyema steadily increased from 1992 through 2000 but then decreased from 2000 to 2002 after introduction of universal Prevnar immunization.[136]

The difficulty in establishing a definite etiology of pneumonia and discrepancies in interpreting chest radiographs complicate the evaluation of vaccine impact on pneumonia. Nonvaccine serotypes may also be responsible for a large proportion of nonbacteremic or noninvasive pneumonia and, therefore, pneumonia caused by these serotypes may be un-affected by the current vaccine. Additionally, serotypes not included in the vaccine (serotype 1) were responsible for increasing cases of pneumonia complicated by empyema in certain geographic locales after introduction of the vaccine.[137] Continued surveillance and serotyping strains isolated in cases of pneumonia will help further clarify these issues.

The species *S. pneumoniae* is subdivided into 90 immunologically distinct serotypes. There are two numbering systems:

the American system, which numbers serotypes in numerical sequence, and, in wider use, the Danish system, which groups antigens according to immunologic similarity.

The distribution of serotypes responsible for invasive infections has varied with geographic locale, age of the patient (child versus adult), clinical syndrome (invasive disease versus otitis media), and immunization status.[138,139] For example, in children in Northern California, types 6B, 14, 18C, 19F, and 23F accounted for 95% of all invasive pneumococcal infections in the prevaccine era. In Connecticut, the same serotypes caused 68.5% of invasive disease in children; the inclusion of types 4, 6A, 9V and 19A encompassed an additional 20% of cases.[140] The two most common serotypes among Israeli children, types 1 and 5, are rare in Western Europe and North America.[139] Thus, the currently formulated pneumococcal conjugate vaccine may have different efficacy in different populations.

Asymptomatic nasopharyngeal colonization by the pneumococcus is common; 20% to 40% of healthy children are colonized at any given time.[141] The rate of isolation of pneumococcus from asymptomatic children is also higher in institutional settings. Virtually all infants are carriers at least once when followed longitudinally.[142] Pneumococcal carriage is infrequent in the first 6 months of life, increases thereafter to reach its peak rate among preschool children, and then declines slowly to a nadir among adolescents. The highest rates of colonization have been found from December to April, although carriers can be detected throughout the year among healthy children.[142] In an unimmunized population the serotypes most commonly associated with asymptomatic carriage—types 6, 14, 19, and 23—are similar to those causing disease. In immunized infants and children, nonvaccine serotypes appear to have replaced vaccine serotypes among nasal carriage strains.[143,144]

With respect to invasive disease, male patients are affected more often than are female patients. Statistically significant risk factors for invasive disease include attendance at day-care, frequent episodes of otitis media (more than three episodes in 6 months), frequent upper respiratory tract infections (at least three episodes in 6 months), premature birth, and previous hospitalization for respiratory disease. Insignificant trends for increased risk included anemia, asthma, and previous insertion of polyethylene tubes into the tympanic membrane.

Certain populations, such as Alaskan,[145] Apache,[146] and Navajo[147] children, were at higher risk for invasive disease prior to introduction of the heptavalent vaccine. Indeed, the incidence of pneumococcal infection among the White Mountain Apache population (156 per 100,000 population [1988 U.S. population]) has been the highest reported; the peak incidence was in children 1 to 2 years of age (2396 per 100,000). Some 79% of these invasive pneumococcal infections were pneumonia.[146] Other individuals at increased risk for invasive pneumococcal disease include those with asplenia, those with congenital or acquired immunodeficiency, recipients of cytoreduction or other immunosuppressive therapies, those who have undergone bone marrow transplantation, and those with cerebrospinal fluid (CSF) leaks, chronic pulmonary or renal disease, congestive heart failure, Hodgkin disease, complement deficiencies, nephrotic syndrome, sickle cell disease, or systemic lupus erythematosus.

In addition to their increased risk attributable to sickle cell anemia or low socioeconomic status, African-Americans may generally be at higher risk for invasive disease. Vaccination has reduced but not eliminated this disparity.[148,149] A series of observations early in the twentieth century established the capsule as the critical virulence determinant of pneumococci. After the recognition that the soluble substance found in serum and urine in patients with lobar pneumonia reacts with specific antiserum to pneumococci of identical serotype and that the capsular polysaccharide is the cell wall component responsible for this reaction, Dubos and Avery[150] demonstrated that pneumococci with enzymatically removed capsules were relatively avirulent in mice. Until this time, only proteins were believed to be immunogenic; this was the first demonstration that the immunogenicity of the capsular polysaccharide in mice protected against subsequent pneumococcal challenge.

The mechanism by which the capsule imparts virulence to the pneumococcus is incompletely understood. The capsular polysaccharide itself is not toxic, but the quantity of elaborated capsular polysaccharide may explain some intraserotypic differences in virulence.[150] Most investigators implicate impaired antibody-mediated, complement-dependent phagocytosis of pneumococci to the capsule to explain its role in virulence, but this traditional explanation may not be sufficient. For example, a clear relation between in vitro opsonophagocytosis and protection in an experimental mouse model of pneumococcal disease for serotype 3 exists, but it has not been possible to establish a similar relation for serotype 1 isolates.[151]

Host defense mechanisms that deal with pneumococcal infection include local respiratory defenses, such as ciliary action, the cough reflex, and the production of mucus. Phagocytosis and the presence of type-specific anticapsule antibody also play crucial roles. The incubation period varies but can be as short as 1 to 3 days. When invasive disease occurs, it is usually shortly after a new serotype is acquired in the upper respiratory tract. An organism associated with prolonged carriage is an unlikely cause of invasive illness.

Factors influencing transmission of the pneumococcus organism from person to person have not been thoroughly studied. The recent application of molecular techniques should result in an improved understanding of this problem. For example, despite few reports of clusters of invasive disease in young children, it is now clear that *S. pneumoniae* may occasionally be readily transmitted from child to child in the day-care setting.[152]

The onset of pneumococcal pneumonia may be preceded by a mild upper respiratory tract infection, purulent unilateral conjunctivitis, or otitis media. The clinical manifestations vary somewhat with age. In infants, a sudden rise in temperature may be accompanied by a seizure, and diarrhea or vomiting may be among the earliest manifestations. Restlessness, apprehension, nasal flaring, rapid and shallow respirations, grunting, abdominal distention, perioral cyanosis, tachycardia, and unilateral diminished respiratory excursion (splinting) may variably ensue. Cough may be absent.

In the older child and the adolescent, the clinical features more closely resemble those in adults. Onset is typically abrupt. The patient may appear ill with shaking chills or rigors, fever, headache, dyspnea, pleuritic pain, and cough.[153]

Sputum production may be apparent in children older than about 8 to 10 years of age. If a viral illness was the predisposing factor, the onset may be more insidious, with coryza and low-grade fever preceding higher fever and possibly sputum production.[154] Pleuritic chest pain reflecting involvement of the visceral pleura may occur. Occasionally, signs and symptoms suggesting bacterial pneumonia may be absent; fever may be the only sign.

Physical examination consists of the features noted earlier in the general section on clinical manifestations of pneumonia.[154] Many patients with pneumococcal pneumonia may have leukocytosis. However, the sensitivity and specificity of the leukocyte count are sufficiently low to preclude reliance on its presence for diagnosis.

As noted earlier, the usefulness of sputum as a diagnostic tool in pneumococcal pneumonia falls between "conclusive" and "occasionally conclusive" in terms of clinical importance in properly collected specimens that contain large numbers of polymorphonuclear leukocytes and typical lancet-shaped gram-positive cocci or that yield *S. pneumoniae* on culture. Antigen-detection techniques have been used in the diagnosis of pneumococcal pneumonia. A blood culture may yield the causative pathogen and should, therefore, be performed during the initial evaluation.

The radiographic changes of acute pneumococcal pneumonia are not pathognomonic. However, pneumococcal pneumonia is frequently associated with the radiographically "classic" acute airspace pneumonia that starts peripherally in the lower lobes or posterior segments of the upper lobes.[154] It then spreads concentrically with no respect for segmental boundaries, unlike bronchopneumonia. This characteristic picture may result in a mass-like round infiltrate, the most common pulmonary mass lesion in children. Alternatively, pneumococcal pneumonia may appear radiographically as a patchy or even linear ("interstitial") infiltrate. A radiographically visible pleural effusion occurs in a small percentage of cases and is more common in young children than in adults. In infants and young children, pneumococcal pneumonia may occasionally be complicated by pneumatoceles, abscess, and empyema.[155] The resolution of radiographic abnormalities may occur 10 to 14 days after appropriate therapy is initiated but more commonly may persist for weeks or even months after recovery.

Once the diagnosis is suspected, antimicrobial therapy should be started. Characteristically, the fever decreases a few hours later, if the isolate is susceptible. Penicillin has been the drug of choice for pneumococcal infections. Until the late 1970s, penicillin resistance was recognized in only a few, sporadic isolates. An outbreak of disease in South African children in 1978 as a result of penicillin-resistant pneumococci signaled that *S. pneumoniae* would henceforth require routine susceptibility testing by microbiology laboratories. These resistant isolates have now been found in many parts of the world, including the United States.

Penicillin-nonsusceptible pneumococci may be of intermediate susceptibility (minimum inhibitory concentration of penicillin = 0.1 to 1.0 μg penicillin/mL) or of absolute resistance (minimum inhibitory concentration ≥2.0 μg/mL). Resistance is mediated by the production of one or more penicillin-binding proteins with altered affinity for penicillin. In some areas of the United States more than 40% of isolates from sterile body sites were nonsusceptible to penicillin and as many as 50% of these isolates were of absolute resistance to penicillin.[156,157] Susceptibility to extended-spectrum (third generation) cephalosporins has been assumed until recently, even among penicillin-resistant isolates. However, extended-spectrum cephalosporin resistance has now been documented in association with treatment failure in patients with pneumococcal meningitis.[158] Moreover, these penicillin-resistant pneumococcal isolates are frequently resistant to multiple antibiotics including macrolides, clindamycin, and trimethoprim-sulfamethoxazole—a fact that further complicates treatment. Serotypes 6B, 9V, 14, 19A, 19F, and 23F are most frequently associated with penicillin resistance.

Pneumonia caused by strains with intermediate resistance to penicillin usually responds to high-dose penicillin or to extended-spectrum cephalosporin therapy.[159] Pneumonia caused by absolutely resistant isolates may also respond to high-dose penicillin or extended-spectrum cephalosporin therapy; however, if the isolate is nonsusceptible to penicillin, treatment with clindamycin (9% of isolates are resistant) or vancomycin may provide greater clinical comfort to the clinician. These compounds may also be appropriate if the child is allergic to penicillin.

Aside from antimicrobial therapy, oxygen and ventilatory support may be necessary. Intensive care may be required, particularly if hypotension is present or hypoxia is severe. Hyponatremia may be present secondary to inappropriate secretion of antidiuretic hormone and may require fluid restriction. Complications of pneumococcal pneumonia may be "local" (i.e., secondary to the pneumonia itself) or "distant" as a result of a concurrent bacteremia. Empyema is the most common local complication[154] and probably arises when bacteria seed a parapneumonic pleural effusion. Adult respiratory distress syndrome (ARDS) does not commonly occur. Most cases of ARDS actually occur in children; leukopenia during acute pneumonia may be a risk factor.[160] Distant complications may include purpura fulminans, meningitis, endocarditis, peritonitis, septic arthritis, and pericarditis.[161]

Clinical features associated with increased morbidity include multilobar involvement, hypoxemia, leukopenia with overwhelming sepsis, bacteremia, and infection caused by serotype 3. Permanent pulmonary sequelae of uncomplicated pneumococcal pneumonia are extremely rare. Slow clinical resolution is usually due to an underlying problem, a mistaken diagnosis, or a superinfection. The mortality rate in those with pneumococcal pneumonia and ARDS may be as high as 50%. Before the introduction of antibiotics, the mortality rate in infants was 20% to 30%; now it is less than 5% in both infants and older children.

In addition to the heptavalent conjugate vaccine, a 23-valent capsular polysaccharide pneumococcal vaccine is recommended for select groups. The antigens in the 23-valent vaccines represent the serotypes causing nearly 100% of bacteremia and meningitis cases in children. However, the polysaccharides have limited immunogenicity in children younger than 2 years of age; hence, the vaccine is not recommended for use in children younger than age 2. The Committee on Infectious Diseases of the American Academy of Pediatrics[162] currently recommends the 23-valent vaccine for children older than 2 years of age who have conditions predisposing them to an increased risk of pneumococcal infection. Exam-

ples of this are sickle cell disease, functional and anatomic asplenia, nephrotic syndrome, chronic renal failure, conditions associated with immunosuppression, refractory HIV infection and other immunodeficient states, or anatomic CSF leaks. Revaccination after 3 to 5 years should be considered for children remaining in a high-risk group. Passive immunization with intravenous immunoglobulin is recommended for preventing pneumococcal pneumonia in children with certain congenital or acquired immunodeficient states predisposing them to *S. pneumoniae* infection.[162-165]

STAPHYLOCOCCUS AUREUS

S. aureus and the coagulase-negative species *Staphylococcus epidermidis* are two important human pathogens that may cause pneumonia in children. Pneumonia caused by *S. aureus* is uncommon but may be increasing in frequency in certain geographic locales. The emergence of MRSA has dramatically changed the importance of this pathogen. *S. aureus* pneumonia may be associated with a rapidly progressive course, particularly in children younger than 1 year of age, and antimicrobial regimens commonly used for the therapy of bacterial pneumonia may not provide optimal *S. aureus* coverage. Pneumonia caused by *S. epidermidis* is rare and occurs almost exclusively in neonates and immunocompromised individuals.

The detection of coagulase and protein A, bacterial products produced exclusively by *S. aureus*, is used as the basis of laboratory tests that distinguish the important pathogen *S. aureus* from other so-called *coagulase-negative* staphylococcal species such as *S. epidermidis*. Morphologically, all staphylococci are gram-positive cocci that resemble clusters of grapes when viewed under the light microscope.[166]

Staphylococcal cell walls are composed of teichoic acid, a ribitol phosphate polymer, and peptidoglycan. The cell wall of *S. aureus* also contains protein A, which binds the Fc fragment of IgG and fixes complement in the process. It has been noted that most pathogenic strains of *S. aureus* have a polysaccharide capsule; four types of capsular polysaccharides have been identified in *S. aureus* isolates.[167] Surveillance in industrialized countries revealed that capsular polysaccharide types 5 and 8 were identified in 80% of adults with bacteremia. These data seem to suggest that these capsules play an important role in the pathogenesis of *S. aureus* invasive infections.[168]

A variety of extracellular factors play a role in the virulence and pathogenesis of *S. aureus* infection. Coagulase clots animal plasma and was once thought to be the determinant of virulence. However, *S. aureus* isolates that do not have free or bound coagulase retain their virulence in animal models. Neither does coagulase inhibit polymorphonuclear cell phagocytosis in vivo, nor is there a correlation between circulating anticoagulase antibody and protection from *S. aureus* infection.[169] Other factors produced by *S. aureus* strains that affect virulence include the α-, β-, γ-, and δ-hemolysins.

Recently there has been renewed interest in the Panton-Valentine leukocidin (PVL) toxin. PVL is found in the majority of community-acquired methicillin-susceptible *S. aureus* (MSSA) and (MRSA) isolates responsible for skin and soft tissue disease, necrotizing pneumonia, pneumonia with empyema, necrotizing fasciitis, and severe sepsis syndrome. PVL is not a newly identified virulence factor, but the epidemiology of *S. aureus* isolates carrying the PVL genes has changed.[170,171] The genes encoding PVL were found in only about 1% to 2% of unselected MSSA isolates.[172,173] However, when examining disease-causing MSSA isolates, the genes encoding PVL were found in 93% of isolates obtained from patients with furunculosis and 85% of isolates from patients with community-acquired pneumonia.[174,175] In contrast, *S. aureus* isolates obtained from the blood rarely contain the PVL genes.[172] PVL genes are also associated with necrotizing pneumonia. In a case-control study of MSSA and MRSA isolates causing community-acquired pneumonia, those containing the PVL genes caused more severe disease characterized by hemoptysis, tissue necrosis, and higher morbidity and mortality than isolates that lacked the genes.[176]

S. aureus pneumonia may be increasing in prevalence as a result of a worldwide increase in community-acquired MRSA infections. Community-acquired *S. aureus* pneumonia typically occurs in very young infants: 30% of cases occur in children younger than 3 months of age, and 70% occur in those younger than 1 year of age. Most cases occur in the colder months, and boys are more frequently affected than are girls. A history of an antecedent viral upper respiratory infection, particularly influenza, is common. In years with influenza epidemics, *S. aureus* pneumonia may occur more frequently.[177-180] The interval between the apparent viral illness and the onset of *S. aureus* pneumonia may be brief.

S. aureus may also cause pneumonia in the nosocomial setting. In fact, epidemics often associated with isolates of phage type 80/81 once plagued neonatal nurseries, but then largely disappeared for unexplained reasons. Descendants of phage type 80/81 that are now methicillin-resistant have re-emerged in the United Kingdom and other countries in the past few years.[181]

S. aureus pneumonia usually follows inhalation of the infecting organism. *S. aureus* pneumonia may also result from seeding of the lung during bacteremia.[182] Predisposing illnesses in this regard include infections of the venous system, intravenous substance abuse, or chronic vascular catheterization for hemodialysis or other purposes. Lung abscesses and pneumonia secondary to septic emboli have been found in patients with deep vein thromboses and bone, joint, or muscle staphylococcal disease in the pelvis or lower extremities.[183] In this instance, the radiographic picture may be that of multiple small, discrete pulmonary infiltrates that may become cavitary within a few days.

There are important differences in the pathology of *S. aureus* pneumonia that depend on the age of the patient and the clinical presentation. In rapidly progressive cases, the large bronchial epithelium may be inflamed, covered with a fibrinous pseudomembrane, or extensively destroyed by infiltration of the underlying walls by polymorphonuclear leukocytes. Necrosis of smaller bronchi leads to pulmonary artery branch thrombosis with septic embolization to the lung parenchyma. The alveoli fill with edematous fluid and contain extravasated blood, polymorphonuclear leukocytes, and hyaline membranes. Destruction of alveoli may lead to the formation of a pneumatocele or tension pneumothorax; unable to escape through a necrosed bronchus, air becomes trapped in an area of necrosed alveoli. A pneumatocele formed in this manner may rupture and produce a pneumo-

thorax or a pyopneumothorax. The pneumatoceles may disappear when the surrounding pneumonia resolves and the trapped area finds an avenue for escape.

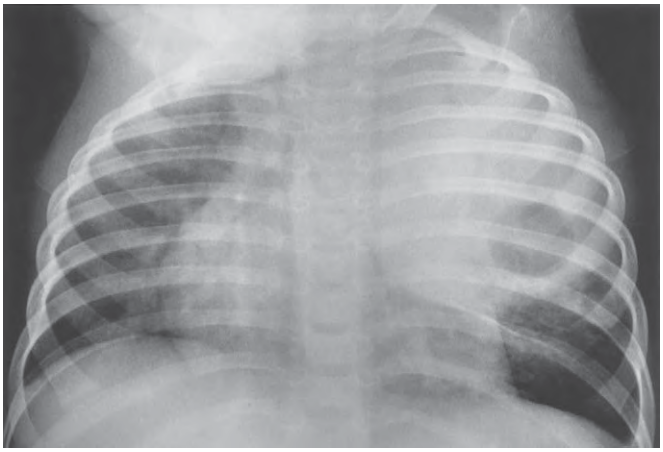
In less rapidly progressive cases, the lungs are firm and consolidated beneath the pleural surface; involvement is more patchy and mainly affects the segments of the posterior lower lobe. These segments may coalesce and form small abscess cavities that may communicate with small bronchi and fill them with pus. In the neonate, the pathology of *S. aureus* pneumonia may resemble both these processes. Alternatively, there may be a more diffuse, non-necrotizing picture consisting of lobular or lobar areas of hemorrhagic consolidation with a well-structured fibrinous layer that may overlie the pleural surface. Abscess cavities are more common and may also be diffusely distributed.

The severity of the clinical picture varies. Typically, a mild upper respiratory tract infection is followed by fever, cough, grunting, and tachypnea.[184] Occasionally, prostration, cyanosis, dyspnea, shock, or even the toxic shock syndrome[185] or severe sepsis syndrome[186] may be present. In neonates, the clinical course of staphylococcal pneumonia is often fulminating and is associated with a high mortality rate shortly after the onset of symptoms. Fever may be absent.

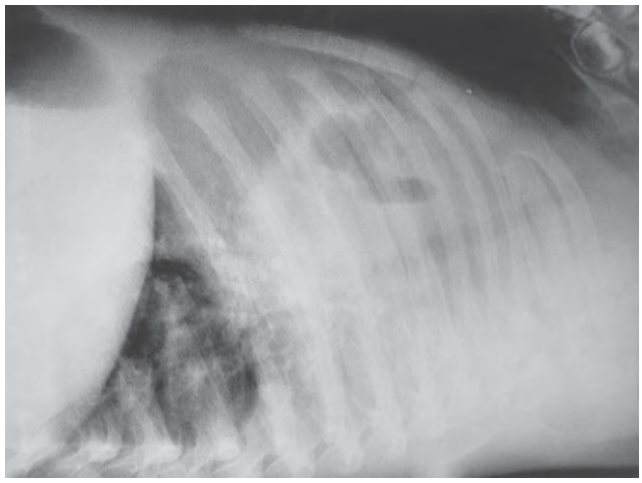
A greatly increased leukocyte count, sometimes called a *leukemoid response*, is said to be classic for *S. aureus* pneumonia but is variably present and nonspecific.[182] Leukopenia may also be an ominous sign and has been hypothesized to result from the cytotoxic effects of the PVL toxin. Some patients are bacteremic, but the proportion is unknown.

At the onset of clinically manifested *S. aureus* pneumonia, the chest radiograph may be normal.[187] However, the radiographic picture of staphylococcal pneumonia is more commonly bronchopneumonia with a patchy, central alveolar infiltrate. Multiple areas may be involved, but the process is generally unilateral. The infiltrates tend to coalesce rapidly and form large consolidations; cavitations may be present within the infiltrate (Fig. 35-9). Indeed, the rapidity of the radiographic progression to a virtual "whiteout" of the lung may be striking and should raise the possibility of *S. aureus* pneumonia when it occurs. In many patients, a pleural effusion is not visible on the first radiograph, but an effusion and empyema develops in about 90% of patients. The pleural effusion may be large and, therefore, may mask the underlying consolidation—the effect being that of an opaque chest. Spontaneous pneumothorax and pyopneumothorax occur in about 25% to 50% of cases. Pneumatoceles occur in more than 50% of cases (Fig. 35-10; see also Fig. 35-9) and may change hourly in number and size during the acute phase. Occasionally, they are sufficiently large to mimic a tension pneumothorax or to cause mediastinal shift. They may also contain fluid. The finding of a pneumatocele strongly suggests the diagnosis of *S. aureus* pneumonia. The radiographic picture of staphylococcal pneumonia, however, is not pathognomonic. Similar findings, including pneumatoceles, may occur with pneumonia caused by *E. coli*, *Pseudomonas* or *Klebsiella* species, other gram-negative bacteria, group A streptococci, and occasionally, pneumococci.

Staphylococcal pneumonia should be suspected in hospitalized infants, particularly those in intensive care units, who develop new pleural parenchymal abnormalities or an unexplained opaque chest without volume loss. In the perinatal



A



B

Figure 35-9 Staphylococcal pneumonia with cavitation. An 11-month-old boy with staphylococcal pneumonia in the left upper lobe. Both radiographs demonstrate the expanded, consolidated left upper lobe, which contains multiple air- and fluid-filled cavities. **A,** Supine anteroposterior chest radiograph. **B,** Supine horizontal beam lateral chest radiograph. At 14 years of age, this boy manifests a hyperlucent, hypoperfused left upper lobe with thin-walled clear cavities.

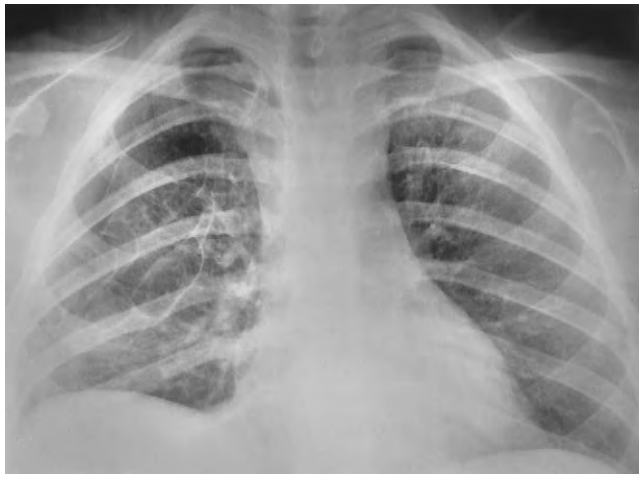


Figure 35-10 Pneumatocele. Staphylococcal pneumonia in this 17-year-old girl resulted in a very large upper right pneumatocele that imitated a pneumothorax. A multiloculated pyopneumothorax with multiple air-fluid levels was also present.

period, staphylococcal pneumonia with cavities or pneumatoceles may radiographically mimic congenital diaphragmatic hernia or cystic adenomatoid malformation.

When used for empirical coverage, extended-spectrum cephalosporins provide some coverage against methicillin-susceptible *S. aureus*. Reliance on these agents, however, is suboptimal when *S. aureus* pneumonia is suspected based on clinical evidence. The production of β-lactamase by nearly all *S. aureus* isolates has rendered ineffective any therapy using compounds hydrolyzed by this enzyme. Thus, for many years, the first-line therapy for suspected *S. aureus* infections, including pneumonia, has been the so-called *β-lactamase-resistant penicillins*, such as methicillin. Although methicillin itself is no longer in use, its modern analogmes (i.e., oxacillin, cloxacillin, flucloxacillin, nafcillin) or first-generation cephalosporins (e.g., cefazolin) are available. The recognition of *S. aureus* isolates resistant to these agents, generically termed *methicillin-resistant S. aureus* (MRSA), has posed a therapeutic dilemma. By definition, MRSA isolates are considered resistant to all β-lactam antimicrobials, including all cephalosporin compounds. MRSA infections that are nosocomially acquired tend to be multiply resistant and have forced reliance on the glycopeptide vancomycin as the agent of choice for serious MRSA infections. Furthermore, community-associated MRSA infections, including pneumonia, have recently become an increasing problem and now account for up to 70% to 78% of *S. aureus* clinically significant infections in certain geographic locales.[187-189] Unlike their nosocomially acquired counterparts, community-acquired MRSA isolates are less likely to be multiply resistant. Clindamycin has been an effective alternative for *S. aureus* infections when the isolate is susceptible. The duration of antibiotic treatment is usually 2 to 3 weeks unless complications arise, although some would recommend up to 6 weeks to minimize the risk of recrudescence or relapse. Supportive therapy should include oxygen administration, maintenance of hemoglobin levels, and fluid and electrolyte maintenance as indicated. Pneumatoceles may persist for many weeks and require no special therapy.

The most important complications of *S. aureus* pneumonia are empyema and lung abscess.[190] *S. aureus* pneumonia may rarely result in the formation of a bronchopleural fistula, which in turn may lead to the formation of tension pneumothoraces that are occasionally bilateral. In adults, these have been managed with synchronous independent lung ventilation.[191] Aortobronchial fistulae have also been reported.[192] In adults, *S. aureus* pneumonia has also been associated with Pancoast syndrome.[193]

The prognosis is variable. Mutisystem dysfunction and death have resulted from MSSA and MRSA primary pneumonia, even when appropriate antibiotics and supportive therapy were provided. Recovery is eventually complete in those with disease limited to lungs and pleura when appropriate therapy is instituted and when complications are identified and treated promptly.

HAEMOPHILUS INFLUENZAE *TYPE B*

Before the introduction of a vaccine, *H. influenzae* type b was an important cause of childhood pneumonia. In many countries where universal immunization is not practiced, it remains an important cause of pneumonia. A precise estimate of its incidence has not been available, mainly because of diagnostic difficulties in identifying the etiologic agent, but one study concluded that *H. influenzae* type b was responsible for 5% to 18% of cases of bacterial pneumonia.[49] The advent of immunization against this important pediatric pathogen has decreased the occurrence of all invasive *H. influenzae* type b syndromes by more than 95% in many developed countries; presumably this includes pneumonia. The importance of *H. influenzae* type b as a cause of pneumonia was emphasized by a vaccine trial completed in The Gambia, which suggested that *H. influenzae* type b pneumonia was an important clinical syndrome and accounted for a substantial proportion of presumed bacterial lower respiratory tract infections in children in developing countries.[194]

The realization that *H. influenzae* was the cause of several important infectious syndromes in childhood, including pneumonia, and not the cause of influenza came from the work of Margaret Pittman; in 1931, she also recognized that the serotype b capsule was the major virulence factor among isolates causing invasive disease.[195,196] Subsequent investigations determined that antibody to polyribosylribitol phosphate (PRP), the serotype b capsular polysaccharide, could protect against invasive disease.[197] This observation spawned efforts to develop immunity by active immunization.

H. influenzae is a fastidious, gram-negative, pleomorphic coccobacillus that requires factors X (hematin, heat stable) and V (phosphopyridine nucleotide, heat labile) for growth. These factors are present within erythrocytes, and the demonstration of their requirement for growth is the basis for speciating *H. influenzae* in the laboratory.

Some *H. influenzae* isolates are surrounded by a polysaccharide capsule. Such isolates can be serotyped into six antigenically and biochemically distinct types, designated *a* to *f*. The most virulent isolates belong to serotype b. Before the introduction of immunization, these were responsible for almost all *H. influenzae* invasive infections in children, including meningitis, cellulitis, epiglottitis, septic arthritis, osteomyelitis, pericarditis, bacteremia without focality, and a variety of other rare syndromes. Disease caused by other capsular serotypes of *H. influenzae*, such as types a and f, was rare[198] but is now proportionally more frequent. Nonencapsulated (nontypable) *H. influenzae* isolates can cause invasive disease in neonates,[199] immunocompromised children,[200] children in certain developing countries,[201] and rarely, children in the United States.[198] Nontypable isolates are common etiologic agents in certain mucosal infections, such as otitis media and sinusitis.[202,203] They have also been associated with chronic obstructive pulmonary disease in adults. Other *Haemophilus* species are occasional causes of invasive disease, including pneumonia. For example, *Haemophilus parainfluenzae* may cause pneumonia with empyema. Humans are the only natural hosts for *H. influenzae*. It is not widely appreciated that this species is a constituent of the normal respiratory flora in 60% to 90% of healthy children and is a frequent isolate from the oropharynx.

Before the introduction of vaccine, a striking feature of the epidemiology of invasive *H. influenzae* type b infections was its age distribution. In the United States, more than 90% of all infections occurred in children 5 years of age or younger, although a few occurred in older children and adults. Most studies showed a predominance among male patients.[203-205]

In the prevaccine era, the annual attack rate of invasive disease was estimated to be 33 to 129 cases per 100,000 children (younger than 5 years of age) per year.[206] In Finland, the reported annual incidence was 41 cases per 100,000 children in the prevaccine era; 40% occurred in children older than 2 years of age.[207] Populations identified as having an increased incidence of invasive disease include Alaskan Inuit, Apache and Navajo Native Americans, and African Americans.[208] In these populations, the number of cases of invasive disease in children younger than 12 months of age was relatively high. People known to be at an increased risk for invasive disease included those with sickle cell disease, asplenia, congenital and acquired immunodeficiencies, and malignancies.

The most common mode of *H. influenzae* transmission is by direct contact or by inhalation of contaminated respiratory tract droplets. The incubation period for invasive disease is variable, and the exact period of communicability is unknown. Among age-susceptible household contacts who have been exposed to a case of invasive *H. influenzae* type b disease, there is a substantial risk of developing "secondary" invasive disease in the first 30 days (estimated at 0.26%). The attack rate for such disease in household contacts is highest in susceptible children younger than 24 months of age (3.2%) and rare in contacts older than 47 months of age (<0.1%). Unlike in the general population, asymptomatic carriage of *H. influenzae* type b is frequent in household contacts of patients with disease. More than 75% of families have at least one colonized household member in addition to the index patient.[209,210]

The precise mechanisms that facilitate colonization of the respiratory epithelium have yet to be identified. In an organ culture of human nasopharyngeal tissue, both type b and non-b strains of *H. influenzae* organisms attach to nonciliated columnar epithelial cells and subsequently can be seen within those cells and in the intercellular spaces.[211-213]

Noninvasive *H. influenzae* infections, such as otitis media, sinusitis, and bronchitis, which are usually caused by nontypable strains, probably gain access to sites such as the middle ear or sinus cavity by direct extension from the pharynx. Serotype b organisms are infrequent causes of these noninvasive infections but probably cause disease by the same mechanism. Antibody directed against the type b capsular polysaccharide, PRP, is acquired in an age-related fashion and facilitates clearance of *H. influenzae* type b from blood in experimental animal models[214,215]; its presence was correlated with protection in several clinical trials that used both active and passive immunization.[197,216]

Before the introduction of vaccination and then later among recipients of unconjugated PRP vaccines, protection from *H. influenzae* type b infection was presumed to be directly correlated with the concentration of circulating anti-PRP antibody at the time of exposure. Most infants had a low or absent level of anti-PRP antibody and were thus susceptible to disease on exposure to *H. influenzae* type b.

Unlike the PRP unconjugated vaccine, the conjugate vaccines behaved as thymus-dependent antigens with the exception of a PRP–*N. meningitidis* type B outer membrane protein complex vaccine (PedvaxHib, Merck), which also has thymus-independent type I properties. The conjugate vaccines elicit serum antibody responses in young infants, although multiple doses may be required, and they prime for memory antibody responses on subsequent encounters with PRP.[217,218] More importantly, the concentration of circulating anti-PRP antibody in a child whose immune system has been primed by a conjugate vaccine may not correlate precisely with protection because a memory response may occur rapidly on exposure to PRP and provide protection.[219]

The signs and symptoms of pneumonia caused by *H. influenzae* type b cannot be distinguished from those caused by pneumonia resulting from many other microorganisms. Associated infectious foci, such as meningitis, are common; pneumonia is frequent in children with acute epiglottitis.[220]

The radiographic manifestations of *H. influenzae* pneumonia vary from a bronchiolitic type of image with central linear infiltrates and overinflation to bronchopneumonia with patchy consolidation and no lobar predilection. Pleural effusion is present in about one third of patients with *H. influenzae;* less commonly, a pericardial effusion may be present. Pneumatoceles are rare but have been reported.[221]

The techniques used in the detection of PRP in CSF, serum, urine, or other relevant body fluids have included counter-immunoelectrophoresis, latex agglutination, staphylococcal protein A coagglutination, and enzyme immunoassay.[222] Latex agglutination is perhaps the most sensitive, versatile, and accessible method for the direct detection of PRP[222] when the results of culture are not revealing.

Children younger than 12 months of age suspected of having *H. influenzae* pneumonia should promptly receive parenteral antimicrobial therapy because of the increased risk for bacteremia and its complications. Older children who do not appear severely ill and are, therefore, unlikely to be bacteremic may be treated with an orally administered antimicrobial; customarily a 7- to 10-day course of parenteral, oral, or combined parenteral-oral therapy is completed.

Before 1974, all *H. influenzae* isolates were presumed to be susceptible to ampicillin. Subsequently as the prevalence of β-lactamase-positive isolates increased, chloramphenicol became the agent of choice for therapy against invasive *H. influenzae* type b disease. Advantages of chloramphenicol have included low cost, good penetration into CSF, and its effectiveness against most isolates of *H. influenzae* type b irrespective of β-lactamase production. The disadvantages of chloramphenicol include the necessity for monitoring serum levels and often emotionally held views regarding the rare occurrence of idiosyncratic aplastic anemia. Chloramphenicol-resistant isolates of *H. influenzae* type b have been identified but have remained relatively infrequent in the United States and worldwide; however, they are more common in a few locales such as Barcelona and Taiwan. Use of chloramphenicol has waned in developed countries, whereas it remains a first line agent in developing countries.

Isolates resistant to both chloramphenicol and ampicillin have rarely been identified. In the United States, less than 1% of isolates were resistant to both compounds. Among antimicrobials used for oral therapy of mild *H. influenzae* infections, resistance to amoxicillin/clavulanate and azithromycin occurred in less than 10% of clinical isolates in a recent survey of isolate susceptibility spanning 13 countries in 1999 to 2000. More than 20% were resistant to trimethoprim-sulfamethoxazole (TMP/SMX) or amoxicillin.

The initial antibiotic therapy of invasive infections possibly caused by *H. influenzae* type b should be a parenterally administered antimicrobial agent effective in sterilizing all foci of infection. Such therapy should also be effective against ampicillin-resistant strains. Extended-spectrum cephalosporins, such as cefotaxime or ceftriaxone, have achieved popularity because of their relative lack of serious adverse effects and ease of administration. To date, resistance to extended-spectrum cephalosporins has not been documented. Alternatively, chloramphenicol can be used with ampicillin. Once the antimicrobial susceptibility of the isolate has been determined, an appropriate agent can be selected to complete the therapy. Oral antimicrobial agents are sometimes used to complete a course of therapy initiated by the parenteral route and even as initial therapy for older children with pneumonia who are not very ill. The principles of therapy are the same: when the isolate is susceptible to ampicillin, it or amoxicillin is the compound of choice. When the isolate is resistant to ampicillin, cefixime or amoxicillin/clavulanate may be used. Chloramphenicol is another option.

In households where one or more children younger than 48 months of age are not fully immunized, approximately 4 days of rifampin prophylaxis is indicated for all members of the household contact group in whom a case of *H. influenzae* type b disease occurs.[209] This recommendation includes the index patient. Relevant definitions and dosing recommendations have been found in the Report of the Committee on Infectious Diseases of the American Academy of Pediatrics.[162] There are no data to address whether a similar approach to non-serotype b disease is appropriate.

With the development of conjugate vaccines that have proved highly immunogenic in young children, PRP vaccine has been replaced by several licensed *H. influenzae* type b conjugate vaccines that differ in the carrier protein used, the saccharide molecular size, and the method of conjugating the saccharide to the protein.[223] The introduction of effective immunization against *H. influenzae* type b with the use of the conjugate vaccines has greatly decreased the occurrence of *H. influenzae* type b infections.[224-226]

STREPTOCOCCUS AGALACTIAE

The designation *group B β-hemolytic streptococci* (GBS) was first applied by Lancefield in 1933[227] to *Streptococcus agalactiae*, an important cause of bovine mastitis known to infect cows as early as the 1800s.[228] In the 1960s, GBS became increasingly recognized as a cause of neonatal infection, including pneumonia. Today, GBS are common causes of pneumonia and other invasive infections in neonates. The incidence of neonatal pneumonia has greatly decreased with the implementation of maternal antibiotic prophylaxis for GBS carriers at the time of delivery.

Group B is distinguished from other streptococcal groups by its distinctive carbohydrate antigen, which is bound to the bacterial cell wall; L-rhamnose is the major antigenic determinant. Nine serotypes have been described; serotypes Ia, Ib, II, III, and V are responsible for approximately 95% of cases in the United States.[229]

GBS infections are often classified by the onset time of clinical manifestations. Although this distinction is somewhat artifactual and there is substantial overlap in the clinical features of so-called *early-onset* and *late-onset* disease, differences in pathogenesis, clinical syndromes, and the responsible serotypes have made separation of these syndromes of some use. Early onset disease is manifested in the first week of life, often on the first day. Serotypes Ia, II, III, and V are most commonly responsible for this syndrome. Transmission of GBS most likely occurs a short time before or during birth. Risk factors for early-onset disease include prematurity, prolonged rupture of the chorioamnionic membranes before birth, or maternal infection. Late-onset disease is manifested after the first week of life, with most cases occurring in children younger than 1 month of age. GBS disease is extremely rare in toddlers and older children; occasionally, very late-onset GBS disease occurring in older children may be an early manifestation of untreated HIV infection.[230] In late-onset disease, serotype III organisms are almost exclusively responsible for infection, but serotype Ia has also been implicated. The transmission of GBS to patients with late-onset disease is believed to occur after birth, either during or after the hospital stay. Carriage, once acquired, may persist for many months.

Antibiotic administration is now routinely used to interrupt the transmission of GBS from mother to neonate at the time of birth. Antenatal antimicrobial treatment of colonized women aimed at eradicating carriage has not been effective.[231] Moreover, Siegel and colleagues[232] administered penicillin to unselected neonates at birth as prophylaxis against GBS disease but found no associated decrease in mortality rates, an increase in the recovery of penicillin-resistant organisms of other genera, and increased mortality from infections caused by these penicillin-resistant isolates. However, intrapartum ampicillin decreased the maternal-fetal transmission of GBS.[233,234] This observation led to recommendations from the Centers for Disease Control and Prevention (CDC)[235] to screen all pregnant women for GBS vaginal and rectal colonization at 35 to 37 weeks' gestation and to manage those with a positive screen with intrapartum chemoprophylaxis. Any woman who had GBS bacteriuria during the current pregnancy or who had a previous infant with invasive GBS disease should also receive prophylaxis during labor and delivery. If a woman's GBS status is unknown at the time of delivery, a risk-based approach is used and intrapartum prophylaxis should be administered to women with pregnancy less than 37 weeks' gestation, prolonged rupture of membranes, or intrapartum fever.

Early-onset disease was more frequent than late-onset disease prior to the introduction of targeted maternal intrapartum antibiotic prophylaxis. Since antibiotic prophylaxis policies have been incorporated, the incidence of early onset disease decreased by 81% to approximately 0.3 cases per 1000 live births and is now equal to the incidence of late-onset disease. Intrapartum antibiotics have not been shown to prevent late-onset disease.

For early-onset disease, the clinical picture is one of sepsis.[236,237] The features may include onset within hours of birth, tachypnea, apnea, and a generally ill appearance. Pneumonia is almost always present. The pulmonary clinical picture may be indistinguishable from respiratory distress syndrome of prematurity.[238,239]

Late-onset disease is more indolent in its presentation. Fever, bacteremia, and meningitis are commonly, but not universally, present. GBS with late presentation is not usually

associated with pneumonia.[240] If present, the clinical features are characteristic of pneumonia caused by other bacteria. Indeed, an identifiable infectious focus may not be evident. In one series, about one third of infants with GBS disease, most of whom had late-onset disease, did not appear ill or irritable, and about one third had no fever.[240] Occasionally, the clinical picture of early onset disease may be evident, and the chest radiograph may resemble that caused by respiratory distress syndrome.

The diagnosis is made by recovery of the organism from blood or another normally sterile body fluid, such as pleural fluid, CSF, urine, or synovial fluid. Detection of the group B carbohydrate antigen in blood or CSF (e.g., by latex agglutination)[241] is useful but requires careful interpretation and should not be relied on as the sole method of bacterial detection. Urine testing in particular has been prone to false-positive and false-negative findings; because of this, in 1997, the Food and Drug Administration advised against using latex agglutination methods in testing of urine specimens.

The treatment for GBS pneumonia in the absence of meningitis involves 200,000 units/kg/day of penicillin intravenously in three divided doses in the first week of life and 300,000 units/kg/day intravenously in four divided doses thereafter. A 14-day course is usually administered for pneumonia. Higher doses and a 21-day course are often used when meningitis is present. Initial therapy with a β-lactam and an aminoglycoside results in more rapid killing in vitro and may be a useful clinical adjunct.[242] When used, the aminoglycoside is usually discontinued after about 5 days and the course completed with the β-lactam. Other options include ampicillin or ceftriaxone. Intravenously administered immune globulin has been used as adjunctive therapy, but data establishing its effectiveness are lacking.

Empyema may complicate group B streptococcal pneumonia. The associations with group B streptococcal pneumonia, group B streptococcal bacteremia, a generalized septic picture, and distant metastatic infectious foci (such as meningitis and skeletal infections) are well described. It is probable that group B streptococcal pneumonia seldom occurs in an infant who is not systemically ill.

Even when appropriate antimicrobial and supportive therapy are initiated in a timely way, the mortality rate from early onset GBS disease is high (about 14%), particularly in cases occurring in the immediate perinatal period and those in small premature infants.[243] Many authors believe that this rate represents a decline from higher rates,[244] possibly as a result of improved supportive care. The mortality rate from late-onset disease is much lower (about 2% to 6%).[240,245]

Some have advocated intravenously administered immune globulin to prevent GBS infections. However, in a prospective trial of 2416 very low birth weight newborns who were randomized to receive either placebo or intravenously administered immune globulin every 2 weeks until the infant weighed 1800 g, no difference was identified in the incidence of GBS infection, length of hospitalization, or mortality rates.[246]

Efforts to prevent GBS disease by vaccination are ongoing. Many investigators have advocated immunizing pregnant women in the hope of transferring antibody produced by immunization to the fetus in utero, thereby offering protection in the neonatal period. A tetravalent polysaccharide vaccine produced only a modest response in healthy adults.[247] Conjugate vaccines consisting of the capsular polysaccharide covalently linked to tetanus toxoid have been shown to be safe in adults and to elicit a good antibody response.[247] It is presumed that immunization of pregnant women would result in passive antibody transfer to the fetus and later protection of neonatal and infant GBS disease. Licensure of such a vaccine will depend on documentation of the efficacy in pregnant women.

Causes of Less Frequent Clinical Concern

ACINETOBACTER *SPECIES*

Members of the genus *Acinetobacter*[248] are gram-negative bacilli with variable morphologic pictures depending on the phase of growth in broth culture and environmental conditions. The organism is a strict aerobe that is ubiquitous in water, sewage, and soil. Several species have been described. From clinical specimens, the most common isolates belong to the *Acinetobacter baumanii*, *A. calcoaceticus* complex, and *A. lwoffi*. *Acinetobacter* species are not members of the resident skin flora but may transiently colonize skin, saliva, or other body secretions. Most often, the organism is a commensal. Invasive infection is associated with a stay in an intensive care unit, immune deficiency, antimicrobial treatment, invasive use of instruments, and prolonged venous catheterization.

Pneumonia caused by *Acinetobacter* species is rare, particularly in children; it has been described only in those with impaired immunity. In adults, *Acinetobacter* pneumonia is usually sporadic, although outbreaks have been described. For example, an outbreak of pneumonia occurred in foundry workers who were presumably exposed to infected metallic dust.[248] Members of *Acinetobacter* species survive well in water; thus the use of respiratory therapy equipment, particularly endotracheal intubation and aerosols, are risk factors for *Acinetobacter* infections. Cases of *Acinetobacter* pneumonia occur more often in the summer than in other seasons.

No unique pathologic or clinical features distinguish *Acinetobacter* pneumonia from other bacterial pneumonias. More than one lobe is involved in most reported cases. Empyema and the formation of intrapulmonary cavitations have been described. Because this species may colonize asymptomatically, isolation of the organism from pharyngeal secretions is not helpful in the diagnosis of *Acinetobacter* pneumonia. Definitive diagnosis is based on lung aspirate or biopsy or isolation of the organism from blood in the presence of a clinical picture compatible with pneumonia.

Susceptibility testing of clinically relevant isolates aid in antibiotic selection. *Acinetobacter* species are variably susceptible to cephalosporins and aminoglycosides. Carbapenems (meropenem, imipenem, or ertapenem) are effective in approximately 90% of cases in the United States and are now often used to treat *Acinetobacter* infectons. Multidrug resistance among *Acinetobacter* strains is an emerging problem and cases of carbapenem-resistant *A. baumannii* are increasing worldwide. Colistin and tigecycline have been successful in treating some multidrug-resistant infections.

ACTINOMYCES *SPECIES*

The term *actinomycosis* was first used in 1877 by Bollinger to describe sarcoma-like masses in the jaws of cattle.[249] Acti-

nomycosis is uncommon in children.[250] About 10% of all cases occur in children younger than 18 years of age.[251,252] It is more common in immunocompromised children and in those with poor oral hygiene. Distribution is worldwide; there is no racial or occupational predisposition. A male predilection has been noted in adults, but studies in children suggest no gender differences.[253] Actinomycosis is not believed to be contagious, and the causative organisms have been isolated only from humans.[251]

Trauma and a favorable anaerobic milieu are important factors in the predisposition to clinical disease.[254] *Actinomyces* species are saprophytic inhabitants of the normal oral cavity and nasopharynx, particularly at the gum margins and in the presence of dental caries. The organism has also been found in tonsillar crypts, periodontal tissue, paranasal sinuses,[255] and gastric and bronchial secretions.[256] Because the onset of the disease can occur at any time after colonization is initiated, the incubation time varies from days to years after initial contact with the organism.[257]

Infection occurs by direct tissue invasion[253] without regard for tissue planes.[258] *Actinomyces* organisms are readily phagocytized by host defense cells but, like mycobacteria, are often not killed after the ingestion.[259] Actinomycosis is classified into the following syndromes: cervicofacial, abdominal, and thoracic. (The last includes pulmonary and extrapulmonary intrathoracic disease.) Overall, about 15% to 20% of patients with actinomycosis have pneumonia.[256] Most have primary pulmonary involvement.[255] Among 48 adults and children with actinomycosis pneumonia, 8 had evidence of bacteremic seeding of the lung or extension from an extrapulmonary site, whereas 40 had lung involvement that was considered to be primary.[251] In this instance, infection usually arises from aspiration of infected material from the oropharynx[251] and rarely arises after esophageal disruption secondary to nonpenetrating trauma or surgery. Previous lung injury increases the likelihood of disease when aspiration or inhalation occurs.

Pulmonary actinomycosis is a chronic, localized inflammatory process.[251] Histologic features include a thick, fibrous wall without necrosis in loculated regions. The finding of so-called *sulfur granules* (small, lobulated, grainy microcolonies of bacteria 1 to 2 mm in size that are cemented together by a protein-polysaccharide capsular complex) is virtually pathognomonic for actinomycotic infection; the granule may be mineralized with calcium phosphate and may sometimes be visible macroscopically.[260] Necrosis rarely occurs,[251] although focal liquefaction without fibrosis is occasionally present.[251] Large macrophages with foamy cytoplasm accumulate around the purulent center. These may be absent in acute lesions, in which mostly fibrin is found.[252]

Symptoms of pulmonary involvement include low-grade fever and cough productive of purulent or blood-streaked material. Sputum, if present, is usually not malodorous. Dyspnea and orthopnea have been noted.[251] Other symptoms may include malaise, anorexia, weight loss, and localized chest pain.[258] Nonspecific laboratory findings may include moderate leukocytosis and anemia, particularly in more chronic cases.

Physical examination may reveal asymmetrical crackles and dullness on percussion. Signs suggesting the presence of a pleural effusion may be apparent. There may be subcutaneous abscesses over the chest wall. Examination of the abdomen may be abnormal and reflect extension of the infectious process through the diaphragm.

A delay in diagnosis is common.[261] The median number of weeks between presentation and diagnosis is 3 to 5 and ranges up to 24 weeks.[261] The initial diagnosis in many cases is malignancy. The presence of chest pain, which is common in actinomycosis but less so in malignancy, may help distinguish this condition from others.[261] Another reason for delay is the lack of a typical picture. Children may be asymptomatic despite the presence of a large pulmonary mass.[255]

The distinctive radiographic characteristics of actinomycosis involving the lung are secondary to its lack of respect for the anatomic boundaries of the chest compartments. Pulmonary actinomycosis may appear radiographically as an infiltrate with associated soft tissue, rib, and pleural involvement. Primary pulmonary involvement may start as a patchy, peripheral, airspace infiltrate similar to that occurring in pneumococcal pneumonia and may resolve completely if treated; basal lobe involvement is frequent. If untreated, however, intrapulmonary cavitation or mass lesions may be present; the process may extend peripherally to cause empyema, rib osteomyelitis with the pathognomonic contiguous dense periosteal reaction[249,255] in multiple ribs, or a chest wall abscess.[262] The radiographic classic triad of actinomycosis, lung infiltrate, and rib or chest wall involvement, as well as empyema,[263] is useful in suggesting the correct diagnosis but is infrequently present.[261,262] Occasionally, there is vertebral destruction.[249,263] Parasitization of the blood supply by these lesions from the chest wall circulation may result in systemic to pulmonary shunting.[115]

As with any other complex thoracic process that involves the chest wall as well as intrathoracic structures, CT, preferably contrast enhanced, is the imaging modality of choice. CT is used when chest radiographs do not clarify the findings[264] or when the suspicion of a malignancy is high.

The differential diagnosis includes other infectious processes that tend to disregard tissue boundaries, such as blastomycosis, cryptococcosis, tuberculosis, and rarely, aspergillosis. Rib destruction associated with intrathoracic opacities may be present with pyogenic osteomyelitis, chest wall tumors (particularly Ewing sarcoma), and primitive neuroectodermal tumors.

Definitive diagnosis is by histopathologic examination.[260] The diagnosis is suggested by the finding of beaded, branched, gram-positive bacilli in pus, and it is strongly endorsed by isolation of the organism; the visualization of typical gram-positive, branching bacilli in histologic sections; or the presence of sulfur granules.

The organism may be isolated from tissue obtained by local resection, lobectomy, transthoracic needle aspiration,[261] or pleural fluid.[265] Resection is most commonly performed because malignancy is incorrectly suspected.[266] *Actinomyces israelii*, the most frequent isolate, grows anaerobically, and usually requires 4 to 8 days for incubation. *Actinomyces meyeri* is occasionally the isolate and has a predilection for the apical region.[267]

Actinomyces species is usually not isolated in pure culture.[255] In about two thirds of cases, another bacterium, often *Actinobacillus actinomycetemcomitans*, was isolated.[254,256] Some have theorized that the presence of an

aerobic bacillus lowers the redox potential of the tissue and thereby promotes the growth of *Actinomyces* species[255] by improving the anaerobic growth conditions.

Both the dosage and duration of penicillin therapy have not been critically evaluated, and clinical experience is, therefore, anecdotal.[249,255] Most experts recommend an initial course of intravenous penicillin at high dosage (e.g., 250,000 units/kg/day) for 2 to 6 weeks and then oral penicillin (e.g., 125 mg/kg/day) for several months thereafter. *Actinomyces* species is susceptible to penicillin, but prolonged therapy for thoracic actinomycosis is necessary to prevent relapse. Some[268] have exclusively advocated oral penicillin V therapy (e.g., 125 mg/kg/day) with reportedly good results. Irrespective of the therapeutic regimen used, the dose and length of penicillin treatment should be related to the amount of induration and fibrosis and the extent of infection at the time of diagnosis.[253,255] Separate therapy directed against concomitantly isolated organisms, such as *A. actinomycetemcomitans*, is traditionally said not to be necessary. Clindamycin, erythromycin, chloramphenicol, and tetracycline (for children 9 years of age and older) are alternative treatment choices.[265] Serial radiography of the chest is useful in documenting the adequacy of therapy.[258]

The main role of surgery is to drain any abscesses or empyema that may be present. Surgery was once believed necessary to cure actinomycosis. Radical surgery is still sometimes performed, particularly in the presence of extensive fibrosis, or unwittingly as a treatment for a commonly presumed diagnosis of carcinoma.[269] Management in the modern antibiotic era must be individualized; even in the presence of extensive disease, it is reasonable to consider that medical therapy alone warrants consideration.

The mortality rate in untreated or inadequately treated cases has been about 90%.[249,255] Conversely, about 90% of those treated recover. Complications of actinomycosis pneumonia include the development of parenchymal abscesses or empyema and the formation of draining sinuses. In one review, such sinuses were present in 25% of patients with thoracic actinomycosis.[251] They may connect with the trachea, esophagus, pericardium, heart, or skin.[270] Rib and vertebral destruction may occur by direct extension.[270] Disseminated disease, although rare in children,[271] may complicate thoracic actinomycosis[254,255,271] and may be fatal despite accurate diagnosis and treatment.[251] Good oral hygiene is the best available prevention against actinomycosis.

Anaerobes

Guillemot and colleagues[272] first reported in 1904 that empyema could be caused by bacteria that did not grow under standard, aerobic conditions. It was realized that because similar organisms were also found in the oral cavity, an aspiration event and pneumonia probably preceded the empyema.[273] Subsequently, more than 2000 cases of anaerobic empyema were reported in the preantibiotic era.[274] With the advent of antibiotics, however, interest in anaerobic pneumonias decreased until the 1970s, when a resurgence of interest occurred because of improved techniques for anaerobic culture, organization of anaerobic taxonomy (to lessen confusion), and trials of therapeutic agents that required bacteriologic confirmation.[273]

It is believed that a major role should be ascribed to anaerobic bacteria as a cause of aspiration pneumonia. It follows that patients predisposed to aspiration, such as children with dysphagia, seizures, neurologic disorders (including cerebral palsy), general anesthesia, drug use, gastroesophageal reflux, or compromised consciousness, are at risk. If aspiration occurs when the child is in the upright position, the basal segments of the lower lobes are the most common sites of pneumonia, whereas if the child is recumbent, the posterior segments of the upper lobes or the superior segments of the lower lobes are more likely locations of pneumonia.[273,275]

In the absence of such a predisposition, the role of anaerobes in uncomplicated pneumonia remains uncertain, particularly in children. In adults, some[276,277] have suggested that pneumonitis caused by anaerobes cannot be distinguished from other bacterial pneumonias, and because the microbiologic evaluation of any pneumonia is often difficult and anaerobic cultures are seldom performed, any existing role for anaerobes in uncomplicated pneumonia may not be adequately appreciated.

Few data exist regarding the specific anaerobic organisms that might cause pneumonia in children. Experience in adults suggests that the most frequent isolates are anaerobic streptococci, such as *Peptostreptococcus* species; microaerophilic anaerobic streptococci such as *Streptococcus intermedius*, *Streptococcus parvulus*, *Streptococcus constellatus*, *Streptococcus morbillorum* (now reclassified as *Gemella morbillorum*); and other anaerobic organisms such as *Bacteroides melaninogenicus* (now referred to as *Prevotella*), *Porphyromonas* species, and *Fusobacterium nucleatum*.[275] The *Bacteroides fragilis* group includes most of the pathogenic anaerobic organisms.[278]

Treatment of pulmonary infections involving anaerobes usually involves one of three strategies. *Bacteroides* species are usually susceptible to penicillin G, ampicillin, and broad-spectrum penicillins. Some authors believe that penicillin G is the drug of choice for anaerobic pneumonia,[279] whereas others favor clindamycin because it is active against almost all mouth and respiratory tract *Bacteroides* isolates.[162,276] β-Lactamase production has been identified in many non-*B. fragilis* species and in fusobacteria.[278] Susceptibility of non-*B. fragilis* isolates was recently surveyed at 28 U.S. centers, and it was found that 64.7% of *Bacteroides* species and 41.1% of fusobacteria elaborated β-lactamase.[278] Anaerobic susceptibility testing is technically difficult, particularly for slow-growing and fastidious organisms such as *Fusobacteria* and non-*B. fragilis* species.[278] Thus, the clinical laboratory seldom provides meaningful guidance in this area. Complications of anaerobic pneumonia include lung abscess and empyema,[275] entities that are dealt with separately in this chapter.

ARCANOBACTERIUM HAEMOLYTICUM

Arcanobacterium haemolyticum[280,281] is a rare cause of pneumonia in children. The organism is a gram-positive bacillus, with humans as the primary reservoir. The incubation period is unknown, although long-term pharyngeal carriage has been identified. The usual manifestation is a skin infection or pharyngitis. However, when this pathogen causes pneumonia, respiratory signs and symptoms, such as tachypnea, fever, and coughing, may be present.

The organism may be isolated from a blood culture. Although serologic antibody tests for *A. haemolyticum* exist, none has been standardized or is commercially available. The organism is susceptible to penicillin, erythromycin, clindamycin, chloramphenicol, and tetracycline. All these agents appear appropriate for therapy.

BACILLUS ANTHRACIS

Anthrax is usually a disease of livestock caused by *Bacillus anthracis*, which are large, aerobic, spore-forming, gram-positive, rod-shaped bacteria. It is found in cattle, sheep, and goats.[282] In the United States, it is endemic in the states where livestock is concentrated.[282] Naturally acquired human infection has all but vanished in the United States. When it occurs, it is acquired via the lungs or skin after contact with hides, furs, wool, or other spore-contaminated animal products.[282] However, intentional contamination of the U.S. mail with *B. anthracis* in 2001 resulted in 22 cases of anthrax, of which 5 cases resulted in death. Its potential use as a biological weapon has renewed interest in *B. anthracis* as a cause of pneumonia. The virulence of *B. anthracis* is due to its weakly antigenic, antiphagocytic, poly-D-glutamic acid capsule and the production of three exotoxins called *edema factor, lethal factor,* and *protective antigen.* The capsule and toxin genes have been localized to plasmids routinely found in virulent isolates.[283]

There are three clinical forms of anthrax. The majority of cases involve characteristic skin lesions and regional lymphadenopathy. Pulmonary involvement (the so-called *inhalational form*) is initiated by inhalation.[283] After inhalation, the spores are transported by lung macrophages to mediastinal and hilar nodes.[282,284] Either during transport or on arrival at the lymph node, the spore germinates, a process that may result in severe, hemorrhagic lymphangitis with marked adenopathy.[282] The bacilli may then enter the bloodstream and disseminate.[282] The lung may be seeded during this bacteremic phase. Rarely, a patient with anthrax may have clinical features of gastroenteritis.

The hallmark of pulmonary involvement is hemorrhagic edema. Microscopically, there is massive hemorrhage and edema fluid in all involved airspaces. A serofibrinous exudate with many large bacilli and an absence of polymorphonuclear leukocytes is typical. In patients who have survived for a prolonged time, the septa become necrosed, and fibrin thrombi obliterate the pulmonary capillaries.

Clinically, the onset of systemic anthrax is insidious, with malaise, a nonproductive cough lasting many days, and low-grade fever. Stridor may also be present secondary to mediastinal nodal compression of the trachea.[282] When bloodstream invasion occurs, there may be a sudden onset of high fever and shock accompanied by dyspnea and cyanosis. These events usually lead to death within 24 hours.[282]

Obtaining a history of exposure to the infectious agent is important; few cases occur in which such an exposure cannot be identified. Because anthrax is rare in the United States and may herald the onset of biological attack, any case should be reported immediately to the local or state health department. The diagnosis of *B. anthracis* infection is made by visualization of the organism after Gram stain of material obtained from a lesion or discharge, growth in culture, or direct immunofluorescence of tissue or culture material. An enzyme immunoassay that measures IgG antibodies against protective antigen can be used for diagnosis but requires a convalescent serum specimen. PCR and a now commercially available QuickELISA Anthrax-PA Kit (Immunetics Inc) are rapid diagnostic tools useful as screening tests.

In anthrax pneumonia, the chest radiograph usually demonstrates marked widening of the mediastinum associated with mediastinal and hilar lymphadenopathy, patchy or diffuse confluent infiltrates, and consolidations seen with hemorrhagic pneumonia. Pleural effusions are common, and areas of localized pulmonary edema secondary to lymphatic blockage may occur either unilaterally or bilaterally.[282]

A high index of suspicion and rapid administration of effective antibiotics are essential for effective treatment of anthrax. Death from the cutaneous form of anthrax is rare. However, the prognosis is poor for inhalation of anthrax. Ciprofloxacin or doxycycline are recommended as part of the multidrug treatment of inhalational anthrax until susceptibility results are known. Both drugs are rarely used in children because of safety and side effect concerns, but should be used in treatment of life-threatening infections. Penicillin, ampicillin, clindamycin, and clarithromycin are other drugs suggested for use in conjunction with ciprofloxacin or doxycycline. Penicillin is the drug of choice when the isolate is susceptible. Treatment of inhalational anthrax should continue for at least 60 days. Complications of respiratory anthrax include meningitis and gastrointestinal tract involvement. Necrotic intestinal lesions have been found at autopsy.[282]

Patients with anthrax should be isolated until antibiotics have been administered for 72 hours. BioThrax (manufactured by BioPort, Rockville, MD) is a cell-free culture filtrate vaccine recommended for use in individuals at ongoing risk of acquiring anthrax, including certain laboratory workers and military personnel. The efficacy of this vaccine has been established in adults. However, no data are available in children, and the vaccine is, therefore, not licensed for use in them. Development of improved component vaccines is underway.[285]

OTHER BACILLUS *SPECIES*

Bacillus species are members of the family Bacillaceae, a group of aerobic, saprophytic, sporulating organisms commonly isolated from dust, soil, air, and water. Although they frequently contaminate clinical specimens, members of the genus may cause endophthalmitis, meningitis, and endocarditis; may contaminate hemodialysis equipment; and may cause food poisoning. As a pulmonary pathogen, the species *B. cereus* has received recent attention in immunocompromised hosts[286] and at least occasionally in patients with normal immune systems. Two premature infants who died with evidence of necrotizing pneumonia with *B. cereus* as the causative agent were recently described.[287] At autopsy, one had scattered "tan" areas with well-demarcated areas of necrosis and large numbers of visualized gram-positive rods, and the other had pneumonitis with well-defined areas of necrosis not associated with substantial inflammatory cellular infiltrates. Acquisition of the organism was believed to be nosocomial. Other *Bacillus* species have been implicated even less frequently; pneumonia and empyema were found to be caused by a *Bacillus* species that resembled *Bacillus*

alvei,[288] and an adult with chronic asthma had a gelatinous pseudotumor of the lung caused by *Bacillus sphaericus*.[289]

Antimicrobial therapy for infections caused by *B. cereus* is complicated by the realization that members of the species are generally resistant to β-lactams and cephalosporins. However, clindamycin, imipenem, vancomycin, erythromycin, chloramphenicol, and aminoglycosides have been highly active. Other *Bacillus* species are usually susceptible to β-lactams and cephalosporins.[290]

BARTONELLA HENSELAE

Cat-scratch disease (CSD) was first described in 1950 by Debre and coworkers[291] It has now been recognized that the causative organism is *B. henselae*, a fastidious, slow-growing, gram-negative bacterium. Pneumonia associated with CSD is exceedingly rare and has been described in only a few children.[292] CSD is a common infection in children[293]; 80% of cases occur in those younger than 20 years of age. Transmission is via contact with a cat or kitten; more than 90% of patients with CSD have a history of feline exposure.

Patients with CSD usually have self-limited regional lymphadenopathy after contact with a cat or more commonly, a kitten.[294] Constitutional symptoms occur in 50% to 70% of cases and are usually limited to fever and, less frequently, emesis, seizures, and respiratory distress.[292,295] Only five cases of pneumonia and pleural effusion were identified in a recent review[292,295]; all had multisystem involvement. The pathogenesis of CSD pneumonia is uncertain; hematogenous seeding of the lung during bacteremia has been proposed.[292,295] Pleural effusion is usually present. The diagnosis of CSD is usually made serologically. An indirect immunofluorescent assay for serum antibodies to *Bartonella* species antigens performed by many commercial laboratories, state public health departments, and the CDC[296] has been the standard. A newer ELISA assay[297] is less sensitive than the immunofluorescent assay performed by the CDC.[298]

Detection of *B. henselae* nucleic acid sequences by PCR is now available in some commercial and research laboratories.[299,300] Identification of the distinctive morphology of *B. henselae* by Warthin-Starry silver impregnation stain is useful if tissue is available. Culturing *B. henselae* has remained problematic; successful cultivation has been largely limited to the CDC laboratory and is performed there by heart infusion agar with defibrinated rabbit blood in the presence of 5% carbon dioxide for 7 to 14 days at 35° C.[301] Administration of antimicrobials diminishes the likelihood of successfully cultivating the organism or visualizing it by Warthin-Starry staining.

No controlled trials of antimicrobial therapy have been performed for the treatment of CSD, and the few cases of pneumonia described in children provide little help. Clearly, CSD even with pneumonia is a self-limited illness. Thus, antibiotics might shorten the clinical course but are unlikely to improve the long-term outcome, which is generally excellent. The choice of antimicrobial agents is another area of uncertainty.[300] Azithromycin, erythromycin, and TMP/SMX have been advocated for severe CSD, as has ciprofloxacin alone or in combination with gentamicin, but no data from controlled trials exist. Adults with severe *Bartonella* infection have responded to azithromycin, erythromycin, doxycycline alone or in combination with rifampin, or rifampin and gentamicin. Patients with bacillary angiomatosis or parenchymal peliosis, which are unusual and severe manifestations of *Bartonella* infection in patients with HIV infection, have responded to erythromycin, doxycycline, and clarithromycin. The development of feline vaccines against *B. henselae* might be useful in decreasing the incidence of transmission and infection in human hosts.[302]

BRUCELLA *SPECIES*

Brucellosis is a rare human disease that may be caused by one of several small, gram-negative rods in the genus *Brucella*, including *B. melitensis*, *B. abortus*, and *B. suis*.[303] Human infection is caused by direct contact, usually via ingestion of unpasteurized dairy products, accidental laboratory exposure, or contact with diseased swine, cattle, or wild animals (e.g., moose).[282,303] Specific to each organism, *B. melitensis* may be transmitted from goats, their carcasses, or their secretions. *B. abortus* may be transmitted by direct contact with cows, their carcasses, or their secretions, including milk. Pasteurization of milk and milk products is especially important in the prevention of disease in children. Humans are also accidental hosts for *B. suis* and contract disease by direct contact with pigs, their carcasses, or their secretions. Rarely has human transmission been thought to occur in family clusters.[303] Infection may also be transmitted by the inhalation of contaminated aerosols. The incubation period varies from less than 1 week to several months; most children are ill within 3 to 4 weeks of exposure.

Brucellosis pneumonia is rare. Histologically, there are fibrinous pleuritis and proliferation of pleural endothelial cells found with a round cell interstitial infiltration. Nodules that resemble a tuberculous granuloma may be found.

Particularly with *B. melitensis*, which is the endemic species, disease can be severe with either an acute or an insidious onset. Although fever is usually present, there are no unique clinical findings, which makes the diagnosis difficult. It has been termed *a disease of mistakes*.[303] Nonspecific complaints, including sweats, weakness, malaise, anorexia, weight loss, arthralgias, myalgias, and backache, abound. Findings on physical examination may include lymphadenopathy and rarely hepatosplenomegaly. Cough is variably present. Chest radiographic findings may include bronchopneumonia, single or multiple nodules, and hilar adenopathy.[282]

Diagnosis is based on the isolation of excised, caseous nodules from the lung. Isolation of the causative organism from the blood is possible, but the yield is low.[304] The laboratory should be alerted that this diagnosis is being considered because the incubation time may be long and the organism may be misidentified by automated identification systems. Serologic testing has been the hallmark of diagnosis. A presumptive diagnosis may be made by showing a high (≥1:160) or rising serum titer of specific antibodies in a child with symptoms consistent with brucellosis. The serum agglutination test is most commonly used and detects antibody to *B. abortus*, *B. melitensis*, and *B. suis* but not *B. canis*. False-negative results may be related to the prozone effect. Newer serologic tests, including an ELISA for antibodies, are under evaluation but are not yet widely available.[304] Recently, the diagnosis of brucellosis has been accomplished by PCR using primers directed at a 31-kD protein from *B. abortus*.[305]

The standard antigen cross-reacts with all *Brucella* species except *B. canis* but may also react with *Yersinia enterocolitica, Vibrio cholerae,* and *F. tularensis*.[303] When brucellosis is being considered, the laboratory should be notified so that multiple serial dilutions of serum can be performed to exclude the prozone effect.[306] Treatment is with tetracycline, 30 to 40 mg/kg/day in four doses daily (if more than 9 years of age), or oral doxycycline, 2 to 4 mg/kg/day in one or two divided doses, both for 4 to 6 weeks. If the clinical symptoms are severe, streptomycin or gentamicin, in addition to doxycycline or tetracycline, may be administered for the first 7 to 14 days of therapy.[303] In small children, TMP/SMX is usually used.[306] The conditions of most children receiving the appropriate antibiotics respond to treatment.[306] Complications include lung abscess, pleural effusion, empyema, and atelectasis secondary to large hilar nodes pressing on a bronchus.[282]

BURKHOLDERIA (PSEUDOMONAS) CEPACIA

Burkholderia cepacia is an increasingly recognized cause of nosocomial pneumonia, particularly in children with immunodeficiency. The organism was first described in 1950 as causing a "soft rot" in onions.[307] It is closely related to *Pseudomonas mallei, P. pseudomallei, P. pickettii,* and other *Pseudomonas* species that are plant pathogens. It is only distantly related to *P. aeruginosa*.[307]

The organism is ubiquitous and versatile; it seems to thrive under adverse conditions and can even use penicillin for its food supply.[307] The organism is durable and resistant to many disinfectants, antiseptics, and preservatives. Children are thought to acquire the organism in the hospital or via contact with colonized siblings.[307] Strain-specific properties are now being identified that may, in part, determine which strains are efficient colonizers of susceptible patients, such as those with cystic fibrosis (CF).[308]

The organism is virtually nonpathogenic in the healthy child or adult. In less than 2% of healthy adults the pharynx is colonized.[309] In patients with altered host defenses,[310,311] such as children with CF, burns, and indwelling catheters or other medical devices, serious infection, including pneumonia, endocarditis, meningitis, bacteremia, peritonitis, postoperative and burn wound infections, skeletal infections, and lung abscess, may occur. *B. cepacia* infection may be the first manifestation of chronic granulomatous disease. Children with CF whose respiratory secretions are colonized with *B. cepacia* tend to have more serious lung disease and poorer pulmonary function than those who are not colonized with this organism.

Virulence factors[312] include an extracellular protease,[313] lipase, and siderophore. The genetic regulation of these exoproducts has been the subject of recent attention[314]; extracellular material from broth cultures of *P. aeruginosa* increase the production of protease, lipase, and siderophore in *B. cepacia.* Such interspecies signaling might allow insight into certain bacterial interactions in the lungs of patients with CF.

Histopathologic examination of lungs infected with *B. cepacia* revealed several disease patterns that included severe necrotizing pneumonia[307] and atypical granulomatous lesions in a patient with chronic granulomatous disease. In patients with *B. cepacia* colonization and CF, lobar and peribronchial pneumonia with neutrophilic infiltrates and microabscess formation occurs most commonly without necrotizing pneumonia or vasculitis.[315] A more chronic inflammatory infiltrate with interstitial pneumonitis in the presence of macrophages, lymphocytes, and plasma cells has also been described.

In adults with CF who are colonized with *B. cepacia,* the following clinical patterns have been observed: (1) chronic asymptomatic carriage, (2) progressive deterioration over many months with recurring fever and weight loss, and (3) rapid, usually fatal, deterioration.[316] In other patients, the clinical picture may resemble that of other bacterial pneumonias.

Diagnosis is by isolation of the organism from blood or sputum. Isolation from the latter may pose a problem for the clinical laboratory because other bacteria are likely to be present in the secretions of patients with CF; selective media, such as PC agar or an oxidation-fermentation base, contain antibiotics and other ingredients aimed at suppressing other flora, thereby aiding in the diagnosis.

B. cepacia is resistant to multiple antimicrobials; thus, treatment poses a challenge. Previously, the most effective antibiotics were chloramphenicol and TMP/SMX. The child with CF, however, is often resistant to these agents. Meropenem is the most active agent against the majority of *B. cepacia* complex isolates.[317] In vitro susceptibilities may guide the choice of compounds, although ceftazidime has been associated with clinical failure despite in vitro susceptibility.[307] High-dose[318] therapy with the chosen antibiotic may be necessary because the pharmacokinetics of many antibiotics are altered in patients with CF.

There are no definitive measures to prevent *B. cepacia* infections. Cohorting of colonized individuals, education regarding optimal infection-control practices, and careful handwashing all decreased colonization of *B. cepacia* in one large CF center; these measures have been widely adopted.[319]

BURKHOLDERIA PSEUDOMALLEI

Burkholderia pseudomallei[320] is a rare but serious cause of pneumonia. The first cases of human infection were identified in 1910 by Whitmore and Krishnaswami[321] in Rangoon. The etiologic agent is *B. pseudomallei,* a short, gram-negative,[322] aerobic,[323] bipolar-staining bacillus.[322] The organism can grow on MacConkey agar, Sabouraud dextrose medium, or eosin-methylene blue; rough, characteristically wrinkled colonies are usually visible after a 72-hour incubation.[324,325] The organism is a free-living bacterium that is found in surface water and in soil; transmission to humans is thought to be via contaminated food,[322] inhalation, or contamination of wounds.[325]

Acquisition of the causative organism in cases of pneumonia probably results from inhalation of contaminated dust[326] or infected laboratory materials.[327] Although animals (especially sheep and swine) may acquire the causative agent of melioidosis, direct transmission from animal to humans has never been reported.[326]

The endemic region lies in a narrow belt in the tropics within 20 degrees north and south latitude.[323] Subclinical infection is common; 29% of healthy Thai adults had detectable hemagglutinating antibody to *B. pseudomallei*[328]; in Thai

children, a trend toward an increasing prevalence of hemagglutinating antibody with increasing age was apparent.

Histologically, the lesions found in pulmonary melioidosis, as well as in infection elsewhere, begin as a collection of neutrophils surrounded by a zone of congestion, and they progress to disseminated, sharply defined, small, pus-filled abscesses with granulomatous margins and are associated with local necrosis. The necrotic regions coalesce with adjacent areas to form a honeycombed lesion.[320] In chronic infections, epithelioid histiocytes, lymphocytes, and multinucleated giant cells surround the abscess, and the lesion becomes granulomatous. Granulomas may become scarred with deposition of dense fibrin; central necrosis of these granulomas may resemble the caseating granulomas found in tuberculosis.[323]

The two clinical patterns are chronic and acute.[329,330] In both, the lung is the most commonly affected organ.[331] The indolent nature of the pulmonary involvement may simulate a mycotic infection or tuberculosis.[325]

Signs and symptoms of chronic pulmonary melioidosis may be minimal or absent[325] and may render the infection subclinical. Alternatively, fever, malaise, dry cough,[322] weight loss, chest pain, or hemoptysis may be present.[323] The white blood cell count is variable,[320,322,323,325] and neutrophilia is uncommon.[323] Nodular infiltrates, often with cavitation, are common findings on the chest radiograph.[325] Some 95% of adults with chronic pulmonary melioidosis have upper lobe involvement, either with infiltrates alone or with cavities, usually single, that vary in size.[323] Chronic pulmonary melioidosis may spontaneously resolve without treatment or advance to fulminant sepsis.[331]

The second pattern of melioidosis is more severe. The clinical picture is of generalized sepsis; skin sores resembling boils are widespread, and abscesses are commonly found in the lung, liver, spleen, and bone marrow at autopsy.[322,325] Most cases are accompanied by malnutrition and debilitation. The clinical course may deteriorate quickly[331]; the mortality rate is 60% to 95%.[331]

The most important factor in establishing the diagnosis is a high index of suspicion. For example, melioidosis should be considered[326] in a child who has a travel history or prior or current residence in Southeast Asia and who has a fever and a localized suppurative process. The diagnosis may be confirmed by isolating *B. pseudomallei* from blood or lung tissue obtained by lung aspiration.[325,326] The laboratory should be notified that *B. pseudomallei* is a consideration because the organism may be misidentified as *P. aeruginosa*, *Klebsiella*, or *Enterobacter* species, or another gram-negative bacterium.[331] Several serologic tests, including hemagglutination and complement fixation test, are useful diagnostic tools.[331] The demonstration of a fourfold or higher rise in paired sera is most helpful. Interpretation of a single titer is more difficult. A hemagglutination titer higher than 1:40 or a complement fixation titer higher than 1:8 had 97% sensitivity in culture-proven cases.[332]

The rapid institution of aggressive antibiotic therapy is important—even when clinical evidence of pulmonary disease is absent—because dissemination and overwhelming sepsis may occur quickly.[325] Combination therapy is preferred, with the theoretical goal of minimizing the development of antimicrobial resistance. Antibiotic courses of short duration and the severity of illness at presentation have both been associated with a high rate of relapse after the cessation of therapy.[333] The antibiotic regimen of choice for patients who appear ill (septic form) is ceftazidime, imipenem or meropenem, and TMP/SMX.[334] A 2- to 4-week course of parenteral antibiotics, followed by a prolonged course (e.g., 6 months) of oral antimicrobial therapy, is recommended.[326,335] For patients who do not appear ill, amoxicillin/clavulanate[336] or tetracycline and chloramphenicol[325] have been used, the last two often given in combination with TMP/SMX.[326] A 30-day course is typical.

Until recently, the mortality rate from melioidosis was as high as 95%,[322,326] especially in patients with the septic form of disease, despite prompt antibiotic therapy. The use of ceftazidime has greatly decreased the mortality rate in adults,[335] although specific data in children are lacking.

CITROBACTER *SPECIES*

Citrobacter species are most often associated with neonatal sepsis and meningitis; species members are rare causes of sporadic pneumonia, which occurs almost exclusively in neonates and immunocompromised individuals. *Citrobacter* organisms were first isolated in 1932 by Werkman and Gillen,[337] who proposed the generic term *Citrobacter* and described seven species. A bewildering array of taxonomic changes[338] ended in 1977, when Brenner and associates[339] designated the following species: *C. freundii*, *C. amalonaticus*, and *C. diversus*. *Citrobacter* organisms are enteric gram-negative rods that are closely related to *Salmonella* organisms. In humans, *Citrobacter* species are most often reported as a cause of meningitis in the neonate.

Most cases are sporadic, although outbreaks have been described. Once introduced into the nursery, *Citrobacter* species colonization may become prevalent. One study in a neonatal nursery identified 11 of 128 infants colonized with *C. diversus*.[340] The umbilicus was the most frequent site of colonization.

The diagnosis is made by identifying the causative bacterium in blood, CSF, or in an older child, in sputum. Treatment is with an aminoglycoside or an extended-spectrum cephalosporin. Almost all isolates are ampicillin resistant.

The fatality rate for *Citrobacter* infections in newborns and older immunocompromised patients with *Citrobacter* pneumonia has been said to be high.[338,341] Recent data defining these rates more precisely are not available.

The complications of *Citrobacter* pneumonia include associated bacteremia with metastatic foci, particularly meningitis. *C. diversus* pneumonia may also be associated with abscess formation in the lung[346] and with empyema.

CORYNEBACTERIUM *SPECIES*

Members of *Corynebacterium* species are gram-positive bacilli that have rarely been implicated as a cause of pneumonia in either immunologically normal or abnormal hosts. Examples are *C. xerosis*,[343] *C. pseudodiphtheriticum*,[344] and *C. jeikeium*.[345] Most patients have an underlying disorder. Fever is often absent. In vitro, *C. pseudodiphtheriticum* isolates were susceptible to ampicillin and other β-lactams but were often resistant to clindamycin and erythromycin. A report from Spain describing a patient with empyema fluid from which *Corynebacterium* species was isolated suggests

that empyema may complicate *Corynebacterium* species pneumonia.[346] This patient was managed with imipenem and clindamycin.

COXIELLA BURNETII

In 1935, the disease caused by the organism *Coxiella burnetii* was given the name Q *fever* by Dr. E. H. Derrick of the Queensland Health Department in Australia because he was unable to diagnose the disease and, therefore, referred to it as Q for "query" fever. The organism was later named *C. burnetii* for Drs. Cox and Burnet, who were instrumental in isolating the organism.[347] The first cases of *C. burnetii* pneumonia were identified in 15 of 153 employees who had contracted the illness in one building of the National Institutes of Health in 1940.[348]

C. burnetii is a gram-negative, pleomorphic, intracellular coccobacillus. The organism is able to form spores, which allows it to survive for more than 40 months in skim milk at room temperature and more than 1 month on or in meat in cold storage.[347] *C. burnetii* infects many different animal species. Sheep, cattle, and goats are the traditional animal reservoirs, although horses, pigs, cats, and dogs may also be infected.[347] Once infected, animals may shed the organism for several months. For example, cows may shed *C. burnetii* in milk for up to 32 months; after birth, sheep may shed it in feces for 11 to 18 days.[349]

Humans are the only animal in which *C. burnetii* infection usually proceeds to illness. The usual route of infection is by dose-dependent aerosol aspiration.[350] Human-to-human transmission is rare.[347]

Initial infections are often asymptomatic and disease attributable to Q fever occurs in acute and chronic forms. Pneumonia develops in 20% to 40% of patients but varies by geographic region, possibly reflecting strain-specific properties.[347]

The clinical features of Q fever have included fever, fatigue, chills, myalgias, nausea, vomiting, pleuritic chest pain, and cough. Headache may be severe and retro-orbital. Signs of Q fever pneumonia vary; clinical evidence of respiratory tract involvement may be absent, despite radiographic evidence of pneumonia. Alternatively, a dry, nonproductive cough may be present. Occasionally, the course is rapidly progressive. Physical examination of the chest of the patient with Q fever pneumonia may be normal; alternatively, inspiratory crackles may be present. Some 5% of patients with Q fever pneumonia have splenomegaly.[347]

The radiographic picture of patients with Q fever pneumonia is variable and includes nonsegmental and segmental pleural-based opacities. A pleural effusion is present in about one third of patients. Atelectasis and hilar adenopathy are infrequent findings.

Most laboratories do not have the facilities necessary for the isolation of Q fever. Serologic diagnosis may be made by the detection of antibodies with a variety of techniques, including complement fixation microagglutination, microimmunofluorescence, and ELISA. A fourfold rise in serum antibody titer between the acute and convalescent phases is considered diagnostic.[347]

Acute Q fever is generally a self-limited illness but treatment may shorten the duration of symptoms. The best therapy for Q fever pneumonia is doxycycline.[347] Fluoroquinolones or chloramphenicol are alternatives. Most cases of pneumonia resolve, although death has been reported in one adult.[347]

An inactivated whole-cell Q fever vaccine has been developed but is not yet available.[351] It would presumably be used for high-risk populations, such as animal handlers and those working in abattoirs.

ESCHERICHIA COLI

Escherichia coli is an extremely rare cause of childhood pneumonia except in neonates or in those with an underlying disease. *E. coli*, the "colon bacillus," was first isolated in 1885 by T. Escherich from the feces of breastfed infants.[352] It is a gram-negative, nonencapsulated bacillus that may be either motile or nonmotile. Typing of strains is based on the following antigens: flagellar (H), somatic (O), and capsular (K or B). The ability of *E. coli* to bind to host tissue via specific fimbriae is an important first step in infection. Hemolysin is another virulence-associated characteristic of severe *E. coli* infections in children.[353]

E. coli is an important cause of neonatal pneumonia when the causative organism is acquired either shortly before or during delivery.[354] The source of the organism is usually the maternal gastrointestinal tract or aspirated amniotic fluid. The incubation period is variable and ranges from birth to several weeks of age. A study of 34 infants with late neonatal pneumonia (onset of symptoms more than 48 hours after birth) suggested that *E. coli* was the probable etiology in 6%; coliforms accounted for 44% of the episodes.[355] *E. coli* strains with K1 capsular polysaccharide antigen are the most common causes of neonatal *E. coli* meningitis and bacteremia and of the less frequent invasive infections that occur in infants. In children older than 2 years of age, the importance of K1 is diminished[356] because invasive *E. coli* infections usually occur only in association with underlying disease.

Nosocomial acquisition of *E. coli* from nursery personnel and equipment has also been documented. Others at increased risk for *E. coli* infections may include neonates with immunologic defects, breakdowns in skin integrity, or asplenia.

E. coli may occur more frequently in malnourished older children in developing countries. In contrast to its rare occurrence in children beyond the neonatal age group in developed countries, a study in Nigeria identified *E. coli* pneumonia by lung aspiration in 8.8% of 99 malnourished children (age, 9 months to 5 years); this organism was the third leading cause of pneumonia in these children.[357] Similarly, 5.3% of malnourished children in Zaire had *E. coli* pneumonia.[358]

E. coli pneumonia may be acquired via inhalation or may result from bacteremic seeding of the lung. The organism is not a usual constituent of normal pharyngeal flora but may be found in the pharynx of ill children or adults, particularly among hospitalized patients. Spread in the hospital is facilitated by hand-to-mouth contact, often with fecal contamination, and by fomites such as contaminated respiratory equipment.

A study of autopsy findings in neonates with *E. coli* pneumonia identified diffuse inflammation as the most common pathologic finding.[359] In contrast, diffuse bilateral lower lobe bronchopneumonia was found with occasional abscess formation in adults at autopsy. The alveoli were typically filled with fluid in the presence of mononuclear cells. The alveolar cells

exhibited cuboidal metaplastic changes with thickened, edematous septa.

The clinical findings of *E. coli* pneumonia are nonspecific[359] and are similar to those of bacterial pneumonia of any etiology in the respective age group. The diagnosis is usually based on recovery of the causative organism from the blood.

A pneumatocele has been reported in a neonate with *E. coli* pneumonia[360]; lung abscesses are rare. In general, if the correct diagnosis is made and appropriate treatment is instituted, recovery usually occurs.

Childhood *E. coli* pneumonia is usually treated with an aminoglycoside, an extended-spectrum cephalosporin, or the two in combination. Although combination therapy is preferred, few explicit data document its superiority. Ampicillin may be substituted for the cephalosporin when the isolate is susceptible. Amikacin may be substituted for gentamicin if the isolate is resistant. At the University of Chicago Hospitals in 1996, 98% and 99% of *E. coli* isolates were susceptible to gentamicin and extended-spectrum cephalosporins, respectively.

FRANCISELLA TULARENSIS

The bacterium *Franciscella tularensis* was first identified in 1910 by McCoy and Chapin in Tulare County, California, as the microorganism responsible for the plague-like disease in ground squirrels in that area.[361] The organism in culture is a fastidious, gram-negative coccobacillus.[362] In nature, however, it is a hardy organism that may survive for several weeks in water and mud, particularly around aquatic mammal dwellings.[363] Although it does not form spores, it resists drying and cold and, thus, may be transmitted as a fomite.[363]

Tularemia is endemic throughout the United States, with the highest number of cases occurring in Arkansas, Missouri, Montana, Oklahoma, Tennessee, Texas, Utah, and Wyoming.[363] Each year, 150 to 300 cases are reported.[364] Tularemia is also endemic throughout Europe and Asia.[282] Male patients in rural areas are most commonly infected,[363] although infections are also well documented in urban environments.[365] Some 6% to 30% of cases of tularemia occur in children,[366] mostly in the second decade of life.

Tularemia is primarily a disease of wild animals; human infection is incidental[367] and can be initiated in several ways, including direct contact with or ingestion of infected animals or animal tissues; bites from ticks, flies, or other arthropods; inhalation of dust from contaminated environments[366]; and consumption of contaminated water. There have been no reports of person-to-person spread.

The causative bacterium has been reported in more than 100 species of wild or domestic mammals, birds, fish, and amphibians. It has been estimated that 15% to 30% of wild rabbits in the United States serve as a natural reservoir for tularemia.[366] Tularemia occurring after bites by ticks represents the third most common tick-borne disease in the United States.[368] Tick bites account for about 50% of all cases of tularemia.[364,369]

Tularemia has traditionally been classified by its *form*, a term referring to a constellation of the clinical features that are initially recognized. The ulceroglandular form accounts for about 80% of reported cases. This disease is characterized by an erythematous, punched-out, indurated skin ulcer and tender, localized lymphadenopathy. Glandular, oculoglandular, oropharyngeal, typhoidal, intestinal, and pneumonic forms also occur. The pneumonic form is said to occur after direct inhalation of infected particles from an animal carcass,[366] a laboratory specimen, or contaminated dust.[363]

Primary tularemia pneumonia can begin after the inhalation of infected particles. Pneumonia may also occur as a consequence of hematogenous spread.[282] After inoculation, lymphatic spread ensues with the development of acute local inflammation, nodal swelling, necrosis, and caseation. The organisms may enter the bloodstream from the lymphatic system and become disseminated. Spontaneous resolution is unlikely once this occurs because *F. tularensis* is able to survive intracellularly, even when entrapped by the reticuloendothelial system.[370] Symptomatic bacteremic seeding of the lungs is manifested as a multifocal lobular or even lobar pneumonia with interstitial involvement. The process may be unilateral or bilateral with segmental, lobar, or patchy infiltrates. Less common manifestations include the formation of multiple small abscesses, cavitation, residual cysts, and a miliary pattern.[282] Microscopically, in patients who die of tularemia with pulmonary involvement, mononuclear cells are found in fibrin-rich alveolar exudate. Thrombosis and necrosis of small- and medium-sized arteries and veins are common. A child with tularemic pneumonia and unrecognized chronic granulomatous disease was found to have discrete, round, nodular, well-localized areas of granulomatous inflammation in a subpleural and parenchymal distribution.[371]

Patients who survive infection are immune. Antibodies do not appear until 1 to 2 weeks after the onset of symptoms.[372] Passively transferred antibody can confer protection on recipient mice,[373] and specific antibody enhances the rate of clearance of *F. tularensis* from blood.[374]

Tularemic pneumonia may pose a considerable diagnostic dilemma, especially when the portal of infection is not obvious. A thorough clinical history, particularly with inquiries about contact with rabbits or other wild animals, provides an aid to diagnosis.[375]

Prodromal symptoms may include malaise, cough, and chest tightness lasting 10 days to 3 weeks. The onset is usually less abrupt than that of pneumococcal pneumonia and may be difficult to pinpoint with certainty. Chills and fever are usual. In Arkansas, 87% of children with pulmonary tularemia had fever.[376] A relative bradycardia may be present; peripheral vascular collapse is rare.

Few laboratory tests contribute valuable diagnostic information. In particular, the leukocyte and platelet count, erythrocyte sedimentation rate, and urinalysis were not found to be helpful.[376]

There is a dissociation between clinical manifestations attributable to pneumonia, which may be minimal or absent, and the chest radiograph, which may be markedly abnormal.[377] This effect may be dramatic when systemic manifestations of tularemia, such as headache, myalgia, and high fever, are apparent.

Hilar adenopathy occurs in about one third to one half of cases and pleural effusion in 25% to 30%[378] Radiographs become positive as early as the second day after the onset of symptoms. Most patients have a distinctive pattern of a single (occasionally multiple) oval consolidation that is frequently

juxtahilar. Early radiographic changes include peribronchial infiltration with a bronchopneumonia pattern; hilar adenopathy is evident in 32% to 64% of cases[378] and may represent an important clue to the diagnosis. Cavitary pneumonia is unusual.[379] Fibrosis and calcification changes may occur late.[282]

Care should be taken when cultivation of *F. tularensis* is attempted because inhalation or inoculation with as few as 10 to 50 organisms can produce pneumonia. Many hospital laboratories refer specimens to a reference laboratory or to the CDC for processing.[380] The organism is fastidious but can be recovered on commercially available chocolate agar and from most automated blood culture systems. The laboratory should be notified that *F. tularensis* is suspected because prolonged incubation may be required. Presumptive isolates are identified by agglutination with commercially available antiserum.[362]

Serologic diagnosis remains the diagnostic gold standard. The commercially available tube agglutination test is most frequently used. Growth on culture may be identified by direct fluorescent antibody, PCR, or rapid slide agglutination tests. Prompt initiation of antibiotics in patients with tularemic pneumonia (often before agglutinating antibody titer is detectable) may be lifesaving, particularly when the clinical course is severe. Streptomycin, gentamicin, or amikacin are recommended for the treatment of tularemia.

Lung abscess formation is rare[381] but may be multiple. Pleural effusion, characteristically exudative, is present in tularemic pneumonia[382] in up to 50% of cases.[383] Pericarditis is a rare complication of tularemia. Meningitis has rarely been identified in patients with tularemic pneumonia.[372] Nonspecific features of severe tularemic pneumonia have included ARDS requiring positive end-expiratory pressure,[384] acute renal insufficiency, neuropathy,[384,385] and encephalopathy.

Handling of wild animal carcasses while wearing rubber gloves, masks, and protective glasses and taking appropriate precautions to prevent tick bites may decrease exposure to the causative organism. Postexposure chemoprophylaxis has not been recommended.[364] Tularemia is reportable to state or local boards of health.[363] For laboratory workers anticipating exposure, a vaccine is available from U.S. Army Medical Research and Development Command at Fort Detrick, Maryland.

KINGELLA *SPECIES*

Although rarely reported outside of Israel, *Kingella kingae* infections have been identified as a cause of childhood pneumonia, especially in the very young. The organism, a member of the so-called HACEK group, is a gram-negative coccus with morphologic characteristics similar to those of *Moraxella* species. In a 5-year observational study in Israel, the incidence of invasive *K. kingae* infection was 31.9 per 100,000 children younger than 12 months of age, 27.4 per 100,000 children younger than 2 years of age, and 14.3 per 100,000 children younger than 4 years of age.[386] Of those with invasive disease, 2 of 25 had a lower respiratory infection, and one had a pulmonary infiltrate; both children with respiratory infections recovered fully after antibiotic treatment with ampicillin or cefuroxime.[386]

Empyema with *Kingella* species has also been described. One article described an adult with empyema from which *K. kingae* and *Coccidioides immitis* were isolated from the pleural fluid; the latter organism had previously been isolated from fluid obtained by bronchoscopy performed for the evaluation of a pulmonary nodule.[387] *Kingella denitrificans* was isolated with *Peptostreptococcus* species from the pleural fluid of another adult with bronchogenic carcinoma and empyema.[388]

KLEBSIELLA PNEUMONIAE

Despite its name, *Klebsiella pneumoniae* is a rare cause of pneumonia in children. The organism was first identified in 1882 by Carl Friedländer, who recognized it as a cause of lobar pneumonia but incorrectly believed that it was a major cause.[389-391] Most cases occur in the neonate or immunocompromised host. In the latter group, it is often nosocomially acquired.

The genus *Klebsiella* is one of four genera in the tribe Klebsielleae of the family Enterobacteriaceae. There are four species, but *K. pneumoniae*, a gram-negative, encapsulated bacillus, is the most important.[392-394] Many different capsular serotypes can cause human disease, and a capsular polysaccharide-based vaccine will need to be multivalent.[395]

Infection with *Klebsiella* can be sporadic and occasionally epidemic in several clinical situations. Community-acquired *Klebsiella* pneumonia in children is infrequent. Among 102 children hospitalized for community-acquired pneumonia, *K. pneumoniae* was isolated from a tracheal aspirate of a single child who also had evidence of infection with respiratory syncytial virus.[30] Among adults, the incidence of community-acquired *K. pneumoniae* pneumonia is also low, with less than three bacteremic cases per year at large municipal hospitals.[396] *K. pneumoniae* bacteremia is more common than pneumonia. Most children with *K. pneumoniae* bacteremia acquire infection nosocomially and are young; only a small number have pneumonia.

Data to define the incidence of *K. pneumoniae* pneumonia in the neonate are not available; inference is made from data regarding the occurrence of *K. pneumoniae* bacteremia. At Yale from 1966 to 1978, *K. pneumoniae* was responsible for 14% of cases of neonatal bacteremia, the third leading cause after *E. coli* and group B streptococci.[397] Risk factors for *K. pneumoniae* neonatal bacteremia included a prior operative procedure, tracheostomy, infected venous cutdown site, and multiple exchange transfusions.[398,399]

In the hospital, *K. pneumoniae* invasive infection, including pneumonia, has been related to prior colonization,[400] which in turn is related to prior antimicrobial therapy. The rates are high in hospitalized patients, particularly those in postoperative situations or intensive care units. Spread of the organism is facilitated by hand-to-patient contact, and hospital staff can be facilitators.[401,402] Patients receiving immunosuppressive therapy also constitute a group at increased risk,[400] especially in the nosocomial setting.

K. pneumoniae probably reaches the lung most commonly by inhalation. Bacteremic seeding of the pulmonary parenchyma may also occur but has been difficult to document with certainty. Among adults, alcoholics are said to be at high risk; presumably the organism is aspirated during binge drinking.

K. pneumoniae pneumonia may occur anywhere in the pulmonary parenchyma; multiple lobe involvement is

common. In adults in whom alcoholism is the predisposing condition and infection is acquired by aspiration, the most common involvement occurs in the upper lobes, particularly on the right side.[403] The capsular polysaccharide of *K. pneumoniae* plays an important role in pathogenesis[404] by interfering with opsonization or by preventing complement activation.

Most information regarding the pathology of *K. pneumoniae* pneumonia comes from postmortem data that often predate the antibiotic era and represent observations from patients with severe disease. No single feature histologically distinguishes *K. pneumoniae* pneumonia. As with pneumococcal pneumonia, the stages of red hepatization, gray hepatization, and resolution may occur. Thrombosis and circulatory impairment follow and terminate in necrosis with sloughing, hemorrhage, and the potential for cavity and abscess formation.[405] Abscesses may be multiple and small, solitary and large, or intermediate between these designations.

The clinical features of *Klebsiella* pneumonia depend on the setting. In the neonate and older child, the clinical features resemble those of bacterial pneumonia of any etiology in the respective age group. Chest pain or discomfort with or without dyspnea may be evident, although the clinical picture in an immunocompromised child may not suggest clear-cut localization to the respiratory tract. *K. pneumoniae* pneumonia may occur with pneumococcal pneumonia, a possibility that should be considered, particularly in an immunocompromised child with an abscess who does not respond to therapy directed against *S. pneumoniae*.[406]

The diagnosis depends on identifying the causative organism in a clinically relevant setting. Sputum, when available (e.g., from older children), may be blood tinged, or "rusty," although this sign was only present in about one third of adults with *Klebsiella* pneumonia. Because asymptomatic colonization may occur, sputum analysis may be misleading,[407] although suspicion should be raised in the presence of monotonous gram-negative rods, a pure or nearly pure culture, or both results.[396]

Isolation of *K. pneumoniae* from the blood during an episode of acute pneumonia is usually accorded diagnostic importance, as is isolation of the organism from pleural fluid.[396] Radiographic findings in adult *K. pneumoniae* pneumonia include a bulging fissure of the involved lobe margin, a sharp infiltrative margin of the pulmonary infiltrate (both occur in about 64% of patients),[408] and a predilection for upper lobes and abscess with cavitation. More importantly, any or all of these "classic" features may be absent, and the radiographic appearance may not be distinct from that of other airspace pneumonias.[409] Lesions consistent with the radiologic appearance of a pneumatocele in patients with *Klebsiella* pneumonia have also been described.

The treatment of *K. pneumoniae* pneumonia in children usually involves an aminoglycoside, an extended-spectrum cephalosporin, or the two in combination. Combination therapy is preferred, although few explicit data document its superiority. Resistance may be a particular problem during nosocomial outbreaks.[410] Lung abscess is a frequent complication in children and adults and may occur in one third to one half of cases.[408] Surgical treatment may be necessary if medical intervention fails. Percutaneous drainage is usually sufficient.[411] Massive pulmonary gangrene, the rapid total destruction of part of the lung, is an extremely rare complication of *K. pneumoniae* pneumonia. Some have suggested that this entity may represent a synergistic infection caused by *K. pneumoniae* and an undetected anaerobe.[396] The process may resemble a lung abscess initially but reveals itself by its rapid, destructive course; fewer than 20 cases have been reported.[396] Other intrathoracic complications include empyema with residual pleural thickening[390,396] and pneumopericarditis.[412]

"Chronic" *K. pneumoniae* pneumonia, which by definition persists longer than 1 month, is an entity described only in adults, primarily in the older literature. Cavitation may be present, and the clinical picture may resemble that of tuberculosis. Some have suggested that chronic *K. pneumoniae* pneumonia, like massive pulmonary gangrene, may reflect a synergistic infection between *K. pneumoniae* and an anaerobic species.[396]

The mortality rate of *K. pneumoniae* bacteremia in the neonatal period is very high[400] despite appropriate antibiotic therapy. Few specific data exist for older children with uncomplicated *K. pneumoniae* pneumonia and intact host response capability. However, recovery is the rule, providing that appropriate antimicrobial therapy is administered and relevant foci are drained.

To date, a polyvalent polysaccharide vaccine prepared from 24 *Klebsiella* serotypes has been well tolerated and immunogenic among the more than 2000 adults to whom it has been administered. More recently, a vaccine based on O side chains has been evaluated; this approach may prove simpler to implement because a vaccine containing 3 to 7 O serotypes could prevent 60% to 90% of disease in patients.[413,414]

LEPTOSPIRA *SPECIES*

Leptospirosis is a rare cause of childhood pneumonia. The clinical illness was first described by Weil in 1886, and the organism was first seen in 1907. The rat was considered the only animal host until the 1940s, when it became evident that leptospirosis was a zoonosis of worldwide distribution that affected many species of wild and domestic mammals. Worldwide, the rat is the most common source of human infection. In the United States, dogs, livestock, cats, rodents, and wild mammals are the most common sources.

The cause is *Leptospira interrogans*, which is a spirochete. *L. interrogans* is further classified into serogroups and serovars (serotypes). About 19 serogroups and 250 serovars have been recognized. In the United States, disease is caused by more than 10 serovars, most commonly *icterohaemorrhagiae* and *canicola*. *L. interrogans* is pathogenic for both animals and humans.

Transmission of leptospires to humans follows contact with the tissues or body fluid of infected animals or exposure to an environment contaminated by leptospires. The occurrence of flooding (e.g., after a heavy rainfall) facilitates spread of the organism. In 1972, an outbreak of leptospirosis in Missouri was traced to contaminated soil in suburban lawns. Dogs have become an increasingly recognized vector and reservoir of this disease in the United States.[415] In urban environments, rats have been increasingly implicated in the maintenance of the *L. interrogans* reservoir.[416] After penetration of the skin or mucous membranes, the organisms invade the bloodstream and are spread throughout the body.

Although presumed to be present, leptospires were not demonstrable in the lungs until recently.[417]

Pulmonary lesions are usually the result of hemorrhage secondary to the vasculitis that characterizes disseminated leptospirosis rather than acute inflammation. Localized or confluent hemorrhagic pneumonitis may be evident. In addition, petechial and ecchymotic hemorrhages may be found throughout the lungs, pleura, and tracheobronchial tree.[417]

Leptospirosis is usually separated clinically into anicteric and icteric (Weil's syndrome) disease. About 90% of patients have anicteric disease. The traditional view has been that pulmonary manifestations are usually mild and of little clinical importance. A dry, hacking cough, occasionally with blood-stained sputum, may be present. A chest radiograph may show infiltrates that may be diffuse, bilateral, and patchy. Rarely, chest pain, hemoptysis, respiratory distress, and cyanosis may be present.[418] Hemoptysis, if present, usually clears by day 5. Physical examination may reveal crackles on auscultation or a friction rub. In light of reports of severe pulmonary symptoms and pulmonary hemorrhage during outbreaks of leptospirosis in Korea, China, and Nicaragua,[419] the disease spectrum of pulmonary leptospirosis may require expansion.

A blood or CSF culture obtained in the first 7 to 10 days of the illness and plated on special media, such as Fletcher, EMJH, and Tween 80-albumin media, may lead to the diagnosis. The organism may also be isolated from the urine if the specimen has been obtained after about the 10th day of illness. Investigators have suggested that it may be possible to diagnose leptospirosis by using dark-field microscopy to examine BAL specimens.[420] Previously, it was widely held that direct dark-field fluid examination was not recommended because the organisms were present in small numbers and perhaps difficult to distinguish from fibrin filaments.

Several serologic strategies for diagnosis have been used. The microscopic agglutination test is the current standard for the serologic diagnosis of leptospirosis and can be arranged at the CDC through referral by state health departments. Indirect hemagglutination, indirect immunofluorescence,[421] ELISA,[422] and dot-ELISA tests have been used well in various circumstances. PCR is available only in research laboratories.[423,424]

Treatment is with high-dose intravenous penicillin, typically given for 7 days. Although endotoxin has not been demonstrated in the causative bacterium, Jarisch-Herxheimer reactions have been described,[425] as has ARDS. Death from leptospirosis is usually associated with severe jaundice, severe oliguric renal failure, and the recently recognized associated pulmonary hemorrhage. Amoxicillin and doxycycline are alternative treatments.

Leptospirosis is a disease that must be reported to state and local health authorities. While the child is in the hospital, strict universal precautions should be followed. Public health measures include controlling rodents, preventing contact with animal urine, wearing protective clothing when exposure is likely, and avoiding contact with potentially contaminated water. Adult prophylaxis is effective with 200 mg of oral doxycycline once a week in those with occupational exposure. There are no current recommendations for prophylaxis in children.

LISTERIA *SPECIES*

Listeria monocytogenes is a gram-positive, facultatively anaerobic rod. It was first recognized as a human pathogen in 1929 and was named after Lord Lister, the British surgeon who developed the technique of antiseptic surgery.[426] The first documentation of infection in infants was published by Burn in the 1930s.[427]

L. monocytogenes accounts for almost all listerial infections in humans, although infections with *L. ivanovii*, *L. seeligeri*, and *L. welshimeri* have rarely been reported. It is an uncommon cause of neonatal pneumonia.[428] Human groups at risk for infection include pregnant women, immunocompromised patients, and neonates.

Human infection is acquired by contact with domestic or wild birds and animals, meat, milk, vegetables, or contaminated soil.[282] The organism has also been found in the gastrointestinal tract in 1% to 5% of asymptomatic individuals. Neonates may acquire infection transplacentally during passage through an infected birth canal or from maternal bacteremic seeding.[429] Some reports have suggested cross-infection in neonatal nurseries. The organism is distributed worldwide,[282] and although there was a suggestion of geographic differences associated with perinatal listeriosis, surveillance conducted by the CDC did not document a geographic or seasonal pattern.[429]

The pathogenesis of listeriosis involves a complex interaction among the organism, the host immunologic response, and the amount of organism present. Both humoral and cell-mediated immunity are important. Efficient opsonization of *Listeria* species is mediated by IgM and complement, which are at physiologically low concentrations in the neonate; it has been suggested that these physiologic nadirs are what place neonates at particular risk.[430] Remarkably, *Listeria* organisms can mobilize actin filaments and usurp the contractile system of the host cell, which allows cell-to-cell spread. This property accounts for its virulence in individuals with defective cell-mediated immunity; it also accounts for the ability of the organism to invade the gastrointestinal tract without erosive lesions and to invade the placenta and fetus during maternal bacteremia.[431]

Early onset neonatal listeria infections are usually manifested as pneumonia or sepsis.[432] Tachypnea, respiratory distress, or apnea may be present. Others have identified heart failure, cyanosis, seizures, and emesis. Some note the presence of roseoles, or tiny focal cutaneous granulomas. These "listeriomas" are usually present in the posterior pharyngeal wall if dissemination has taken place. In the older literature, a septic-like clinical picture with diffuse granulomas was termed *granulomatosis infantiseptica*. Transmission of the organism is thought to be from mother to infant, with high concordance of recovery of an organism of identical serotype from mothers of infected infants. For late-onset disease, meningitis is more frequent, and there is less likelihood of recovering the infecting organism from the mother.[432]

Careful bacteriologic evaluation of a patient with possible listeriosis is essential because the organism may be mistakenly identified as a *Corynebacterium* species contaminant on Gram stain. Certainty regarding the diagnosis involves isolation of the organism from a normally sterile site (e.g., blood). The organism will usually grow in culture within 36 hours. Serologic testing is not helpful. PCR coupled with fluorescent

antibody reagents and DNA probes may be helpful in the diagnosis, especially when the organism is in a nonsterile environment where isolation from culture may be difficult. Radiographically, *L. monocytogenes* pneumonia may produce diffuse, bilateral infiltrates that may be miliary, patchy, or interstitial.[282]

The most commonly recommended medication for the therapy of listeriosis is ampicillin, either alone or with the addition of an aminoglycoside, such as gentamicin, for synergy. Treatment failures are common with cephalosporins, so their use should be avoided. The optimum length of treatment has not been fully established, but most clinicians treat neonates for 2 to 3 weeks.

The risk of food-borne listeriosis may be decreased if pregnant women and immunosuppressed or immunodeficient patients avoid raw vegetables, unpasteurized dairy products (especially soft cheeses), undercooked meats, or ready-to-eat foods left standing at temperatures at which bacteria may survive and grow. Other measures include avoidance of bovine or ovine contamination of foods meant for human consumption and antimicrobial management of listerial infections diagnosed during pregnancy. Mortality rates depend on the clinical syndrome. Early onset neonatal infection, especially granulomatosis infantiseptica and listeriosis in immunocompromised hosts, are risk factors for high mortality.

MORAXELLA CATARRHALIS

M. catarrhalis is a gram-negative diplococcus morphologically similar to *Neisseria* species. It was first identified by Frosch and Kolle in 1896 and was given the name *Mikrokokkus catarrhalis;* it was placed in the genus *Neisseria.* In the early 1970s, however, its taxonomy was reconsidered on the basis of DNA base content, fatty acid composition, and genetic transformation, and the organism was then placed in the genus *Branhamella* (named in honor of Dr. Sarah Branham, a *Neisseria* researcher).[433] The correct taxonomic designation for this and related organisms is the subject of current debate,[434,435] but most clinicians have adopted the name *Moraxella catarrhalis*.

It was thought for many years that *M. catarrhalis* was a nonpathogenic inhabitant of the respiratory tract.[436] In Sweden, 17% to 36% of healthy preschool children were found to harbor *M. catarrhalis* in the nasopharynx.[437] It is now clear, however, that this organism is an important cause of otitis media and sinusitis. In addition, it may rarely cause pneumonia[436,437] and a variety of other infections in children.[438]

Establishing a role for *M. catarrhalis* as a pulmonary pathogen has been a complex task because of the frequency with which this organism colonizes the respiratory tract.[438] The following lines of evidence suggest a strong likelihood that *M. catarrhalis* is at least an occasional cause of bacterial pneumonia:

1. It has been occasionally isolated from the pleural fluid of patients with empyema.[438]
2. It was isolated from the lung of a few patients who died from bronchopneumonia.[438]
3. Serologic methods have identified a subset of patients with pneumonia who have increased antibody to *M. catarrhalis* on convalescence.[437]
4. A few children and adults with underlying illnesses have been described with a clinical illness consistent with pneumonia and *M. catarrhalis* bacteremia.[439]

The peak incidence of *M. catarrhalis* infection is believed to occur in the winter.[438] Transmission of the organism may be via person-to-person spread; nosocomial spread in a pediatric intensive care unit may play a role as well.[440] The role of environmental spread remains to be defined, although the organism survives in sputum for weeks.[438] The clinical features of *M. catarrhalis* pneumonia are not specific and resemble pneumonia caused by other bacteria. The diagnosis is made by isolating the organism from a normally sterile site such as blood in a relevant clinical situation. Serologic diagnosis has not been reliable.[441]

Because most strains of *M. catarrhalis* produce β-lactamase, antibiotics useful in the therapy of *M. catarrhalis* infections include amoxicillin/clavulanic acid, erythromycin and other macrolides, TMP/SMX, and extended-spectrum cephalosporins. It has been suggested that the presence of β-lactamase producing *M. catarrhalis* strains may confound the treatment of pneumonia caused by other β-lactam susceptible bacteria. For example, in a mouse model of pneumococcal pneumonia, animals inoculated with *S. pneumoniae* and β-lactamase producing *M. catarrhalis* had a poor outcome when treated with penicillin compared with mice inoculated with *S. pneumoniae* and β-lactamase–negative *M. catarrhalis;* clavulanate therapy ablated this difference.[442]

NEISSERIA MENINGITIDIS

Meningococcal pneumonia is rare, especially in children.[443] The organism *N. meningitidis* is a gram-negative diplococcus. Members of the species usually produce one of several antigenically and immunologically distinct capsular polysaccharides that are designated *A, B, C, X, Y, Z, 29E, W135, H, I, K,* and *L*.[444] The organism was first identified in 1886 by Anton Weichselbaum in the CSF of a patient who died of purulent meningitis. Meningococcal pneumonia was first recognized by Holm and Davison during the influenza epidemic in 1918 and 1919.

The initial colonization of meningococci is through adherence to the microvilli of nonciliated epithelial cells that line the respiratory mucosa. The mucosal barrier is breached by first entering the apical side of epithelial cells by a process that involves host actin. The bacteria then transcytose through the cell and exocytose at the basolateral side. Once the pathogens are in the subepithelial space, invasion of the bloodstream is likely achieved by entry through endothelial cells lining the blood vessels. M cells in the tonsillar sites of the nasopharynx might also be a portal of entry for invasion. Once bacteremia occurs, overt signs of disease are often present, and meningococci may be spread to target sites for metastatic infection.[445,446] The integrity of the mucosal barrier is the first line of defense against meningococcal infection. Serum specific antibody against meningococcal proteins and capsular polysaccharide causes lysis of bacteria, enhances phagocytosis by monocytes and polymorphonuclear neutrophils, and neutralizes endotoxin. Underscoring the importance of complement in the defense against meningococcal bloodstream invasion is the observation that people with deficiencies in certain complement components, such as C5, C6, C7, C8,

and properdin, are more prone to meningococcemia, despite the presence of protective antibody. Mucosal IgA may be important in mucosal defense against meningococci.

Infection with the meningococcus results in several clinical entities. The most common is asymptomatic carriage, which results in natural immunity. Humans are the only known reservoirs for transmission.[447] Meningococcemia is a rapidly progressive syndrome with an aggressive, downhill course and high mortality. Meningococcal meningitis is a more indolent disease with meningitis clinically resembling that caused by other bacteria. Chronic meningococcemia is a low-grade febrile illness frequently associated with arthritis and rash.

Meningococcal pneumonia may occur as a part of disseminated meningococcal infection variably accompanied by meningitis, arthritis, myocarditis, pericarditis, or endophthalmitis. Systemic illness may be mild.[448] Meningococcal pneumonia also occurs in the absence of the clinical picture of sepsis. Primary pneumonia is rare in children and adolescents. An association with antecedent viral pneumonia, particularly that caused by influenza and adenovirus, has been described.[449] However, the studies have been small, and the nature of the relationship has been unclear. Others have described a similar association between viral or *M. pneumoniae* infections and bacterial meningitis, but this relationship also requires further study.[447]

The presumed pathogenesis of meningococcal pneumonia begins with inhalation of the organism. Attack rates are highest in infants 6 to 12 months of age. The serotypes of *N. meningitidis* that have been described to cause pneumonia differ from those usually responsible for invasive disease. For example, serotype Y has repeatedly been cited as an important cause of primary meningococcal pneumonia despite its relatively minor role as a cause of septicemia.[450] Serotype W135 has been similarly implicated.[451] The incubation period is 1 to 10 days but is usually less than 4 days. Most cases of *N. meningitidis* pneumonia have been presumed to be community acquired. However, nosocomial pneumonia has also been described.[452]

Macroscopically, meningococcal pneumonia is lobular and rarely, lobar. The pleura is seldom involved. Histologically, affected bronchioles and alveoli are filled with polymorphonuclear cells that contain gram-negative intracellular diplococci.

No distinct clinical features distinguish meningococcal pneumonia from pneumonia caused by other bacteria[453]; adults usually have cough, fever, chest pain, and dyspnea.[282] The diagnosis is based on isolation of the causative microorganism from blood, sputum (when available), or both fluids. Bacteremia is infrequently reported in primary pneumonia but commonly found when pneumonia is part of generalized sepsis. Group-specific meningococcal antigen can sometimes be detected in CSF, serum, and urine, which allows for the possibility of rapid diagnosis; however, false-negative results commonly occur. This diagnostic tool may be particularly helpful if antibiotics have been administered. Detection of a meningococcal insertion sequence IS1106 and ribosomal RNA genes[454] by PCR in CSF is currently available only on a limited basis.[455] Radiographically, patchy or confluent densities in one or both lungs may be present with occasional cavities. A pleural effusion may sometimes be evident.[282]

Meningococcal pneumonia is treated with parenteral penicillin G. Isolates have generally remained susceptible to penicillin. Recently, relatively resistant isolates (minimum inhibitory concentration, 0.1 to 1.28 μg/mL of penicillin) have been reported from several countries.[447,456] Susceptibility testing is infrequently performed but guidelines may soon change. In a recent case report, a patient with meningococcal sepsis developed pneumonia and empyema while receiving treatment with penicillin; the meningococcal isolate was found to have intermediate susceptibility to penicillin.[456] In the presence of meningococcemia, meningococcal meningitis, or both conditions, the dosage of penicillin should be high (e.g., 300,000 units/kg/day; maximum, 24 million units/day) and divided into 4 to 6 daily doses. In uncomplicated meningococcal pneumonia, a lower dosage (e.g., 100,000 units/kg/day) will probably suffice. Extended-spectrum cephalosporins such as cefotaxime and ceftriaxone are alternatives but are more expensive. Chloramphenicol remains an excellent alternative and is useful for the child allergic to penicillin. Although specific data are lacking regarding duration of therapy, a 7-day course is usually sufficient.

There are few complications of meningococcal pneumonia when the infection is not disseminated. Empyema may occasionally complicate meningococcal pneumonia.[456,457]

Respiratory isolation is indicated for 24 hours after the initiation of effective therapy. Control measures also include careful observation of exposed school, household, or child care contacts. If a febrile illness develops in a contact, the person should receive prompt medical evaluation, and if indicated, antimicrobial therapy should be started. Antimicrobial prophylaxis is indicated within 24 hours of illness in the index case for all contacts, including those normally residing in the household of the index patient and day-care and nursery school contacts. Respiratory tract cultures are not helpful in decisions regarding prophylaxis. Rifampin or ceftriaxone are appropriate drugs for chemoprophylaxis in children; ciprofloxacin is an alternative for adults.

In the United States, Canada, and many European countries, a serotype-specific quadrivalent conjugate meningococcal vaccine is available against groups A, C, Y, and W135 *N. meningitidis*. The duration of protection is expected to be longer than that conferred by the polysaccharide vaccine. The vaccine is recommended for universal administration to young adolescents, patients who are anatomically asplenic, those with terminal complement component deficiencies, military recruits, or to those traveling to countries with hyperendemic or epidemic *N. meningitidis* disease. The meningococcal polysaccharide quadrivalent vaccine is recommended for use in those between ages 2 and 11 as well as those older than age 55, for whom the conjugate vaccine is currently not recommended.

NOCARDIA *SPECIES*

The first known recognition of nocardiosis occurred in 1888 when Nocard identified a disease that resembled glanders in cattle on Guadeloupe.[458] The first case in a patient was described in 1890 by Eppinger, who visualized the organism in pus from a brain abscess. In 1904, Stokes recognized that *Nocardia* species could cause pneumonia in children when he reported a case occurring in a 28-day-old infant.

In 1889, it was suggested that the organism be designated *Nocardia*, although it was not until a better classification system for the order Actinomycetales was derived in 1943 that the term was widely used. *Actinomyces* species and *Nocardia* species are microbiologically similar and cause diseases with overlapping clinical and radiographic findings, although the treatments differ.[459]

Nocardia species are bacteria that are distinguished by their filamentous growth with true branching. Members of the genus are acid-fast, gram-positive organisms found in parasitized soil and dust. They are rarely commensals in humans or animals. The most common species causing disease in humans is *N. asteroides;* other human pathogens include *N. brasiliensis*, *N. otitidis-cavarum (N. caviae)*, and *N. farcinica.*

The most frequently isolated pathogen, *N. asteroides*, is found worldwide. Infection caused by this organism has been reported in patients 4 weeks to 70 years of age.[460] A higher percentage of cases occur in male patients.[461] There are no seasonal predilections. *N. asteroides* pneumonia in children is rare[460,462,463] and usually occurs among immunocompromised patients, especially those with HIV infection,[464] chronic granulomatous disease, or other impairments of cell-mediated immunity.[465] Among adults and children, only 500 to 1000 cases were reported in the United States in 1974[466]; 75% were immunocompromised.[461]

The lung is the usual portal of entry; infection begins with inhalation of the organism. The inflammatory response is suppurative and necrotizing with the formation of abscesses filled with neutrophils and inflammatory debris. In chronic infection, the abscesses may be multiple and separated by fibrotic areas. The process is similar to that found in actinomycosis except that the abscesses are less well defined and the fibrinous reaction is sparse.[467] There may be coalescence with cavity formation. A granulomatous reaction that surrounds a central area of caseous necrosis[467] and that forms a nodule similar to the one found in tuberculosis has been described, but sometimes it may represent concomitant tuberculosis.

The clinical presentation is not specific. The child with pulmonary nocardiosis may have fever, cough, anorexia, weight loss, night sweats, fatigue, malaise, chest pain, and dyspnea.[460] Leukocytosis is usual (≤50,000 leukocytes/mm^3).[460] Disease progression may be acute, subacute, or chronic; remissions and exacerbations may occur.[468,469]

The radiographic findings are also not specific.[464] There may be evidence of segmental infiltrates or large lobar consolidations. Pleural involvement is variable. The lower lobes are more frequently affected.[458] One or more lesions typical of a lung abscess may be present, as may small or large cavities with thin walls. Hilar involvement is unusual; bronchiolitis obliterans has been described.[470]

The diagnosis is made by the identification of typical beaded, branched, weakly gram-positive rods in sputum or pus. The organism grows slowly; cultures should be maintained for 7 to 10 days or longer. Although rarely isolated in the absence of infection, recovery of *N. asteroides* from an immunocompromised child should be regarded as proof of active infection until it is proved otherwise.[469,471] Demonstration of *Nocardia* species in tissue is best done by Brown and Brenn stain or Gomori methenamine silver stain. The clinical and radiographic picture of pulmonary nocardiosis may mimic malignancy[472] or tuberculosis.

Treatment is with a sulfonamide, usually in combination with TMP.[473] Immunocompetent children are usually treated for 6 to 12 weeks, whereas immunocompromised children or those with hematogenous spread are treated for 6 to 12 months,[474] and those with AIDS may require an even longer course.[475] Treatment failures have been reported.[476] When a patient's condition fails to improve, assessing compliance, measuring serum sulfonamide levels, performing susceptibility tests on the isolate, and draining the abscess may be appropriate. Alternative therapy in this instance may consist of increasing the dose of TMP/SMX; when TMP/SMX is contraindicated, treatment may consist of an alternative agent, such as ampicillin, erythromycin, amikacin, or minocycline. Cefotaxime and ceftriaxone have good in vitro activity, but there has been little clinical experience.[477]

Lung abscess and cavity formation may complicate *Nocardia* pneumonia; multiple draining sinus tracts and empyema may be present.[478] Hematogenous spread to the liver, brain, kidney, and other organs occurs in about 30% of cases.[460,467] The central nervous system is the most commonly seeded distant site.[479] Brain abscesses are usually surgically drained. Relapse has been reported years after therapy.[474]

Most children with *Nocardia* pneumonia recover after TMP/SMX therapy. Concomitant corticosteroid or antineoplastic chemotherapy and disseminated disease are associated with increased mortality rates, even when prompt, appropriate treatment is provided.[460,474,480]

PASTEURELLA *SPECIES*

The genus *Pasteurella* consists of eight species of small coccobacilli that are animal pathogens. One of these, *Pasteurella multocida*, is further divided into the following subspecies: *multocida*, *septica*, and *gallicida.* Human infections, rarely including pneumonia, are usually caused by *P. multocida* subspecies *multocida* and subspecies *septica.* Other genus members, *P. canis*, *P. stomatis*, and *P. dagmatis*, are rarely responsible for infections in humans.

P. multocida is a short, ovoid, gram-negative bacillus that may vary to a coccobacillary shape with convex sides and rounded ends. It may appear in pairs, chains, or clusters or may appear as a single organism. It may exhibit bipolar staining and may become increasingly pleomorphic on subculture. Distinguishing *P. multocida* from *H. influenzae* on morphologic grounds is sometimes difficult, but the former does not require X or V factors for growth. The virulence of the organism is believed to be partly related to the presence of a capsule.[481]

P. multocida is found in the oropharyngeal flora of 70% to 90% of cats and 25% to 50% of dogs and in the pharynx and gastrointestinal tract of many other mammals and birds. Human *P. multocida* infections follow dog or, more typically, cat bites or scratches, although infections have been reported with no identifiable animal contact.[482-484] Respiratory spread from animals to humans also may occur. Human-to-human spread has not been documented. One study identified a dog bite–related seasonal variation in human infection, with the highest incidence occurring in the autumn and winter,[485] although others showed no seasonal differences. There is no

gender difference in attack rates. The incubation period is usually less than 24 hours.

Patterns of infection in humans with *P. multocida* include local soft tissue infection, chronic respiratory tract infection, and bacteremia.[486-488] Local disease usually occurs within 24 to 48 hours of the animal bite or scratch and may include swelling, tenderness, erythema, and serous or sanguinopurulent discharge. Osteomyelitis and septic arthritis may reflect direct inoculation of the bacterium into a bone or joint. Regional lymphadenopathy, chills, and fever may occur. Pneumonia is most often associated with chronic upper respiratory tract colonization or bacteremia.[489] The former may continue for an undetermined interval before bloodstream invasion or organism spread to contiguous structures (e.g., middle ear, mastoid bone, sinuses, epiglottis, lung) occurs. The bacteremic pattern may be associated with pneumonia, empyema, or septic arthritis. The diagnosis of *P. multocida* pneumonia can be made definitively by recovering the causative organism from relevant sites. These sites include sputum, pleural fluid, and blood.

The antimicrobial therapy of choice is penicillin, ampicillin, or amoxicillin. These agents in combination with clavulanic acid are often used empirically to manage dog and cat bites in which *P. multocida* and *S. aureus* are potential pathogens. In children allergic to penicillin, appropriate alternatives are TMP/SMX, chloramphenicol, and tetracycline. More important, oral cephalosporins (such as cephalexin), semisynthetic β-lactams (such as oxacillin or nafcillin), and the macrolide erythromycin are unlikely to be effective. The duration of therapy is measured against the clinical course; useful guidelines are 7 to 10 days for local infection and 10 to 14 days for invasive infections.

Reported complications of *P. multocida* pneumonia include several cases of lung abscess,[490] pleural effusion, and empyema.[491]

PROTEUS *SPECIES*

Infections by *Proteus* species in children are infrequent and are most often associated with neonatal sepsis and meningitis and with childhood urinary tract infection. Pneumonia has also been described.[492]

Members of the genus *Proteus* are motile, gram-negative, enteric bacilli; the most commonly isolated species is *Proteus mirabilis*. The organism is found in soil, sewage, and manure. Epidemic spread in a newborn nursery has been described, with multiple cases of invasive *Proteus* infections occurring in a span of several years.

There are no pathognomonic features of *Proteus* pneumonia. In the neonate, the signs and symptoms are the same as those of other causes of neonatal bacterial pneumonia or sepsis. In the older child, the clinical features of *Proteus* pneumonia are also typical of those of any bacterial pneumonia and include fever, chills, chest pain, dyspnea, and cough.

The diagnosis is usually made after isolation of the causative organism from infected pleural fluid, lung abscess material, blood, or another normally sterile site. Radiographic findings of consolidation are common and usually involve an upper lobe (posterior segment) or the superior segment of the right lower lobe.

Most *P. mirabilis* isolates are susceptible to ampicillin; thus this compound is usually the mainstay of treatment. For invasive infections such as pneumonia or meningitis, empirical combination therapy with an aminoglycoside is often used. An extended-spectrum cephalosporin provides an acceptable alternative.

The complications of *Proteus* pneumonia include associated bacteremia with metastatic foci, particularly meningitis. *Proteus* species pneumonia may also be associated with abscess formation in the lung and with empyema.

PSEUDOMONAS AERUGINOSA

Pseudomonas aeruginosa is a rare, opportunistic cause of community-acquired pneumonia and an occasional cause of nosocomial pneumonia in children. Infection in immunocompetent hosts is unusual. This bacterium is a special problem for patients with CF.

The organism is a usually motile, gram-negative bacillus that lives in soil and water and grows easily on most media. Most strains have a polar flagellum and fimbriae or pili on the cell surface. More than 90% of strains produce the blue-green pigments pyocyanin and pyoverdin. For epidemiologic distinction, strains are sometimes differentiated by serotyping on the basis of immunochemical distinctions of lipopolysaccharides, phage typing, and typing of pyocyanin, a bacteriocin elaborated by many clinical isolates.

P. aeruginosa isolates elaborate a variety of virulence factors,[493,494] including adhesins, elastases, and proteases. *P. aeruginosa* can be part of the transient flora of the skin or the gastrointestinal tract. Hospitalization may lead to high rates of colonization on the skin of patients with burns, in the respiratory tract of patients receiving mechanical ventilation, in the gastrointestinal tract of patients receiving cytoreductive chemotherapy, or at any site in people receiving antibiotics. Because it has few nutritional requirements, the organism can be found in swimming pools, hot tubs, contact lens solutions, mop water, and dilute disinfectant solutions.[493]

Childhood infections with *P. aeruginosa* usually occur in patients with neutropenia resulting from chemotherapy for cancer and are associated with prior hospitalization, the receipt of previous antibiotic therapy, disruption of mucocutaneous barriers, and the presence of indwelling central lines. The bacterium may reach the lung by aspiration or by bacteremic seeding. The latter mechanism occurs mainly in patients with malignancies or those who are neutropenic because of chemotherapy for their malignancies. Children and adults with HIV may also have serious *P. aeruginosa* infections, which include pneumonia[495] in the absence of neutropenia or prior hospitalization.[496] *P. aeruginosa* is also an important pathogen in the neonate, who may acquire the bacterium in utero[497] or during passage through the maternal genital tract with associated early onset septicemia. *P. aeruginosa* pneumonia in healthy children is rare.

Children with CF constitute a population at unique risk for *P. aeruginosa* lower respiratory infections. The rate of *P. aeruginosa* colonization in patients with CF is related to age. About one fifth of patients are colonized in the first year of life, whereas older patients (in their late twenties) have rates exceeding 80%.[498] The bacteria are present in large numbers in the thick mucus that occupies the intra-airway space. The bacteria (mucoid) are often coated with a thick, alginate polysaccharide capsule, which is rarely seen in patients with

other disorders.[499] The observation that patients with CF rarely develop *P. aeruginosa* bacteremia suggests that these organisms are uniquely adapted for parasitism of the respiratory tract of patients with CF and less effective at survival elsewhere.

P. aeruginosa colonization of the respiratory tracts of patients with CF is also positively correlated with clinical score, extent of pulmonary disease, severity of radiographic changes, and serum immunoglobulin concentrations.[500] Similarly, *P. aeruginosa* has been associated with acute exacerbations and chronic progression of disease. Moreover, there is growing recognition of inflammatory airway disease, the presence of neutrophils, and progressive airway disease in association with the presence of *P. aeruginosa*. These views have caused reassessment of the once-prevalent view that *P. aeruginosa* colonizations in the lungs of CF patients were harmless commensals.

The persistence of *P. aeruginosa* in the lungs of children with CF has been related to the presence of one or more sputum factors that interfere with bactericidal activity. Blocking IgG antibodies stops the normal bactericidal IgM activity of human sera.[501] During chronic infection with *P. aeruginosa* in the CF population, there may be conversion of the mucoid colony morphology and rough lipopolysaccharide; these mutations occur in global regulators (i.e., alternative σ factors and their accessory elements).[502]

In addition to its important role in the pathogenesis of CF lung disease, *P. aeruginosa* can cause pneumonia in other patients. When pneumonia occurs in this context, it is usually secondary to aspiration of the infecting organism. There are microabscess formation, necrosis of the alveolar septa, and focal hemorrhage. When it results from seeding of the lung during bacteremia, the lesion begins as a small area of necrosis around a medium-sized pulmonary artery; poorly defined hemorrhagic nodular areas that are frequently subpleural may surround the infected vessel. Alveolar necrosis may be present. Because this histopathologic picture usually occurs in severely immunocompromised patients, substantial inflammatory response may be minimal or even absent.[503] Alternatively, a lesion resembling the one caused by intraparenchymal ecthyma gangrenosum may be present. In this instance, bacteria can be seen to invade small muscular arteries and veins with adjacent small, firm, yellow-brown nodules and hemorrhage into the lung parenchyma; microabscess formation may be present with leukocytes and liquefaction necrosis.

P. aeruginosa is an important cause of so-called *ventilator-associated pneumonia* (VAP),[504,505] defined as bacterial pneumonia occurring more than 24 hours after the initiation of mechanical ventilation. VAP is the result of the microaspiration of oropharyngeal bacteria, which occurs in up to 35% of patients whose lungs are mechanically ventilated.[506] The oropharynx of a critically ill patient is often colonized with aerobic gram-negative bacilli, including *P. aeruginosa*,[507] which may originate from contaminated respiratory therapy equipment or the stomach of an ill patient with diminished production of gastric acid.[508]

The clinical features of *P. aeruginosa* pneumonia resemble the age-specific features of other bacterial pneumonias. In the immunocompromised or chronically hospitalized child, signs may include chills, systemic toxicity, apprehension, confusion, and severe dyspnea with progressive cyanosis.

The findings on physical examination of the chest are nonspecific. The chest radiograph may show bilateral bronchopneumonic infiltrates, more often in the lower lobe with a distinctive nodular pattern. The picture of lobar consolidation is unusual. An interstitial pattern may also be present. Small pleural effusions are common; empyema is rare.

P. aeruginosa isolates are often resistant to a variety of antimicrobial agents; thus susceptibility testing of available isolates may be helpful in planning appropriate antimicrobial therapy for suspected or proven *P. aeruginosa* pneumonia. An extended-spectrum cephalosporin with antipseudomonal activity, such as ceftazidime, or an antipseudomonal penicillin, such as mezlocillin, ticarcillin, or piperacillin, is often used with an aminoglycoside, such as gentamicin or tobramycin. Whether such cephalosporin/aminoglycoside or antipseudomonal β-lactam/aminoglycoside combination therapy improves the outcome compared with ceftazidime alone is the subject of some controversy. The preponderance of evidence suggests that routine use of combination therapy is warranted[509] because *P. aeruginosa* pneumonia is often a severe infection and occurs in the clinical setting of an immunocompromised host. Antipseudomonal penicillins should not be used as the sole therapy for *P. aeruginosa* pneumonia; they have not been shown to be effective in this regard, and they may be too vulnerable to hydrolysis by the *P. aeruginosa* β-lactamases for effective therapy. β-lactamase inhibitors, such as clavulanate, do not inhibit *P. aeruginosa* β-lactamases, and thus fixed combinations, such as ticarcillin/clavulanate (Timentin), offer no advantage over, for example, ticarcillin alone. Ciprofloxacin, a quinolone antibiotic, offers good activity against many isolates of *P. aeruginosa*. Although there is concern regarding arthropathies occurring in growing children who receive this antibiotic, accumulating evidence suggests that this concern may be more theoretical than real.[510] Resistance may develop quite rapidly.

High doses of antimicrobials may be needed to achieve a therapeutic effect in patients with CF. Increased nonrenal clearance, decreased tubular reabsorption, and increased renal tubular secretion all play a role in this regard.[511] Thus serum aminoglycoside levels should be monitored to ensure that therapeutic levels of these compounds are achieved.[512] Some investigators have used aerosolized antibiotics with intravenous antibiotics as suppressive therapy in an outpatient setting in patients with CF who are chronically colonized with *P. aeruginosa*. In this regard, therapy with aerosolized aminoglycosides, antipseudomonal penicillins, and ceftazidime has been attempted with some success as measured by improved pulmonary function and decreased need for hospitalization.

The prognosis depends largely on the underlying disease process. Most deaths in children with CF are from progressive pulmonary insufficiency; in almost all of these patients, *P. aeruginosa* is recoverable from the lungs. In other patients, *P. aeruginosa* pneumonia in association with bacteremia may follow an aggressive clinical course, with death ensuing shortly after onset.

In cases of ventilator-associated pneumonia in which *P. aeruginosa* is the major cause, the duration of intubation has increased the risk by a mean threefold; ventilator-associated pneumonia contributes to 60% of infection-related hospital

deaths.[504] Reported mortality rates from *P. aeruginosa* pneumonia have varied widely but may be as high as 90%.[513]

SALMONELLA *SPECIES*

Bacteria of the genus *Salmonella* are gram-negative, aerobic, enteric organisms. Numerous attempts have been made to order the complex taxonomy of *Salmonella* species. More than 2460 *Salmonella* serotypes exist. It is still useful to divide *Salmonella* on clinical grounds into typhoidal and nontyphoidal strains. Typhoid fever continues to be a global health problem, although great progress has been made in controlling this problem in the United States and many other countries. In contrast, the incidence of invasive nontyphoidal *Salmonella* infections is on the increase in the United States. Transmission to humans from contaminated food, either from animal colonization or during processing, continues to be the most important mode of spread. In addition, the severity of *Salmonella* infections in adults and children with impaired immune systems, particularly as a consequence of HIV infection,[514,515] has been increasing.

Despite the importance of typhoid fever as a childhood health problem in developing countries, *Salmonella typhi* is seldom implicated as a cause of pneumonia,[516] even though a dry cough occurs in many patients with typhoid fever. Indeed, when a pulmonary infiltrate is recognized during the course of typhoid fever, another, supervening bacterium is most often the etiologic factor.[517] Nontyphoidal *Salmonella* species rarely cause childhood pneumonia; the pathogenesis is most often believed to be a consequence of seeding of the lung during bacteremia. Gastroenteritis may be absent.[518] No particular *Salmonella* serotype has been implicated in *Salmonella* pneumonia; many, including *S. choleraesuis*, *S. typhimurium*, *S. oranienburg*, *S. paratyphi*, *S. stanley*, and *S. suipestifer*, have been isolated from lungs and empyema fluid.[283]

Pulmonary involvement by nontyphoidal *Salmonella* species has been manifested as several infectious syndromes. Radiographically, bronchopneumonia, lobar consolidation, miliary lesions, pleural effusion (empyema),[283] lung abscess, and bronchopleural fistula have all been reported.[519] Pulmonary involvement by *Salmonella* species may also reflect transdiaphragmatic spread from a splenic abscess. Pericarditis has also been reported as a complication.[283]

The treatment of *Salmonella* infection, typhoidal and nontyphoidal, has been a subject of controversy. Currently, antimicrobials are not routinely recommended in instances of uncomplicated *Salmonella* gastroenteritis because the disease is self-limited; therapy does not shorten the course, and antimicrobial use may encourage resistance. A possible exception is in young infants, in whom extraintestinal complications are relatively common. Antimicrobial therapy is always indicated for typhoid fever or when extraintestinal infection is suspected or proved. Antimicrobial resistance has been a major problem that reflects in part the human-to-animal transmission of many *Salmonella* strains and the use of antibiotics in livestock feed as well as injudicious antibiotic use by physicians and patients. In addition, some compounds to which *Salmonella* species are often susceptible in vitro (such as aminoglycosides) may not perform well in vivo, perhaps because the organisms are pathogens that gain access to the intracellular milieu as an early step in the pathogenesis. Thus, selection of an antimicrobial involves a decision as to whether any treatment is necessary as well as knowledge regarding the susceptibility of the infecting isolate. Useful compounds with good therapeutic effectiveness when the isolate is susceptible include ampicillin, chloramphenicol, and extended-spectrum cephalosporins such as ceftriaxone and cefotaxime. A 14-day course is sufficient to manage uncomplicated pneumonia, but empyema and lung abscess may require a longer course.

SERRATIA MARCESCENS

The genus *Serratia* contains many named species, but only one, *Serratia marcescens*, is associated with human disease. The organism is a gram-negative aerobe and may cause childhood pneumonia, particularly in patients with compromised immunologic integrity in the nosocomial setting.[520,521] *Serratia* organisms are now recognized as important but relatively infrequent causes of hospital-acquired infections, including pneumonia, bacteremia, urinary tract infections, and surgical wound infections. Most are associated with intravenous, intraperitoneal, or urinary tract catheterization and instrumentation of the urinary or respiratory tracts.

The clinical features of *Serratia* pneumonia are not specific. Exceptions are pseudohemoptysis and red sputum secondary to the production of prodigiosin (a red pigment made by some *S. marcescens* strains). This is a dramatic clinical sign but in the authors' experience is seldom present. Radiographically, *S. marcescens* typically appears as confluent or patchy infiltrates; cavitation is usual, and a pleural effusion may be present.[282,520]

S. marcescens may be resistant to a variety of antimicrobials, perhaps because of its hospital habitat. Extended-spectrum cephalosporins (ceftriaxone or cefotaxime) may be useful; these are typically combined with an aminoglycoside.

Local complications include empyema and lung abscess. Concomitant pneumonia and bacteremia caused by *S. marcescens* may lead to distant, infectious complications.

SPIRILLUM MINUS *AND* STREPTOBACILLUS MONILIFORMIS *(RAT-BITE FEVER)*

Rat-bite fever, a rare, febrile illness, follows a bite from a rat or another small rodent.[522] Although rat-bite fever has been recognized for many centuries, Wilcox[523] published the first account of it in 1839.

Streptobacillus moniliformis is a microaerophilic, gram-negative pleomorphic bacillus transmitted by a bite or scratch from rodents (such as rats, mice, or squirrels) or carnivores that prey on them (such as dogs, pigs, ferrets, cats, or weasels). Oral ingestion by drinking of milk or eating of food products contaminated by an infected animal has been associated with erythema arthriticum epidemicum (Haverhill fever), an illness resembling rat-bite fever. The incubation period ranges from 1 to 22 days but usually lasts less than 10 days.

Clinical manifestations include the bite (which heals quickly), fever, vomiting, severe headache, and chills. A blotchy, irregular, maculopapular rash usually occurs 1 to 8 days after the onset of the fever and can be found over the extensor and lateral surfaces, most prominently over the joints. The rash may last from 1 to 21 days; it may become purpuric and, ultimately desquamate. Migratory arthritis and arthralgias are common. Polyarthritis or true septic arthritis

may ensue. The fever spontaneously subsides but may relapse for weeks or months; arthritis may persist for up to 2 years. Focal infections may be manifested as endocarditis, pericarditis, and meningitis.[524,525] Pneumonia is rarely recognized in children or adults, although an interstitial pneumonitis was appreciated at the postmortem examination of a 2-year-old child who died of *S. moniliformis* infection.

Diagnosis is aided by a history of animal contact or other close-contact cases. Direct visualization of typical pleomorphic bacilli by material from an infectious site that is stained with Gram or Giemsa stain may provide a diagnostic clue. *S. moniliformis* may be isolated by the culture of blood or wound lesion material. Because the organism is fastidious, the laboratory should be notified that *S. moniliformis* is suspected. Rapid identification is possible by gas-liquid chromatography of washed growth from 24-hour broth cultures.[526] Specific agglutinins appear within 10 days of the onset of clinical symptoms and persist for several months. A fourfold rise in the titer or a single titer higher than 1:80 is considered diagnostic. False-positive, nontreponemal tests for syphilis have been described in patients with rat-bite fever.[527]

Treatment is with intravenous penicillin G. A 7- to 14-day course is typical. The last 5 to 7 days can be completed with oral phenoxymethyl penicillin. For penicillin-allergic patients, erythromycin, chloramphenicol, or streptomycin may be substituted. Tetracycline is another alternative for children older than 9 years of age.

Before the advent of penicillin treatment, the mortality rate for *S. moniliformis* rate-bite fever was about 10%. Death is still a possible outcome, particularly if the diagnosis is not considered as a cause of the pneumonia.

STREPTOCOCCUS PYOGENES *(GROUP A STREPTOCOCCI)*

Despite its continued importance as the major cause of bacterial pharyngitis and many other infectious syndromes in children, *Streptococcus pyogenes* is a rare cause of pneumonia. When it does occur, however, the necrotizing nature of pneumonia caused by this organism often makes the clinical course rapidly progressive, severe, and protracted—even when antimicrobial therapy is promptly initiated.

The organism, group A β-hemolytic streptococcus, also called *S. pyogenes*, is gram-positive and has a slimy, hyaluronic acid capsule. Among the determinants of virulence are M protein, pyrogenic exotoxins, C5a peptidase, hyaluronidase, streptolysins S and O, and streptokinase. M protein is a major virulence factor, partly because of its antiphagocytic activity. Anti-M antibody is opsonic and contributes to the bactericidal activity of blood. There are more than 80 distinct antigenic M protein types[528]; three types—1, 3, and 18—are more likely to be associated with invasive disease.[529] Lipoteichoic acid is the basic chemical component of hairlike fimbriae that protrude through the hyaluronic acid capsule and mediate the adherence of group A streptococci to epithelial cells.[530]

S. pyogenes makes many extracellular products that are important to its virulence. One such product is streptolysin O, an oxygen-labile hemolysin that targets bronchiolar macrophages and is useful in the diagnosis of group A streptococcal infection because of its immunogenicity. Streptolysin S is a hemolysin that injures the cell membranes of a variety of cells (including those of the myocardium),[531] but it is not immunogenic. In addition, four deoxyribonucleases (DNAses)—A, B, C, and D—are elaborated; hyaluronidase, streptokinase, proteinases, amylases; esterases are also produced. These last products facilitate the liquidation of pus and the spread of streptococcus through tissues. In addition, considerable attention has recently been given to a family of molecules produced by group A streptococci called *streptococcal pyrogenic exotoxins*. In the older literature, these have been called *erythrogenic* and *scarlet fever toxins*. Streptococcal pyrogenic exotoxin-A can maximally stimulate the production of tumor necrosis factor-α by peripheral monocytes, which with interleukin-1β, contributes to the pathogenesis of shock and tissue injury.

Before the advent of antibiotics, group A streptococcal pneumonia accounted for 3% to 25% of childhood bacterial pneumonia and had a mortality rate of 75% to 90%.[532] Epidemic pneumonia occurred in military adolescents in the early part of the century[533] and in the 1960s.[534] Many believe that certain antecedent viral illnesses predispose to group A streptococcal pneumonia.[535] Few specific data have been gathered by modern epidemiologic techniques, but the recognition that epidemics of influenza, measles, and varicella have occurred with group A streptococcal outbreaks would seem to support this anecdotal association.[535] The incidence of streptococcal pneumonia increases after 5 years of age into adolescence.[535] The peak incidence is in winter; most cases occur from late autumn through early spring.

Streptococcal pneumonia is usually acquired by the inhalational route but may also arise from secondary seeding from a bacteremic focus.[536] There are two distribution patterns: Most patients have a patchy, interstitial bronchopneumonia, whereas about one fourth have a lobar pattern.[533] Histologically, the lungs have thickened bronchiolar walls, necrosis of the mucosal lining[535] with formation of ragged ulcers, purulent engorgement of the lymphatic system, and microabscesses that can rupture into the pleura. Pleural effusion is usually present; it is serous initially but may become serosanguineous with rapid progression to fibrinopurulence.

Most children are ill for 2 to 3 days before experiencing an abrupt progression of the symptoms associated with respiratory compromise. Fever, chills, lethargy, myalgia, dyspnea, cough, pleuritic chest pain, and hemoptysis are common presenting complaints.[535] Weight loss is typical and may be profound. About one third of children have an associated streptococcal pharyngitis. Rarely, group A streptococcal pneumonia may be associated with purpura fulminans[537] or streptococcal toxic shock syndrome.[538]

The diagnosis is made by recovery of the causative organism from the lung, pleural fluid, or blood. Suggestive evidence allowing a presumptive diagnosis includes recovery of the organism from the oropharynx or sputum. Serologic diagnosis includes demonstration of a rising titer against a relevant streptococcal antigen. Included in this regard are antistreptolysin-O, antihyaluronidase, and anti-DNAse B. The detection of antibody to streptokinase and anti-DNAase A may also be of use, but these tests are not performed by many laboratories. The Streptozyme test may also be useful for detecting antibodies to streptococcal "extracellular products," but it is less specific. Leukocytosis is variably present; mild to moderate anemia may reflect intrapleural blood

loss. Radiographically, group A streptococcal pneumonia is manifested as a patchy bronchopneumonia or lobar pattern with frequent cavitation, parapneumonic effusion, and empyema.[537]

Treatment consists of intravenous penicillin G at a high dose. Resistance has not yet been recognized. A 2- to 4-week course is usual, and the medication may be given orally after satisfactory clinical improvement. Despite the susceptibility of the causative organism to penicillin, the resolution of pneumonia may be slow; fever and pleuritic chest pain may persist for 8 to 10 days.[535]

Pulmonary complications include pneumothorax, pneumatocele, bronchiectasis, persistent atelectasis, and bronchopulmonary fistula.[536] Pleural effusions may be copious in volume and average 100 to 150 mL/day in infants and considerably more in adults.[535] Empyema occurs in a high number of cases.[537] The fluid may be tenacious, and drainage may be difficult[535]; thus, surgical drainage or decortication may be required.[539] Pericarditis has been reported in about 10% of children.[535]

Other Streptococcal Species

Pneumonia may occasionally be caused by viridans streptococci, nutritionally deficient streptococci, the *S. intermedius* or *Streptococcus milleri* group, or β-hemolytic streptococci groups C and G. The taxonomy of these organisms has been imprecise and controversial. Viridans streptococci possess general characteristics of all streptococci. When cultivated on blood agar, they characteristically produce a zone of greening, so-called *α-hemolysis*, which is a phenomenon reflecting partial hemolysis. They are distinguished from pneumococci, many enterococci, and nonenterococcal group D streptococci by their resistance to optochin and inhibition of growth in 6.5% sodium chloride. Some viridans streptococci react with Lancefield grouping antisera, but many isolates cannot be grouped. Clinically important species belonging to the viridans group include *Streptococcus anginosus*, *S. constellatus*, *S. crista*, *S. gordonii*, *S. mitis*, *S. mutans*, *S. oralis*, *S. parasanguis*, *S. salivarius*, *S. sanguis*, *S. sobrinus*, and *S. vestibularis*.

The viridans streptococci (including the nutritionally deficient streptococci) and the *S. intermedius/S. milleri* group are endogenous flora and are normally carried in the upper respiratory tract, particularly the oropharynx (gingival crevices, dental plaque, teeth surfaces), intestinal tract, female genital tract, and skin. Groups C and G streptococci have been identified as constituents of the normal flora of the nasopharynx, skin, and genital tract. Group C organisms have also been isolated from the umbilical surface of healthy newborns and from vaginal cultures of puerperal women. Group G organisms have also been found in the intestinal tract.

Viridans streptococci are rarely proved to be the cause of pneumonia in adults and children. In a few adults[540-542] and children,[543] they have been isolated from the blood during a clinical illness consistent with bacterial pneumonia. In a Canadian study of 1118 patients with pneumonia, 76 of whom were bacteremic, 7 (9%) of the 76 bacteremic patients had viridans streptococci isolated from the blood.[544] Some of these isolates may, of course, have represented procedural contaminants. More commonly, invasive viridans group infection results in bacteremia or endocarditis. Nongroup D α-hemolytic organisms have been implicated as a cause of neonatal sepsis.[545] Identifying viridans streptococci as a more frequent cause of pneumonia has been difficult, partly because of their presence among the normal flora and because of their susceptibility to many antimicrobials used to treat presumed bacterial pneumonias. It is possible that they have a greater role in the pathogenesis of pneumonias associated with aspiration, but even in this situation, they are usually recovered with other microorganisms, particularly anaerobes. This fact further complicates the understanding of their role. It has even been suggested that the pathogenicity of the *S. intermedius/S. milleri* group in the lung might be related to synergy with an anaerobic organism.[546]

Members of the *S. intermedius/S. milleri* group are also infrequently implicated as etiologic agents in patients with pneumonia. In a review of *S. milleri* infections in 51 adults, no cases of pneumonia were identified, although 8 cases of pleural empyema occurred.[547] Among 186 patients with *S. milleri* infection in New Zealand, 12% of the infections were of pleuropulmonary origin.[548] *S. milleri* has also been reported as a cause of neonatal sepsis.[549,550] In this instance, the organism may be acquired antenatally from the maternal vaginal tract or during the birthing process.[551]

Group C streptococcus is an uncommon cause of pneumonia, but the clinical picture may be severe and may resemble that of pneumonia caused by group A streptococci.[552] The pneumonia is usually lobar, with associated bacteremia occurring in most cases. Group G streptococcus is also a rare cause of pneumonia that occurs in both immunologically normal and immunocompromised patients.

The diagnosis is usually based on recovery of the organism from a culture of blood, sputum, abscess, or pleural fluid. In one review of viridans pneumonia in adults, the chest radiographs were not distinctive: A segmental alveolar opacity was the most common abnormal finding.[180] In a separate report, radiographs of four cases of community-acquired viridans pneumonia in South Africa demonstrated a segmental or subsegmental consolidation, which appeared "mass-like" in two of four patients.[553]

The organisms are usually susceptible to many antibiotics, including penicillins, cephalosporins, clindamycin, and vancomycin. In the neonate, ampicillin and gentamicin are effective. In the child allergic to penicillin, erythromycin may be used.[554] Group C streptococcal pneumonia has been treated with penicillin G; however, because few cases have been well documented, information about the performance of other compounds is limited.

Empyema and lung abscess are common with viridans pneumonia and may require drainage for effective treatment. Complications of group C streptococcal infection include metastatic infectious foci, empyema, and intraparenchymal cavitation.

In adults, the mortality rate reported was 28% in one study[180] and 26% in another.[555] In neonates, the mortality rate from viridans streptococci infection appears to be lower than that from GBS infection.

YERSINIA *SPECIES*

Several species of *Yersinia* organisms—*Yersinia enterocolitica*, *Y. pseudotuberculosis*, and *Y. pestis*—can cause disease in humans. The most important species, particularly regarding

pneumonia, is *Y. pestis*, the cause of plague. The organism, a gram-negative, nonmotile coccobacillus,[363] was first identified in 1894 by Alexandre Yersin during an epidemic in Hong Kong[556] and was named *Pasteurella pestis* to honor his teacher, Louis Pasteur; it was subsequently renamed *Y. pestis* to honor Dr. Yersin. The disease has played a prominent role in world history since the start of civilization. In the United States, however, cases in crowded, urban settings have disappeared, with the last known urban plague occurring in Los Angeles between 1924 and 1925.[363,557]

Plague occurs worldwide. It has been suggested that there is a decreased incidence of human plague in the past several years.[558] Most human cases have been reported in developing countries, especially in South America, Asia, and Africa.

In the United States, human plague is infrequent but more than one half of the cases occur in children.[559] Most cases occur in the southwestern states.[559-562] Plague is maintained in well-established foci among the wild rodent population.[363] Worldwide, more than 200 species of mammals and 80 species of fleas have been implicated in keeping *Y. pestis* in enzootic foci.[563]

Y. pestis multiplies in the esophagus of the flea and is regurgitated when the flea sucks blood. Once it gains access to the human host, the bacterium may multiply intracellularly and spread from the lesion to the regional lymph nodes, with bacteremia following 5 to 10 days later.

Plague has been classified clinically into the following syndromes: bubonic, septicemic, pneumonic, and meningitic. The term *pneumonic plague* indicates the presence of pneumonitis. The lung may become infected by two routes. Inhalation of the organism from an infected person or animal, such as a cat,[564,565] produces primary pneumonia, which is rare. Secondary pneumonic plague, in which the lung is seeded during bacteremia, is more frequent; it usually represents bloodstream invasion from an infected lymph node or bubo.[566]

Primary pneumonic plague has a short incubation period (≤3 days). Clinical features include cough, chest pain, bloody sputum, high fever, and chills.[567] In addition, nausea, vomiting, diarrhea, and abdominal pain may be present. In children, encephalopathy may be present and is characterized by lethargy, ataxia, and confusion.[566] The course may be fulminant.

The diagnosis is suggested by the demonstration of typical, gram-negative, bipolar, safety pin–shaped coccobacilli in the sputum. When available, sputum is the specimen of highest yield.[558] A smear and culture of a bubo aspirate or other relevant body fluid and a blood culture may be useful. A fluorescent antibody test is available in some laboratories[363] and can be performed directly on clinical specimens. Confirmation by culture should be obtained, but definitive identification may require input from the Plague Branch of the CDC in Fort Collins, Colorado, where a passive hemagglutination serology test is available; a fourfold rise or a single titer higher than 1:16 is diagnostic.[567]

The antimicrobial agent of choice is streptomycin. Other aminoglycosides said to be effective include gentamicin and kanamycin.[363] Tetracycline, doxycycline, chloramphenicol, trimethoprim-sulfamethoxazole, and ciprofloxacin are effective alternatives.[363] TMP/SMX is less effective than streptomycin.[568] Chloramphenicol should be used when meningitis or endophthalmitis is present.

A child with plague should be placed into respiratory isolation. If pulmonary involvement is documented, precautions may be discontinued when 48 hours of antibiotic therapy have been administered.[363,559,567]

If the condition is untreated, the mortality rate in patients with pulmonary plague is 100%.[567] Survival is rare when treatment is not initiated within 18 to 24 hours after the onset of clinical symptoms. However, with appropriate and timely antibiotic therapy, the condition usually improves within 24 to 48 hours. In reviewed cases of pneumonic plague from 1970 to 1995, the case fatality rate was 40%.

A formalin-killed vaccine is available in the United States and is recommended for laboratory personnel working with *Y. pestis*, people who are exposed to materials or animals with possible infection, isolated park or forest rangers, or wildlife workers. In addition, people traveling to epidemic or hyperendemic areas are possible candidates for immunization.[363] Vaccine-induced immunity is short-lived and probably wanes after 6 months, so reinoculation is recommended.[569,570] There are no recommendations for the use of this vaccine in children.

Prophylactic agents should be given to people exposed to a patient who has pneumonic plague.[363] For children younger than 8 years of age, TMP/SMX is usually recommended.[567] For older people, doxycycline or ciprofloxacin is recommended.

Y. enterocolitica is widely distributed in nature and is isolated from animals, particularly pigs, horses, and dogs. It typically causes acute gastroenteritis and enterocolitis[282] and is a rare cause of pneumonia in both immunocompetent and immunocompromised patients.[571] Its epidemiology is obscure. Radiographically, hilar adenopathy may be the only finding,[282] although fluffy infiltrates, consolidations, or nodules may be evident. The organism is susceptible to streptomycin, chloramphenicol, tetracycline,[282] TMP/SMX, aminoglycosides, extended-spectrum cephalosporins, and quinolones.[572] There is no clear therapy of choice. Necrotizing *Y. enterocolitica* pneumonia in an immunocompromised adult was successfully treated with an extended-spectrum cephalosporin for 6 weeks,[573] and a child was treated with cefuroxime followed by TMP/SMX.[572] Complications of *Y. enterocolitica* pneumonia have included lung abscess, empyema,[572] and erythema nodosum as part of a sarcoid-like syndrome with hilar adenopathy.[282]

LUNG ABSCESS

A lung abscess is an accumulation of inflammatory cells, especially polymorphonuclear leukocytes, accompanied by tissue destruction or necrosis that produces one or more large cavities in the lung. It is probably arbitrary to designate larger cavities by the term *lung abscesses*, and smaller, multiple cavities with similar histologic appearance by the term *necrotizing pneumonia*. However, because a lung abscess has distinctive pathophysiologic and clinical features, it will be considered separately here.

Lung abscess is unusual in children. Among 230,325 consecutive admissions to Children's Memorial Hospital in

Chicago from 1985 to 1990, only 28 children had a discharge diagnosis of lung abscess—a rate of 1 case per 8226 admissions.[574]

Some authors classify a lung abscess according to whether it occurred in a patient with no underlying disorder (primary) or in a patient with an underlying or predisposing condition (secondary).[575-577] We have not found this distinction clinically helpful. Rather, consideration of the relevant pathogenesis of a lung abscess provides a more useful consideration for the approach to diagnosis and therapy.

Pathophysiology

Aspiration is the most important factor predisposing a child to lung abscess. Therefore children who have relevant conditions (e.g., achalasia, chronic neurologic conditions) are at increased risk. Aspiration alone, however, is not sufficient to cause lung abscess because all children and adults aspirate daily to some degree. It is likely that the number of aspirations, the volume of the aspirated material, and any impairment of normal respiratory tract clearance mechanisms of aspirated material contribute to the likelihood of abscess formation. The most common sites of lung abscess formation are the most frequent destinations of aspirated material (i.e., those most dependent in the recumbent position: the right and left upper lobes and the apical segments of both lower lobes). If periodontal disease is present, the potential for lower respiratory tract infections with aspiration is increased because these children have more oropharyngeal organisms.

After a known aspiration event has occurred, it takes several days for an abscess to develop and for signs and symptoms to occur.[578] The localized inflammatory process that constitutes the host response to the aspirated material may paradoxically induce a delay in healing by mechanically obstructing the vascular supply to the area. The result may, therefore, be an inability to physiologically drain the affected area and to transport other defense mediators to the region. Tissue necrosis may ensue, with the dead tissue forming a spherical cavity bounded by a fibrous wall. Such a walled-off cavity may then lead to a large solitary lung abscess or small regions of necrosis with or without air-fluid levels.

A single abscess is clinically recognized more frequently than multiple abscesses. An abscess may vary from a few millimeters to 5 to 6 cm in diameter. After cavitation has occurred, a putrid oral discharge may be noted in more than 50% of children. This discharge is often copious, fetid, and green-black (hence the name *gangrene of the lung*).[579]

Other predisposing factors may also place a patient at risk for lung abscess. For example, a lung abscess may evolve from untreated pneumonia that progresses to abscess formation or from antecedent bronchiectasis; alternatively, a subdiaphragmatic, intra-abdominal infection may extend into the lung or pleural space via the lymphatic system.[578] Recently, epidemic community-associated MRSA disease including pneumonia with multiple pneumatoceles or abscesses has been described in pediatric patients.[183] A lung abscess may also result from airway obstruction by a foreign body, an enlarged mediastinal lymph node, or a neoplastic mass. It may occur with infection in a congenitally abnormal lung (e.g., sequestration, lung cysts). Although rare in children, a lung abscess may result from extension of a parapharyngeal abscess. Seeding of the lung by a septic embolus from bacterial endocarditis (usually right sided in origin), a distant suppurative thrombophlebitis as has occurred in some community-associated MRSA infections, or seeding of the lung during any bacteremia may also occur. In these instances, multiple small abscesses or cavities may be present in the lung, even though the initial lesion may appear to involve only a single lobe. Seeding of other lobes may have occurred but may not become clinically apparent until later.[578]

Clinical Features

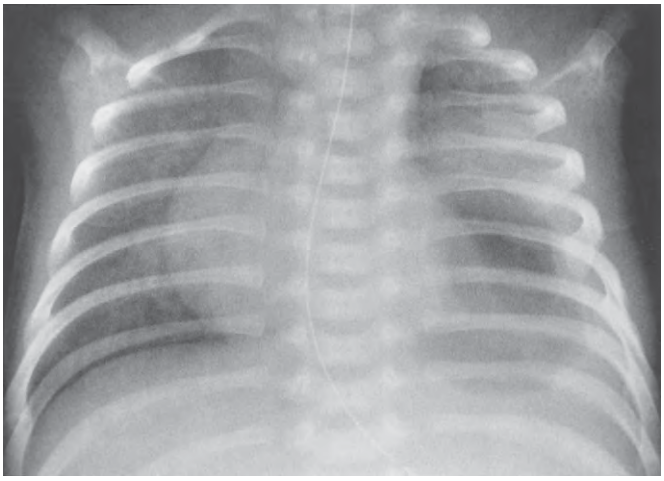
The clinical spectrum of illness in children with lung abscess is variable and often indistinct from related pulmonary infectious syndromes such as pneumonia. Tan and coworkers[575] summarized the symptoms and signs of 45 children with lung abscess of varying pathogeneses; only fever (84%) and cough (53%) occurred in the majority of the patients. Other symptoms and signs included dyspnea (35%), chest pain (24%), anorexia (20%), production of "purulent" sputum (18%), rhinorrhea (16%), and malaise and lethargy (11%). Infrequently, diarrhea, vomiting, or irritability may be present. Minor hemoptysis is common in adults but may be life-threatening in children.[580] The course of a lung abscess before medical intervention may be surprisingly indolent and may last several weeks. Weight loss may occur. Conversely, the clinical course is occasionally more aggressive; apnea and hypotension may be present.[578]

The physical findings in children with lung abscess resemble those found in early pneumonia and include tachypnea and audible crackles on auscultation. If the abscess persisted for a time before medical intervention, amphoric or cavernous breath sounds may be evident. Digital clubbing is rare.[581]

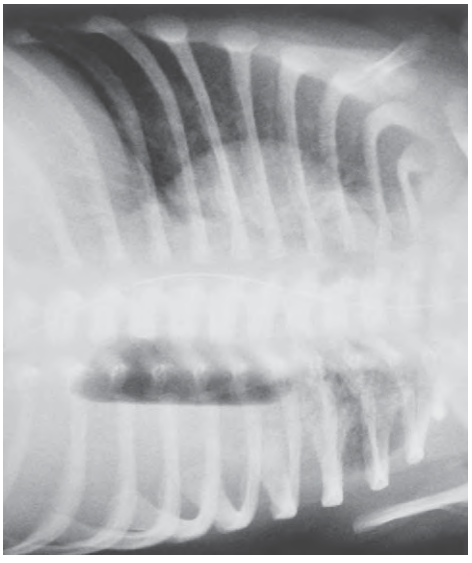
Laboratory findings are not specific. White blood cell counts range from 14,000 to 23,000/mm^3.[575] Mild anemia may be present.

The diagnosis of lung abscess is often suggested by a chest radiograph in which an abscess appears as a thick-walled cavity with an air-fluid level (Fig. 35-11). Initially, however, the lung abscess appears as a solid lesion within the parenchyma, most often surrounded by an alveolar infiltrate. At this stage, the chest radiograph may be misleading (Fig. 35-12) because the abscess may appear as a solid mass and may be indistinguishable from the surrounding infiltrate or from a concomitant pleural effusion or an empyema; gas may be absent. Particularly at this stage, an abscess must be distinguished from a loculated empyema and a pneumatocele. The latter have thin walls and do not contain air-fluid levels.[582] Suspicion of an abscess may arise when the "consolidation" is unusually persistent, when "pneumonia" remains persistently round or mass-like, or when a bulging fissure representing increased volume of the involved lobe is present.[583]

Gas may be present in an abscess as a result of bacterial metabolism by gas-forming organisms or as a result of a communication with a bronchus. Once gas is present within the abscess cavity, its appearance by radiography is characterized

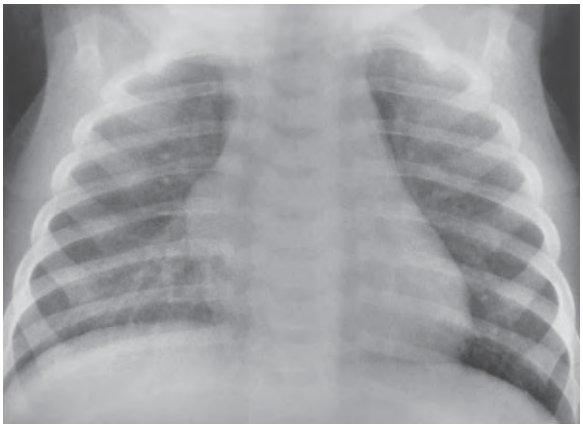


A



B

Figure 35-11 Lung abscess in a 2-week-old boy with a cavitary lesion in the left side of the chest. A, Supine anteroposterior chest radiograph demonstrates a large cavity in the left lower lobe, causing a mediastinal shift to the right. **B,** Left side-down decubitus film shows a large air-filled level within the cavity.



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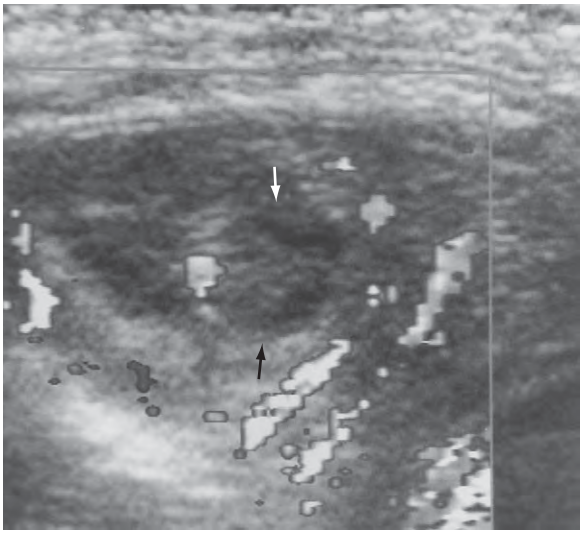


B

Figure 35-12 Occult lung abscess. Pneumonia in the right middle lobe in an 18-month-old boy did not respond to antibiotic therapy as expected. **A,** Chest radiograph demonstrates a straightforward pleuropneumonia in the right middle lobe without volume expansion or an air-containing cavity. **B,** Sonography demonstrates a mostly avascular hypoechoic lesion within the consolidation (*arrows*). Black-and-white rendering of a color Doppler examination of the infiltrate demonstrates pulmonary vessels supplying the lung around the abscess and a still-vascular nodule within the abscess.

by irregular, thick walls; air-fluid levels may be multiple and are optimally demonstrated when the radiographs are taken with a horizontal beam (upright or decubitus cross-table). Mediastinal adenopathy sometimes accompanies the parenchymal infection and may also be evident on the chest radiograph.[584]

Lung abscesses may occur at any site. A review of several series of children with lung abscesses suggested that occurrence in the right lung was more frequent (about 70%) and that although any lobe may be involved, the upper, middle, and lower lobes accounted for about 40%, 20%, and 40%, respectively, of right-sided lung abscess in children.[574,575,577] As noted, the location of a lung abscess may provide a clue as to pathogenesis. For example, abscesses resulting from septic embolic events tend to be multiple and more diffusely situated than the solitary abscess secondary to aspiration, which is often situated in the right upper or lower lobe.

Diagnosis

Contrast-enhanced CT may aid the clinician in localizing an abscess and in distinguishing it from empyema, pneumatocele, bronchopleural fistula, congenital anomalies (such as bronchogenic and duplication cysts), pulmonary sequestration, or rarely, persistent pneumonia (Fig. 35-13).[583] CT is also used to guide diagnostic and therapeutic drainage procedures.[583] The classic findings of a lung abscess by this modality include a thick, ragged wall; central fluid; acute angle with the chest wall; and surrounding parenchymal consolidation. An air-fluid level may be seen even when it is not apparent on the plain radiograph. Helpful features that distinguish abscess from other entities include the well-marginated nature of the abscess mass, distinction between it and the pleura, greater density of the abscess than of water, and contrast enhancement in adjacent tissues. Bolus contrast injection may demonstrate pulmonary vascular branches in

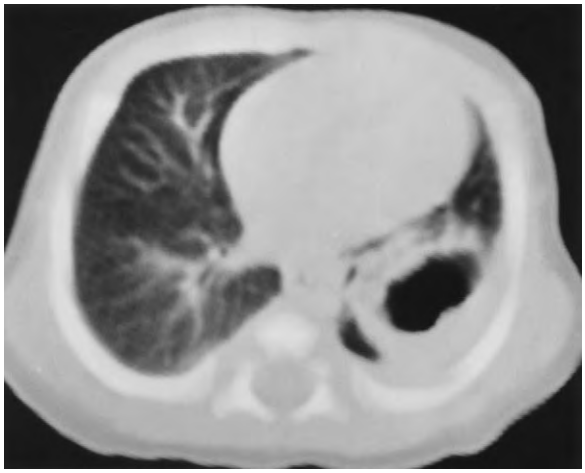


Figure 35-13 CT scan of a lung abscess. The cavity has thick, irregular walls and an acute angle with the chest wall—features typical of a lung abscess. A sonographically-guided fluid aspiration yielded pus. The lesion healed without further intervention.

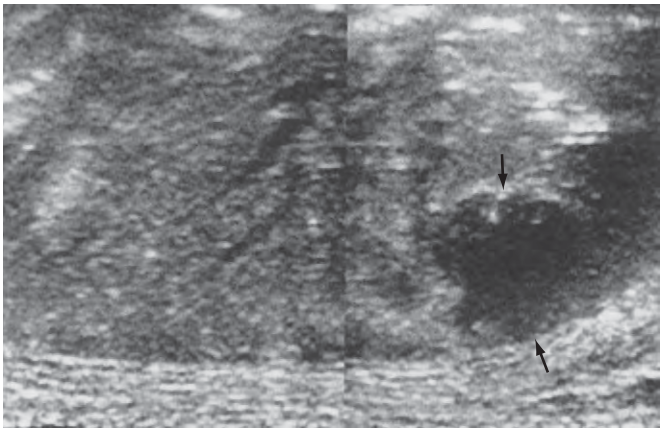


Figure 35-14 Sonography of lung abscess. An irregular cavity (*arrows*) with irregular walls, an acute angle with the chest wall, a hypoechoic center, and an absence of separation of pleural layers characterize this lung abscess in a 3-year-old girl who developed fever, cough, and a persistent infiltrate in the left lower lobe after trauma.

the territory of an equivocal lesion and thereby reveals its pulmonary rather than its pleural origins.[85] Occasionally, an abscess may rupture into the pleural cavity and result in a combined lesion with CT features of both pleural and pulmonary pathology.

Sonography is also a valuable tool, particularly in patients in emergency situations and in critically ill patients in whom the abscess abuts the chest wall, diaphragm, or mediastinum and thereby provides an acoustic window. With this technique, a lung abscess has a thick, irregular wall with a blurred outer margin and an oval or round shape. It forms an acute angle with the chest wall, and pleural layers are absent.[585] Color and spectral Doppler may allow demonstration of the abscess within the territory supplied by the pulmonary artery. However, any long-standing inflammatory process in the lung, including an abscess, may parasitize the blood supply from the chest wall; thus, the abscess may be supplied by the intercostal and bronchial arteries. A lung abscess may possess an avascular hypoechoic center even before it contains air. If the abscess is adherent to the chest wall, real-time sonography shows absence of gliding against the chest wall (Fig. 35-14). A lung abscess was identified by technetium-99m white blood cell scintigraphy[582] in a patient in whom this diagnosis was not suspected.

Defining the bacteriologic diagnosis of a lung abscess in children poses some practical problems; bacteremia is infrequent.[586] Material for culture from the abscess cavity itself is usually not obtained because of the procedure's invasive nature. Sputum cannot usually be obtained from young children, and even when available, sputum culture may reflect pharyngeal flora. Diagnostic evaluation of a concomitant pleural effusion associated with a lung abscess may provide an opportunity to isolate the causative organism.

Diagnostic needle aspiration of a lung abscess depends on accessibility of the abscess and a size sufficient to allow procurement of an adequate specimen. It is often performed with ultrasound or CT guidance. Both the sensitivity and the specificity of this procedure are high, although the procedure is not without risk.[587] Among six studies using needle aspiration for diagnosis, 24 complications occurred among 800 children, 2 of which were serious (pneumothorax).[588]

Useful information may be obtained from needle aspiration of a lung abscess when it is performed in appropriately selected cases. Among 35 consecutive patients in Taiwan with lung abscess (31 adults, 3 adolescents, and 1 child), needle aspiration was successfully performed in 33.[589] Two patients developed a pneumothorax of minor clinical importance. One or more microorganisms were recovered from 31 of the 33 patients, many of whom were receiving antibiotics. In contrast, the offending pathogen was recovered from only 3% of blood cultures, 11% of sputum cultures, and 3.1% of alveolar lavage fluid cultures.

Transtracheal aspiration, a procedure once commonly used to obtain material in adults for the etiologic diagnosis of lung abscess, is unsuitable in small children for technical reasons and may not yield the offending pathogens. BAL in adults has compared favorably with transtracheal aspiration for identifying aerobic and anaerobic organisms.[590] However, no data are available regarding this modality in the diagnosis of lung abscess in children.

Etiology

Because the techniques required to obtain material for culture are often invasive, only a subset of patients with lung abscesses are subjected to such procedures; therefore, published information regarding the etiology may reflect selection bias. Nevertheless, it seems reasonable to conclude that the organisms causing lung abscess secondary to aspiration are generally those normally inhabiting the upper respiratory tract. Thus, anaerobes are often implicated in the etiology of lung abscess. Important clues that suggest anaerobic lung infection are observed aspiration, disease in a dependent segment, cavitation or abscess formation with or without empyema, and foul-smelling sputum. Anaerobes, either alone or with aerobes, have been recovered from about 30% of adults with lung abscesses.[591] In one study of children with lung abscess, anaerobes were identified by transtracheal aspiration in all

10.[592] The most common anaerobic isolates were gram-positive cocci, pigmented *Prevotella* species, members of the *Porphyromonas* group, and *Fusobacterium* species. The predominant aerobic bacterial isolates were α-hemolytic streptococci, *E. coli*, *K. pneumoniae*, *S. pyogenes*, *P. aeruginosa*, and *S. pneumoniae*. *S. aureus* has also been implicated as a cause of lung abscesses, especially when they are multiple or believed to occur as an embolic complication of an intravascular infection, such as endocarditis or septic thrombophlebitis. In addition, many other bacterial species have occasionally been isolated from lung abscesses. *Mycobacterium fortuitum* may cause lung abscess.[593] *Arcanobacterium hemolyticum* was identified as a cause of lung abscess in a child, and it was also isolated from expectorated sputum and from material obtained from bronchoscopy in an otherwise healthy, immunologically normal adolescent.[594] In immunodeficient patients or those receiving immunosuppressive therapy, *Alcaligenes xylosoxidans*[595] and *Pseudallescheria boydii*[596] have been isolated. *Selenomonas artemidis*[597] was isolated from a patient with lung abscess and tuberculosis. Community-acquired *Lactobacillus casei (L. rhamnosus)* has been reported as a cause of lung abscess,[598] and botryomycosis abscess has been reported as a presentation of chronic granulomatous disease.[599] *Salmonella* species have been associated with lung abscess—rarely in healthy patients but in a patient with Wegener granulomatosis.[600]

Lung abscess is rare in neonates[601]; six were found in a review of medical records spanning 20 years at Parkland Memorial Hospital and Children's Medical Center in Dallas. Predisposing factors may include congenital lung cysts or pneumonia. At one time, *S. aureus* pneumonia was an important predisposing factor and recent increases in MRSA disease may impact the epidemiology of lung abscesses again.[602] Lung abscess in this age group may also be caused by GBS, *E. coli*, and *K. pneumoniae*.[603]

Treatment

Antibiotic therapy is the mainstay of treatment; the length of therapy depends on the rate of abscess resolution, the extent of the abscess, and the severity of illness at presentation. On average, parenteral antibiotic therapy is provided for 2 to 3 weeks. Oral therapy may then be administered for 4 to 8 weeks.[575] Neonates should receive the entire course parenterally.

For the therapy of lung abscess that results from the introduction of pharyngeal flora into the lung (e.g., aspiration), penicillin has long been the front-line agent. However, presumably because of β-lactamase-producing anaerobes, some clinicians have preferred metronidazole or clindamycin in addition to penicillin in patients with lung abscesses who are critically ill.[604] Others have suggested ticarcillin or ampicillin/clavulanic acid or piperacillin/tazobactam. Care should be taken to ensure that the chosen antimicrobial regimen includes optimal coverage for *S. aureus* (both MRSA and MSSA) when a lung abscess appears to complicate a preexisting pneumonia or there is metastatic seeding from a distant focus (e.g., endocarditis, distant bone/joint disease, or intravascular focus in the pelvis). In addition to antimicrobials, physiotherapy, particularly postural drainage, is an important mainstay of therapy.

The success of medical treatment with antimicrobials and physiotherapy is related to age. The prognosis for resolution is better in children older than 10 years of age because the child may have a productive cough; thus the abscess can be physiologically drained through the larger airways.

Sometimes surgical intervention is required to provide adequate drainage for a child with a lung abscess. Indications include failure to respond to antimicrobial therapy, especially in neonates, and severity of illness (e.g., critically ill patients).[605] Newer, invasive radiologic techniques aimed at providing drainage generally approach the abscess percutaneously with the guidance of CT, ultrasonography,[583,606,607] or fluoroscopy.[608] Drainage procedures have included needle aspiration or the insertion of small-bore or Malecot or "pigtail" catheters. In many instances, these techniques have replaced more traditional, more invasive procedures. Occasionally, however, the necessity for drainage may still require operative catheter insertion or wedge resection.[609] The need for definitive lobectomy should be infrequent, although in the presence of an underlying immunodeficiency (such as Job syndrome), elective resection may be the procedure of choice[610] because the involved area may be a nidus for recurring abscesses.

Complications

A lung abscess may rupture into adjacent tissue compartments, an important complication occurring most frequently in abscesses caused by *S. aureus*. Rupture into the pleural space leads to empyema, pyothorax, or pneumothorax. Empyema may sometimes be accompanied by the formation of a bronchopleural fistula. Localized bronchiectasis may also occur as a complication. If the pathogenesis of the lung abscess was associated with bacteremia, distant metastatic foci may also be present.

Prognosis

The prognosis is good if effective therapy and close follow-up are provided and the predisposing causes can be eliminated. Asher and colleagues[577] reported that 9 of 11 patients with "primary" lung abscess (no underlying condition) had normal pulmonary function when assessed approximately 9 years after diagnosis. All these children were growing normally. Radiologic resolution may be delayed and may require more than 6 months for complete resolution.[577]

PLEURAL EMPYEMA

A pleural empyema is the presence of purulent material usually consisting of polymorphonuclear leukocytes and fibrin, in the pleural space. The pleural space is normally a theoretical one between the visceral and parietal pleura—the former covering the lung parenchyma and the latter lining the interior of the thoracic cavity. The parietal pleura is sometimes said to consist of *costal, mediastinal, and diaphragmatic* parts, descriptive terms referring to the relevant, adjacent anatomic regions.[611]

Normally, a small amount of fluid is evenly distributed in the pleural space and lubricates the movement of the visceral pleura on the parietal pleura during respiration. It was believed that this physiologic pleural fluid was a passive trans-

udate from blood; however, important differences between the composition of serum and pleural fluid suggests that this is not the case. Cells (1500 to 2400 cells/mm^3) are normally present in pleural fluid in experimental animals; the majority are mesothelial or mononuclear cells, but neutrophils may constitute 2% of the resident leukocyte population.[612]

The lymphatic vessels of the costal pleura drain ventrally to nodes along the internal thoracic artery and dorsally toward the internal intercostal lymph nodes near the insertion of the ribs. The lymphatic system of the mediastinal pleura drains to the tracheobronchial and mediastinal nodes; drainage of the diaphragmatic parietal pleura is to the parasternal, middle phrenic, and posterior mediastinal nodes. The lymphatic vessels communicate with the pleural space by means of stomas [2 to 6 nm in diameter] that are found on the mediastinal pleura and intercostal aspects of the costal pleura.

Pathophysiology

Pleural empyema is usually secondary to an infection at another site, most often pulmonary. Indeed, it occurs most commonly after infection of a parapneumonic pleural effusion, commonly present in bacterial pneumonia. Progression of such an effusion to empyema is said to have a three-stage evolution. The first stage is exudative. Antimicrobial therapy for "pneumonia" is often initiated at this stage and may abort disease progression.

The second stage is termed fibrinopurulent and is heralded by the arrival of bacteria, most often by pleural invasion from the contiguous pneumonic process. Progression occurs with neutrophil accumulation and fibrin deposition; frank pus is present, membrane formation occurs, and the developing empyema may become compartmentalized or loculated. With time, the pleural fluid pH and glucose concentration decrease, and the concentration of lactic acid dehydrogenase may increase.

The third stage is characterized by organization; fibroblasts grow into the exudate from the visceral and parietal pleural surfaces. An inelastic membrane called the *pleural peel* is formed and may encase the lung, with the potential to restrict respiration. The thick exudate may drain spontaneously through the chest wall or into the lung and produce either a pleurocutaneous or a bronchopleural fistula.

Less frequently, an empyema may occur in the absence of a parapneumonic process. For example, empyema may complicate a thoracic surgical procedure, especially pneumonectomy.[613] After the pneumonectomy, the space vacated by the procedure fills with serosanguinous fluid. By 2 weeks after surgery the pleural space is about 80% to 90% filled with fluid, and by 2 to 4 months the space is completely filled. As fluid accumulates, the mediastinum also shifts ipsilaterally to fill the vacated space. Failure of this shift to occur or a return to symmetry of the mediastinum should prompt consideration that empyema is present. The infecting bacterium may be introduced during the surgical procedure or may seed the collected fluid during a bacteremia that may be clinically inapparent. The time from surgery to identification of the empyema ranges from 8 days to 7 years, although most cases are evident within 1 month. Empyema may complicate any invasive intrathoracic procedure, such as thoracentesis, thoracotomy, or esophageal perforation.

Empyema may also be found in association with a bronchopleural fistula. The presence of such a fistula should be suspected when a child with a collection of pleural fluid produces "sputum" only when lying in one position. By radiography, a bronchopleural fistula usually has an air-fluid level in the pleural space in the upright position; CT is valuable in making this diagnosis.

Empyema may also reflect the spread of infection from an adjacent site. Such direct extension was the predisposing factor in 10% of the cases of empyema in one study.[614] Implicated in this regard were periodontal, retropharyngeal, peritonsillar, and subdiaphragmatic abscesses—as well as subcutaneous abscesses of the neck.

Clinical Features

The diagnosis of empyema may pose a clinical challenge because the clinical features of empyema (classically heralded by tachypnea, tachycardia, dyspnea, cough, irregular breathing, pleuritic chest pain, and possibly cyanosis) resemble those of uncomplicated pneumonia or pneumonia in the presence of an uninfected parapneumonic pleural effusion.[611] Inflammation of the parietal pleura, which has pain fibers, leads to the so-called *pleuritic chest pain*. Some children with pleural effusion have a dull, aching chest pain rather than pleuritic pain,[615] especially if the underlying process directly involves the parietal pleura (e.g., with a lung abscess). Pleuritic pain that is simultaneously perceived in the ipsilateral shoulder and in the lower chest is highly suggestive of a paradiaphragmatic pleural effusion.

A dry, nonproductive cough may be present. Dyspnea may be associated with a pleural effusion of any etiology. The degree of dyspnea may be out of proportion to the size of the pleural effusion and may reflect splinting caused by pleuritic chest pain. Fever, anorexia, malaise, headache, nausea, vomiting, and prostration are variably present in patients with empyema. In a very young child, signs and symptoms pointing toward an abdominal process may dominate the clinical picture; abdominal distention may be present. The absence of fever and symptomatology involving the chest does not exclude the presence of empyema, especially if the patient is debilitated or receiving immunosuppressive therapy.

The findings on physical examination may reflect the presence of empyema or any pleural effusion and include decreased chest movement, scoliosis or splinting toward the affected side, flushed face, nasal flaring, and sternal retractions. On inspection of the chest, a discrepancy in the size of the hemithorax may indicate ipsilateral increased pleural pressure on the larger side. Bulging of the intercostal spaces may be present. Conversely, a relatively small hemithorax may indicate decreased pleural pressure on the same side of the effusion. In this situation, the size of the intercostal spaces may be exaggerated and may retract with inspiratory efforts. Scoliosis may be present; in 44% of children with empyema the curvature of the spine was greater than 5 degrees.[616] Splinting may occur in an attempt to reduce tension on the inflamed pleura or as a result of contraction of the pleural lining on the affected side.

In children with pleural effusion, palpation of the chest may be helpful in determining the extent of the effusion.

Tactile fremitus is absent or attenuated in areas of the chest where the pleural fluid separates the chest wall from the lung because the fluid absorbs the lung vibrations. This sign is more reliable than percussion in identifying the upper border of the pleural fluid and the proper location for thoracentesis. Palpation may also be useful in determining whether the cardiac point of maximal impulse is shifted. The trachea should also be palpated because its location indicates the relationship between the pleural pressures in the hemithoraxes.

Percussion over a pleural effusion is flat or dull and maximal at the base of the lung where the fluid is the thickest. If only a thin rim of fluid is present, however, there may be no change in dullness. On auscultation, breath sounds are decreased or absent over the empyema. Paradoxically, breath sounds may be increased near the upper border of the fluid because of increased sound conductance in the partly atelectatic area under the fluid. A rub may also be present, especially if the effusion is diminishing in size, and may be associated with localized pain on breathing.

Empyema may also become apparent during the resolution of seemingly uncomplicated bacterial pneumonia; thus an apparent "relapse" of bacterial pneumonia should prompt a search for empyema. An empyema may occasionally be chronic; in this instance, symptoms involving the chest may be absent, and therefore only constitutional abnormalities, such as low-grade fever or weight loss, may provide a clinical clue.

Epidemiology

Historically, the rate of occurrence of empyema has been expressed as a percentage of children hospitalized with pneumonia. In the preantibiotic era, 10% of hospitalized children with pneumonia had empyema; *S. pneumoniae* was the most common pathogen. With the availability of sulfonamide antibiotics, the percentage of hospitalized children with pneumonia diminished greatly but surged in the 1950s to 14% of children hospitalized with pneumonia, with *S. aureus* accounting for 92% of the cases. In the 1970s, the percentage of children hospitalized with pneumonia who had empyema decreased to about 2%.[617]

Recently, studies have suggested that the worldwide incidence of empyema is increasing.[618-623] The reasons for this increase are unclear, but may be due to the emergence of more virulent pneumococcal and community-associated MRSA strains. In Salt Lake City, Utah, the percentage of children hospitalized between 1993 and 1999 with community-acquired pneumonia that had empyema was 28.3%, with 5 cases per 100,000 children in 1999.[618] The majority of pneumococcal empyema was caused by serotype 1. A retrospective review of patients discharged from a large tertiary care children's hospital in Texas from 1993 to 2002 found that the discharge diagnosis of empyema increased from 1993 to 2000 when it peaked at 23 cases per 10,000 admissions. In England, investigators analyzed the number of admissions under the International Classification of Diseases code "pyothorax" between 1995 and 2003 and found that the rate of admissions increased from 14 per million in 1995/1996 to 26 per million people in 2002/2003.[623]

Etiology

S. pneumoniae and *S. aureus* are the most common etiologic agents.[615] *H. influenzae* type b was an important cause[624] in the prevaccination era but is now rare. Group A streptococcus and *N. meningitidis* are infrequent causes of empyema.

The introduction of the pneumococcal conjugate vaccine has had a variable impact on the incidence of empyema with pneumococcal pneumonia. Overall, the incidence of pneumococcal pneumonia has decreased. However, the incidence of pneumococcal empyema caused by serotypes not included in the vaccine has increased in some geographic locales. In contrast, a decrease in the prevalence of pneumococcal empyema was documented in other locales after the introduction of the vaccine in 2000 with a corresponding increase in empyema due to community-associated MRSA.[625]

Brook[626] called attention to the role of anaerobes in empyemas occurring in children. Anaerobic bacteria (*Bacteroides* species, *Fusobacterium* species, *Peptostreptococcus* species, *Veillonella* species, *Propionibacterium acnes*, and *Clostridium perfringens*) were isolated from blood or pleural fluid in pure culture from 24% of the children studied and in combination with an aerobe in an additional 10%.[626] Foul-smelling pleural fluid was not always present when an anaerobe was isolated.[627] Presumably, anaerobic bacteria associated with empyema originate from a pulmonary process such as pneumonia or a lung abscess, or an extrapulmonary process such as a retropharyngeal or lymph node abscess or a paravertebral abscess.

When empyema occurs as a result of external introduction of organisms related to trauma, surgery, or thoracentesis, important causes include *S. aureus* or aerobic gram-negative bacilli.[614] Anaerobes should also be considered in this instance.

Empyema may also complicate a subdiaphragmatic abscess; in this instance, the flora may be mixed and may include enteric gram-negative bacilli, other aerobic intestinal flora, or anaerobes. Other causes of empyema are extremely infrequent. However, it is probable that any bacterium capable of infecting the lung can also be associated with a parapneumonic pleural empyema.

Diagnosis

A parapneumonic pleural effusion and empyema should be considered in the evaluation of any patient for bacterial pneumonia. The presence of an effusion is usually demonstrated by radiography of the chest. However, because uninfected parapneumonic effusions resolve with the resolution of the pneumonia, distinguishing such an uninfected effusion from empyema is of clinical importance and may be challenging. Several distinguishing features may be useful. For example, the rapid loculation of an empyema results in an inability to shift the pleural effusion. Thus demonstration of "layering," a shift in the location of the effusion with change of patient position, suggests that empyema is absent. In practice, this distinction is often made on the basis of lateral decubitus radiographs. Furthermore, a fusiform, pleural-based shadow may be present and is sometimes large enough to obliterate the entire chest and shift the mediastinum contralaterally. Empyema is also more likely when a pulmonary alveolar

consolidation is adjacent or when a lung abscess or cavitary pneumonia is present.[628,629] Such an associated cavitation may have eroded into the pleural space.

The occasional complication of a bronchopleural fistula may result in a pyopneumothorax that is manifested radiographically as an air-fluid level within the pleural effusion. Unlike a pulmonary abscess, which has similar length in different projections because of its round nature, the flat geometry of empyema results in an air-fluid level that is long in one projection and much shorter in the perpendicular plane.

CT provides an excellent global view of the abnormality and enables evaluation of the extent of pleural involvement (Fig. 35-15). CT has not been helpful in distinguishing between empyema and parapneumonic effusion but CT with contrast can be helpful in identifying loculated pleural fluid. With this modality, an empyema appears with a lentiform shape at an obtuse angle with the chest wall, separation of the two pleural layers, compression of the adjacent lung, and uniform chest wall width with a sharp interface with the lung.[630,631] Contrast enhancement may demonstrate an unexpectedly thick, enhancing rind surrounding an empyema that may fail to resolve after therapy with drainage and antibiotics. Such thick, enhancing walled empyemas may be caused by *S. aureus* or other pathogens[632] and often require surgical decortication. Radiation exposure from a CT can be high.

Sonographic characteristics of pleural empyema are similar to those described for CT (Fig. 35-16). Sonography has the superior ability to assess the quality of the fluid within the pleural space and can differentiate free from loculated pleural fluid. Doppler sonography may aid in the differentiation of pulmonary and pleural lesions by demonstrating intercostal artery enlargement and increased flow velocities associated with an adjacent empyema.[633] Ultrasound can be used to guide chest tube insertion and can be conveniently used at the bedside.

Ultimately, diagnostic thoracentesis is necessary to obtain the information that allows distinction between uninfected

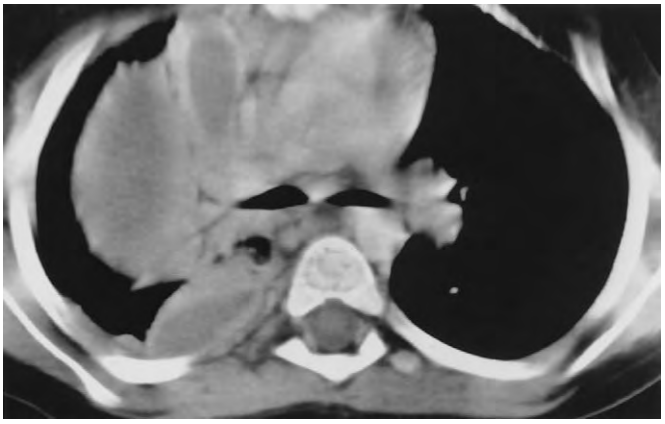
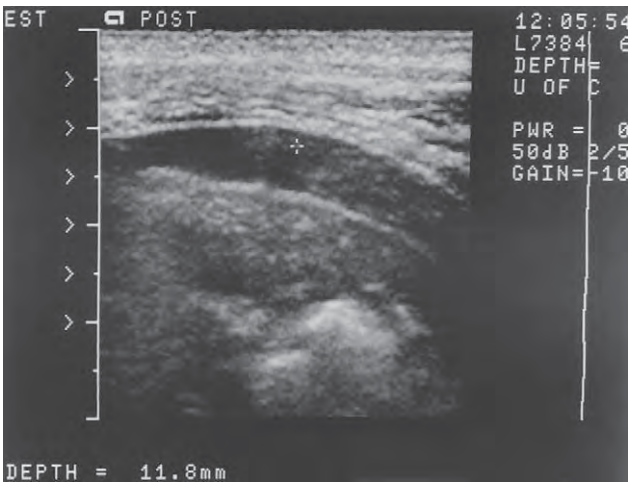
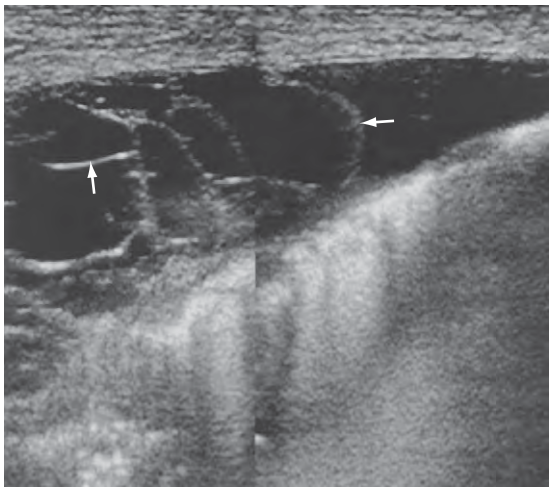


Figure 35-15 CT scan of pleural empyema in a 5-year-old boy with extensive right pleuropneumonia (*Streptococcus pneumoniae*). CT was performed to clarify the various components of a complex chest radiograph with diffuse opacities. An apical, complex empyema demonstrates the classic characteristics: fusiform shape; smooth, uniform walls; an obtuse angle with the chest wall; and peripheral location (along the mediastinal, apical, and posterior pleural surface).



A



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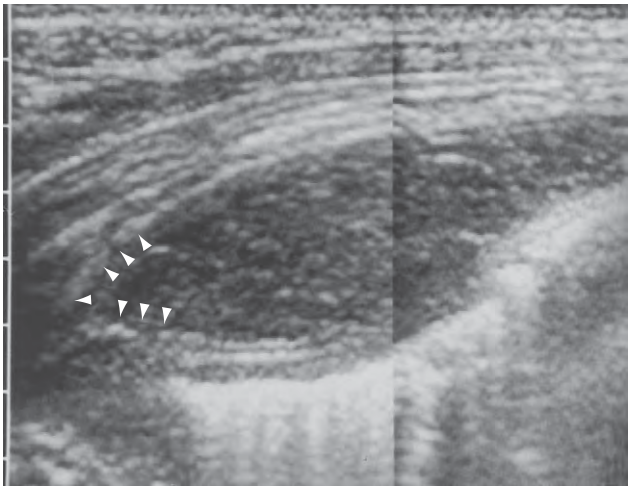

C

Figure 35-16 Sonography of pleural empyema in three patients. **A,** In a 3-year-old boy with group A streptococcal pneumonia, an empyema with fluid containing debris (+) separates the chest wall from the consolidated lung. **B,** Empyema with multiple septations in a boy 3 years and 10 months old who has pleuropneumonia (*arrows*). **C,** Typical mature empyema: fusiform shape; thickened, separated pleural layers; uniform wall width; echogenic fluid within the empyema; and obtuse angle with the chest wall (*arrowheads*).

parapneumonic effusions and empyema. The decision to perform this procedure must be individualized; all parapneumonic pleural effusions do not require diagnostic thoracentesis. However, because the presence of empyema usually necessitates drainage of the infected material, most often via the insertion of a chest tube, thoracentesis should be performed when empyema is suspected.

The diagnosis of empyema is strongly supported by the presence of thick pus, bacteria demonstrable when the fluid is subjected to Gram stain, a pH less than 7.3, or a glucose concentration less than 60 mg/dl. In exudative pleural effusions, the protein concentration is rarely less than 3.0 g/dl, and the lactate dehydrogenase concentration is high. The average white blood cell count in empyema fluid is 19,000 cells/mm^3 but may be somewhat lower (about 11,000 cells/mm^3) in a patient with chronic empyema. Culture of the pleural fluid should include procedures appropriate for the growth of aerobic and anaerobic bacteria, fungi, and mycobacteria. Importantly, these findings may be variably present and must be interpreted in their clinical context.

Detection of bacterial antigens in pleural fluid is potentially useful in the diagnosis of empyema.[634] The advantages are the rapidity with which the test can be performed and the possibility that antigen may be present (despite the presence of too few organisms to allow their visualization by Gram stain or despite a pleural fluid culture rendered sterile by prior antimicrobial therapy). The disadvantages of antigen detection tests lie in the limited availability of reagents for antigen detection for the organisms that commonly cause empyema (among the common causes, only *S. pneumoniae* capsular polysaccharide can be detected with commercially available reagents) and the imperfect sensitivity and specificity of the available tests.

Treatment

The mainstay of therapy in empyema consists of antimicrobial therapy[635] and adequate drainage of infected material in the pleural space. The choice of medications depends on the knowledge of the likely causative microorganisms. An appropriate empirical regimen for empyema presumptively caused by aerobic bacteria usually includes coverage for *S. aureus* and *S. pneumoniae*. In regions that have not experienced epidemic CA-MRSA disease, a semisynthetic or β-lactamase resistant penicillin such as oxacillin, and an extended-spectrum cephalosporin such as ceftriaxone, are often used together as initial therapy. In regions with epidemic CA-MRSA disease, empirical therapy includes clindamycin or vancomycin in combination with an extended-spectrum cephalosporin. Most antibiotics diffuse well into the pleural fluid.[644] The duration of therapy has received little critical evaluation, but a 14- to 28-day course of therapy seems appropriate.

Several options are available when it is determined that a pleural effusion constitutes an empyema that requires drainage. The choice is often dictated by local experience and beliefs as well as the early clinical response to treatment. Variation in practice reflects the paucity of randomized controlled trials comparing different treatment modalities. Children most frequently recover, irrespective of the treatment they receive, but newer treatments may be less invasive and decrease the length of hospital stay. Regimens in use include antibiotics alone or in combination with thoracentesis, chest-drain insertion, chest drain and fibrinolytics such as urokinase, open decortication, and video-assisted thoracoscopic surgery (VATS).[636]

Closed-chest drainage via a chest tube is often performed when empyema is suspected. Such drainage may not be necessary in patients with small serous effusions that remain stable. Repeated ultrasound-guided needle thoracentesis has not been shown to be more effective than chest tube placement and requires repeated trauma. The chest tube should be positioned in a dependent part of the empyema and should be of sufficient diameter to prevent clogging. The tube should be connected to a drainage system with an underwater seal. Clinical and radiologic improvement should be evident within 24 to 72 hours, and the tube may be removed when the pleural drainage is lower than 50 mL/24 hours and the fluid is clear or yellow.

Despite these measures, the condition in some patients may fail to improve or may have a protracted, acute course; there are many reasons for this. Antibiotics may have a suboptimal antibacterial effect because of previously undetected resistant bacteria, poor penetration into an abscess-like loculation, inactivation of the antibacterial compound (e.g., a β-lactam antibiotic by β-lactamase), suboptimal antibacterial activity in the presence of low pH, or a high degree of protein binding.[637] Alternatively, pleural drainage may be inadequate. The most common explanations are loculation with obstructed communication of empyema fluid or tenacity of the exudate with obstruction of the drainage tube. Ultrasonography or CT may help clarify this situation.

Management of a patient whose condition is unresponsive to standard therapy may include reformulation of the antibacterial regimen, placement of one or more additional chest tubes, or use of fibrinolytics or surgery. The use of urokinase as a thrombolytic agent instilled into the pleural space via an existing chest tube has been enthusiastically received as a strategy for dissolving fibrinous loculated walls of an empyema before fibroblast collagen production has ensued.[638] This enzyme, produced by the human kidney, is less often associated with the allergic reactions attributed to streptokinase and streptodornase. Typically, it is instilled into the chest tube and left in the pleural space for 2 to 4 hours[639] or overnight.[640] The dose instilled should be 10% of the dose used intravenously to lyse clots.[638] A prospective trial randomized patients older than 1 year to receive either 40,000 units of urokinase in 40 mL saline or 0.9% saline instilled in the pleural space twice a day over 3 days. Patients in the urokinase group were discharged from the hospital an average of 2 days sooner than those in the saline control group, a difference that was statistically significant.[641]

Surgical options are also available in the treatment of empyema complicated by fibrinous peel and loculations. Open decortication involves removal of the pleural peel and irrigation of the pleural cavity through a large incision made in the chest wall. In video-assisted thoracoscopic surgery (VATS) 2 or 3 small incisions are made in the chest wall; a camera and 1 or 2 grasping instruments are then used to disrupt adhesions in the pleural space, drain loculated effusions, and mechanically lyse intrapleural septations. Proponents of VATS have suggested that it results in less morbidity to skin,

muscles, and nerves and faster healing times than open decortication. Proponents of open decortication believe that those who undergo that procedure recover more quickly. Prospective randomized trials comparing the two surgical procedures are lacking.

A recent prospective randomized trial compared the use of percutaneous chest drain with urokinase and VATS for the treatment of empyema in children. Outcome measures studied included number of hospital days after intervention, number of chest drain days, total hospital stay, failure rate, radiologic outcome at 6 months, and total treatment costs. There was no difference in clinical outcome, hospital stays, or failure rate but the treatment cost of patients in the urokinase group was significantly lower.[642]

Some have proposed that VATS should occur early in treatment rather than reserving intervention for cases in which medical management has failed. One small trial involving 20 patients suggested that patients treated with immediate VATS had higher immediate success and shorter hospital stays than patients who received intrapleural streptokinase instilled into a chest drain.[643] Research in this area to clarify the roles of the various treatment modalities is needed.

Chronic empyema is a vaguely defined term used to refer to a situation in which the patient's condition fails to improve despite therapy and there is evidence of restrictive lung function, increasing fibrosis, and lung fixation.[638,644] Decortication and even rib resection or permanent external drainage have rarely been used to treat a patient with this diagnosis. Empyema complicating pneumonectomy may also be refractory to standard therapies and therefore "chronic." In addition to these measures, treatment for postpneumonectomy empyema has included irrigation of the thoracic cavity with antibiotic solutions, open window thoracotomy, and obliteration of the cavities with muscle flaps—although the last is a therapeutic effort of last resort.[638]

Complications

Complications associated with empyema include the creation of a bronchopleural fistula by direct extension of infected pleural fluid into the lung (empyema necessitatis) or the formation of a cutaneous fistula. Other infectious complications include bacteremia and pericarditis by direct extension or bacteremic seeding and pneumothorax.[611]

Prognosis

Morbidity and mortality rates from empyema remain high even in the modern era. Risk factors for bad outcome include inadequate antibiotic therapy (choice of medications, duration of therapy, or poor compliance with a prescribed unsupervised regimen), inadequate surgical management (when indicated), and probably certain underlying conditions that compromise the immune response. An important long-term consequence of untreated empyema relates to the formation of restrictive scar tissue or peel in the pleural space and includes decreased exercise tolerance, chest contour changes, and chronic restrictive pulmonary disease. Some have suggested that scoliosis can complicate empyema.[638]

The mortality rate among patients with empyema has been estimated at 2% to 15%.[638] Risk factors for death include duration of illness, severity of infection, and young age.[638]

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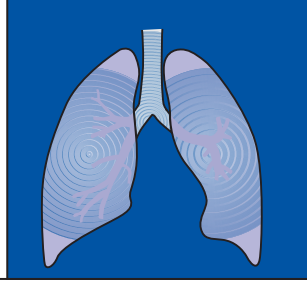


CHAPTER 36 Respiratory Infections in Immunocompromised Hosts

Dennis C. Stokes and Surender Rajasekaran

TEACHING POINTS

- Pulmonary infections are common among patients with altered host immunity.
- The numbers of patients at risk have increased owing to improved overall survival and new patient risk groups.
- As therapy and preventive strategies for common bacterial and fungal infections have improved, new resistant pathogens have continued to emerge.
- Many noninfectious processes occur in these populations and complicate the diagnosis of infection.
- Outcome for many pulmonary infections in immunocompromised hosts is poor, particularly when specific diagnosis is delayed.

The use of the term *immunocompromised host* is relatively new. Utz first described the terms *opportunistic pathogens* and *immunodeficiency* in 1962, and in 1967, Ruskin and Remington used the term *compromised host*.[1,2] The numbers of individuals at risk for infection owing to altered immunity have expanded greatly since that time, primarily because of improved survival of childhood cancer patients with aggressive but effective treatment protocols, expanded use of solid organ and bone marrow transplantation, and the human immunodeficiency virus (HIV) epidemic. The list of pathogens that can cause pulmonary infections in immunocompromised hosts is extensive and continually growing. As effective therapy and preventive therapies have reduced the impact of some infections such as *Pneumocystis* and varicella, other infectious agents including rarer saprophytic fungi, multiply resistant bacterial pathogens, and common viral infections such as adenovirus and respiratory syncytial virus (RSV) continue to plague this population. Many noninfectious pulmonary complications also occur in immunocompromised pediatric patients, including those with acquired immunodeficiency syndrome (AIDS) and must thus be included in the differential diagnosis of infectious pneumonias. Newer diagnostic studies, including bronchoscopy with bronchoalveolar lavage (BAL), and computed tomography (CT)-guided needle aspiration biopsy coupled with new molecular diagnostic techniques have helped in making earlier specific diagnosis possible. Although outcome for many infections (particularly with early diagnosis) has improved significantly, care of the critically ill immunocompromised host with pulmonary involvement remains a difficult challenge and the prognosis for many patients with advanced lung disease is often poor.

EPIDEMIOLOGY, RISK FACTORS, AND PATHOGENESIS

Epidemiology

During the 1960s, improved therapeutic programs for childhood malignancies, principally acute lymphocytic leukemia (ALL), resulted in longer survival times and increased numbers of children at risk for opportunistic infections. Children who no longer died quickly during initial therapy were at risk for pulmonary infections over prolonged remissions while receiving maintenance chemotherapy for at least 5 years. *Pneumocystis jiroveci* (previously *carinii* and some still prefer this name), previously identified as a pathogen primarily in outbreaks in malnourished infants, emerged as a major problem for these children.[3-5] Varicella-zoster pneumonia was also a major problem because of its frequency in childhood and the lack of effective antiviral therapy.[6] During the late 1960s, the first bone marrow transplants were attempted in children with refractory malignancies. Bacterial pneumonias were generally treatable with effective antimicrobial therapy, but fungal pneumonias became a major problem in children with prolonged neutropenia, such as those with aplastic anemia or those receiving intensive chemotherapy. *Aspergillus* pneumonia was a common problem, and the association with hospital construction and other risk factors such as prolonged neutropenia was recognized.[7] In 1976 and 1977, Hughes and colleagues[8] described effective treatment and prophylaxis for *P. jiroveci* pneumonia (PCP) in oncology patients with trimethoprim/sulfamethoxazole (TMP/SMX). This replaced the more toxic medication pentamidine that was available only for biopsy-proven PCP. The use of TMP/SMX prophylaxis effectively eliminated PCP as a cause of pneumonia in this population, and the availability of a safer alternative to pentamidine provided a rationale for the empirical treatment of pneumonia in immunocompromised patients.[9] This often delayed more invasive diagnostic studies such as open-lung biopsy and generated considerable controversy on the role and timing of open-lung biopsy.[10-12] In the late 1970s, pediatric flexible bronchoscopy became increasingly available as

an alternative to surgery, providing a specific diagnosis for many opportunistic infections.[13-17] In the 1980s the epidemic of HIV infection and AIDS resulted in a major new group of immunocompromised children, first in those who received contaminated blood transfusions for cancer, hemophilia, or other indications and later in infants of HIV-infected mothers. *P. jiroveci* re-emerged as the major pulmonary pathogen in this group, both as the presenting infection and as the cause of death.[18] In addition to patients with AIDS, new high-risk groups included patients with acute nonlymphocytic leukemia, lymphoma, and solid tumors (including brain tumors) who were receiving aggressive combined therapy with chemotherapy and radiation therapy.[19] The number of bone marrow and other tissue transplants also continued to expand, and major noninfectious pulmonary complications were described in these populations, including bronchiolitis obliterans organizing pneumonitis (BOOP) in recipients of bone marrow transplants and lymphoid interstitial pneumonia in pediatric patients with AIDS.[20,21] The use of varicella-zoster immune globulin (VZIG) for prophylaxis and acyclovir for treatment significantly reduced the importance of varicella-zoster virus (VZV) as a cause of mortality.[22]

Since the late 1980s and 1990s trends in the epidemiology of infections in immunocompromised hosts include re-emergence of gram-positive organisms, including *Staphylococcus epidermidis*, methicillin-resistant *Staphylococcus aureus*, streptococci, and C*orynebacterium jeikeium*, as major causes of sepsis and bacteremia. Effective antiviral therapy with ganciclovir and immunoglobulin have provided a significant advance in preventing and treating cytomegalovirus (CMV) pneumonitis in high-risk populations.[23-26] Cytokines to accelerate marrow recovery and activate macrophages have helped reduce the risk of bacterial and fungal pathogens in many patients.[27] Fungal pathogens, particularly the rare saprophytic organisms, remain a major problem because of their resistance to antifungal therapy. Use of highly active antiretroviral therapy has reduced the prevalence of PCP in HIV.[28]

Risk Factors

Many nonimmunologic aspects of pulmonary host defense, including physical barriers, mucociliary clearance, and cough, predispose to pulmonary infections when altered. However, the primary groups of immunocompromised children are those with either congenital or acquired defects in immunologic defenses of the lung. A detailed discussion of pulmonary immunologic defenses is beyond the scope of this chapter but Table 36-1 and Box 36-1 summarize the major host defenses of the lung and associated disorders that predispose to pulmonary infections.

HUMORAL IMMUNITY

Immunoglobulin G (IgG) and IgA are major components of respiratory secretions, with IgA (and secretory IgA) most important in the upper airway. In the lower respiratory tract, IgG provides primary protection against local and systemic infections. Humoral immunity deficiencies account for 70% of all immunodeficiencies. Defects of subclasses of IgG, including both IgG2 and IgG4, have been associated with recurrent sinopulmonary infections, although the importance of minor reductions of subclasses in patients with recurrent pneumonias is debated.[29,30] Some individuals with normal levels of total antibody are unable to make IgG to certain important pathogens.[31] Although patients with complement deficiencies are more likely to have systemic infections, some with such defects have pneumonias.

CELLULAR IMMUNITY

Alveolar macrophages are the major phagocytic cells in the lung and are able to handle small numbers of pathogenic

Table 36-1
Host Defense Disorders Leading to Pneumonia

Pulmonary Host Defense	Defective in
Upper airway	
Turbinates	Intubation
Epiglottis	Tracheostomy, aspiration syndromes
Mucociliary clearance	
Cilia	Primary ciliary dyskinesia (PCD), infections
Mucous blanket	Cystic fibrosis, bronchitis
Cough	Muscle weakness, sedation
Immunoglobulin	
Secretory IgA, IgA	IgA deficiency
IgG, including subclasses	Agammaglobulinemia, hypogammaglobulinemia, IgG subclass deficiency
IgE	Elevated in hyperimmunoglobulinemia E with recurrent infections (Job syndrome)
Cells	
Alveolar macrophages	Corticosteroids, chemotherapy, chronic granulomatous disease
Polymorphonuclear leukocytes	
Numbers	Chemotherapy, congenital neutropenia
Motility	Motility disorders
Function	Chronic granulomatous disease
Lymphocytes	
Numbers	AIDS
Function	T cell disorders, including severe combined immunodeficiency disease, others
Other	
Surfactant	Adult respiratory distress syndrome (?), edema
Fibronectin, lysozyme complement	C3 or C5 deficiency

BOX 36-1 Attack Rates for *Pneumocystis jiroveci* Pneumonia (PCP) by Underlying Condition*

Underlying Disorder	Attack Rate (%)
Acute lymphoblastic leukemia	6.5-42.9
Severe combined immunodeficiency syndrome	27-42
Rhabdomyosarcoma	4-25
Wegener granulomatosis	3.5-12
Hodgkin disease	1.3
Collagen vascular disease	2
Primary or metastatic central nervous system tumor	1.3-1.7
Organ transplantation	
Heart-lung/lung	6.5-43
Heart	2-41
Renal	0.6-14
Liver	3-11
Allogeneic bone marrow	5-16

*Patients not receiving prophylaxis.

Table 36-2 Noninfectious Processes Complicating or Simulating Pneumonia

Process	Association
Chemical pneumonitis	Aspiration syndromes, smoke inhalation
Immune-mediated infection	Hypersensitivity pneumonitis, collagen vascular disease
Atelectasis	Reactive airways disease, endobronchial obstruction
Hemorrhage	Hemosiderosis, thrombocytopenia, coagulopathy, infection (*Aspergillus,* cytomegalovirus [CMV]), drug therapy (retinoic acid)
Pulmonary embolus	Condition secondary to intravascular abnormalities
Pulmonary edema	
Cardiogenic	Anthracycline cardiotoxicity, sepsis, myocarditis
Noncardiogenic	Acute respiratory distress syndrome, pancreatitis, fluid overload
Drug-induced lung injury	Chemotherapy agents, azathioprine
Radiation pneumonitis	Radiation treatment 6-8 wk previously
Leukostasis	Hyperleukocytosis, use of amphotericin B, transfusions of white blood cells
Leukemia, lymphoma	Active disease
Lymphocytic interstitial pneumonitis (LIP)	HIV infection in children
"Idiopathic pneumonitis"	Allogeneic bone marrow transplant
Other	Thymus, sequestration, tumor

organisms. Neutrophils are present in the lung in small numbers but can be rapidly recruited from the vascular compartment via a variety of chemotactic factors produced by complement activation or secreted by macrophages. A reduction in the number of circulating neutrophils is a major cause of pneumonias in immunocompromised hosts. Chronic granulomatous disease, neutrophil motility disorders, and other forms of phagocytic dysfunction also lead to pulmonary infections.

SECRETORY FACTORS

Macrophages secrete a number of important cytokines, such as tumor necrosis factor-alpha (TNF-α) and interleukin-1, which have local immunomodulating effects within the lung and systemic effects such as fever and shock. Nonspecific antibacterial defenses such as lysozyme and surfactant proteins may also be important when altered by lung injury.

Pathogenesis: Common Causes of Pneumonia in the Immunocompromised Host

NONINFECTIOUS PULMONARY DISEASE

Immunocompromised patients are at risk for a variety of noninfectious complications that simulate infection and complicate the diagnostic work-up (Table 36-2).

INFECTIOUS PNEUMONIAS

Viruses

HERPESVIRUSES

The herpesviruses that cause infectious viral pneumonia are cytomegalovirus (CMV), varicella-zoster virus (VZV), herpes simplex virus (HSV), and human herpesvirus type 6 (HHV-6).

Cytomegalovirus. CMV is a herpesvirus that commonly infects both neonates and older immunocompromised children.[23,32] Whether the virus results in disease depends on the age and the immune status of the infected individual. The organism can be transmitted through an infected birth canal and via breast milk, saliva, and blood (through infected white cells). Both humoral and cellular immune mechanisms are important in establishing protection against CMV. Individuals who are CMV negative before acquired immunosuppression resulting from organ or marrow transplantation and who acquire the virus by transfusion are particularly at risk for disease. CMV-positive individuals who are then immunosuppressed also run a significant risk for "reactivation" pneumonia.

CMV-infected cells typically contain nuclear inclusions that are deeply basophilic and surrounded by a clear halo, giving the "owl's eye" appearance (Fig. 36-1). Typically, inclusions are seen in alveolar cells. The pathologic situation varies from small hemorrhagic nodules scattered throughout the

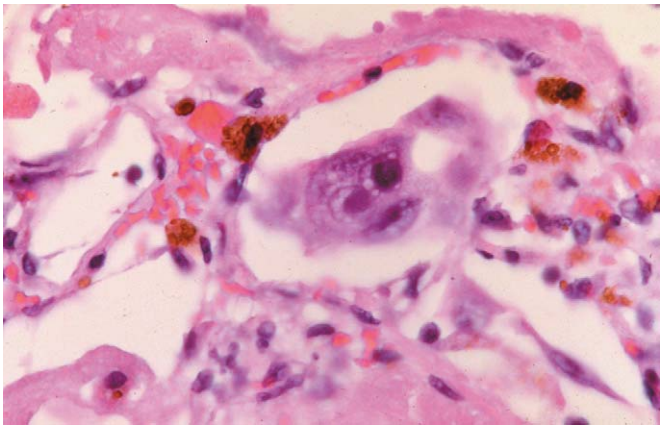


Figure 36-1 Lung biopsy from cytomegalovirus (CMV) pneumonia showing typical "owl's eye" inclusion.

lung and surrounded by relatively normal lung to diffuse alveolar damage or chronic interstitial pneumonitis.

Unless they acquire the virus before birth, most infants infected with CMV are asymptomatic, although occasional cases of protracted pneumonia have been reported. The major risk factors for CMV pneumonia include AIDS, congenital immunodeficiencies, and organ transplants, particularly kidney, bone marrow, and heart-lung. The radiographic pattern of the pneumonia is usually a diffuse reticulonodular pattern that is less alveolar in pattern than PCP. Approximately 50% of patients with aplastic anemia or hematologic malignancy treated by allogeneic marrow transplantation develop CMV infection, and CMV pneumonia had a 90% mortality rate in this population before the availability of antiviral therapy. CMV frequently is found as a co-pathogen with other opportunistic organisms, including *P. jiroveci* and *Aspergillus* species, particularly in patients with AIDS.

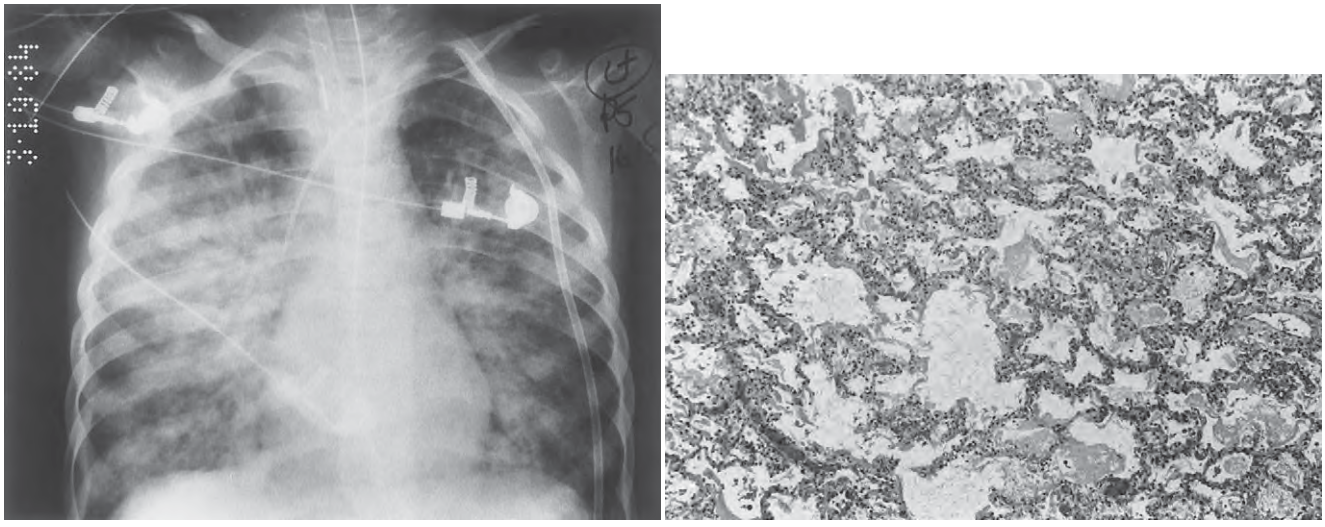
The diagnosis of CMV pneumonia is usually made by demonstrating typical inclusions in lung tissue. The isolation from the urine is not sufficient evidence that CMV is the cause of the pneumonia. Recently, immunofluorescence, deoxyribonucleic acid (DNA) hybridization, and shell-vial culture have been combined to provide rapid diagnosis of CMV infection from bronchoalveolar lavage fluid.[33-35] Although highly sensitive, the results from such techniques must be interpreted cautiously because CMV can be detected in asymptomatic individuals.

The use of CMV-negative blood products reduces the incidence of CMV pneumonia in seronegative but not seropositive recipients of transplants. Polymerase chain reaction (PCR) for CMV has been used in recipients of bone marrow transplants in an attempt to predict the development of CMV disease. PCR had excellent negative predictive value but a positive predictive value of only 61%. Acute graft-versus-host disease (GVHD) is associated with CMV disease, as is the development of lymphopenia (predominantly CD4+ T cells) starting 49 days after transplant. PCR evidence of viremia and lymphopenia predicted CMV disease 100% of the time.[35] PCR detection precedes culture isolation of CMV by 1 week, and the organism can be detected longer with PCR than with culture. Lack of PCR resolution or a positive culture has a positive predictive value of 60% for the development of CMV disease in recipients of bone marrow transplants.

Varicella-Zoster Virus and Herpes Simplex Virus. VZV and HSV are DNA viruses that typically cause benign infections of the skin and mucous membranes.[6,22] However, in certain groups (including neonates; patients with cancer, AIDS, and congenital defects of cell-mediated immunity; and recipients of bone marrow transplants), VZV and HSV can lead to visceral dissemination and pneumonia. In patients with cancer, pneumonitis occurs in 85% of cases of visceral dissemination and is the principal cause of death. Before the availability of specific antiviral therapy, the VZV pneumonitis mortality rate was 85%. Pneumonitis is much less common with reactivation of herpes zoster, but it is a potentially serious infection in recipients of bone marrow transplant. HSV is a less common cause of dissemination in oncology patients but is a significant infection in neonates.

The clinical presentation is nonspecific and includes fever, cough, dyspnea, and chest pain. Patients with VZV who have an increasing number of skin lesions, abdominal or back pain, or persistent fevers are at high risk for dissemination and pneumonia. HSV pneumonitis may be more subtle in its presentation, and pneumonitis can occur in the absence of mucocutaneous lesions in newborns and recipients of bone marrow transplants. Chest radiographs of herpesvirus pneumonias typically show ill-defined nodular densities scattered through both lung fields, often beginning at the periphery (Fig. 36-2A). These nodules progress and coalesce into extensive infiltrates. Secondary infections such as staphylococcal pneumonia were more commonly seen in the era before antibiotics. Microscopically the infection involves the alveolar walls, blood vessels, and small bronchioles (see Fig. 36-2B). Electron microscopy shows intranuclear inclusions of herpesvirus. Hemorrhage, necrosis, and extensive alveolar edema are seen in severe areas of involvement. The trachea and large bronchi are often involved.

Human Herpesvirus-6. HHV-6 is a DNA virus that is the etiologic agent for roseola. It persists in normal hosts and can



A B

Figure 36-2 Varicella-zoster virus (VZV) pneumonia. **A,** Chest radiograph. **B,** Histologic section.

be isolated from lymphocytes and other sites. In the abnormal host, reactivation can lead to fever, hepatitis, bone marrow suppression, and pneumonia.[36-38]

Cone and associates[37] described identification of HHV-6 by PCR in all of 15 lung biopsy specimens from patients with idiopathic pneumonitis after bone marrow transplant; serologic studies also supported its role in pneumonitis after transplant. Further studies are documenting other clinical situations in which HHV-6 causes disease in immunocompromised populations, including renal transplant and AIDS.[38,39]

Adenovirus

Adenovirus is a DNA virus that commonly causes community-acquired lower respiratory disease. Serotypes 1, 2, and 5 are common causes of sporadic respiratory disease, and types 3 and 7 are associated with epidemics of bronchiolitis and pneumonia in the general population. In immunocompromised patients, adenovirus is one of the most important viral causes of serious morbidity and mortality.[40-43] Adenoviral pneumonia acquired by immunocompromised patients often originates as a nosocomial infection from infected members of the hospital staff.

Adenovirus typically causes fever, pharyngitis, cough, and conjunctivitis. Pneumonia is usually mild in normal hosts, but rapid progression can occur in immunocompromised patients with necrotizing bronchitis and bronchiolitis (Fig. 36-3). The radiographic picture is nonspecific and resembles that of other causes of diffuse pneumonia. The diagnosis is usually made by lung biopsy or brushings demonstrating typical adenoviral inclusions or by culture, but the diagnosis may be delayed by the institution of empirical antibiotic and antifungal therapy and a delay in open biopsy. Viral titers may provide a delayed diagnosis. Failure of diffuse pneumonia to respond despite therapy, particularly when there have been epidemics of typical acute respiratory disease in the community or when there is associated renal or liver involvement, should raise the strong possibility of adenovirus.

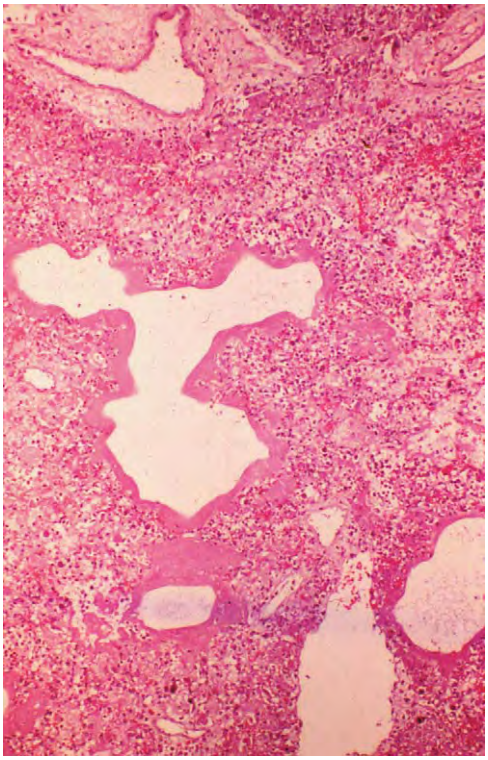


Figure 36-3 Adenovirus pneumonia: histologic section showing severe interstitial pneumonia in a recipient of a bone marrow transplant.

Fungi

Aspergillus *Species*

Aspergillus is a group of ubiquitous fungal organisms found in soil and other settings, including the hospital. *Aspergillus fumigatus* is the most common cause of pneumonia in immunocompromised hosts, but other pathogenic species include *Aspergillus niger* and *Aspergillus flavus*. In tissue, the organisms form septate hyphae with regular 45-degree dichotomous branching that is best seen with methenamine-silver staining (Fig. 36-4).

Aspergillus species causes both acute invasive pulmonary aspergillosis and a more chronic necrotizing form. The former occurs most commonly in patients undergoing cancer therapy as well as other immunocompromised patients such as those with aplastic anemia. *Aspergillus* infection of the lung is often preceded or accompanied by invasion of the nose and paranasal sinuses in susceptible hosts. In a series on invasive *Aspergillus* infection in children (24 definite cases, 15 probable), Walmsley and colleagues[44] confirmed observations in other populations, including those with the major risk factors of prolonged neutropenia, concurrent chemotherapy, and steroid therapy—as well as therapy with broad-spectrum antibiotics. The common occurrence of cutaneous aspergillosis in this pediatric series was also noteworthy. A total of 15 of the 16 patients with pulmonary disease in this series died, and premorbid diagnosis was often difficult. In the lungs, *Aspergillus* species can cause tracheobronchitis, pneumonia, abscesses and cavity formation, and diffuse interstitial pneumonia. The organisms often extend along blood vessels, and nodular lesions of necrosis surrounded by air often develop within an area of pneumonia, leading to the typical air crescent sign.

Computed tomography of the chest is often very helpful in patients with disseminated fungal disease caused by *Aspergillus* species and other fungal pathogens. In a review of computed tomography findings from the chests of 14 pedi-

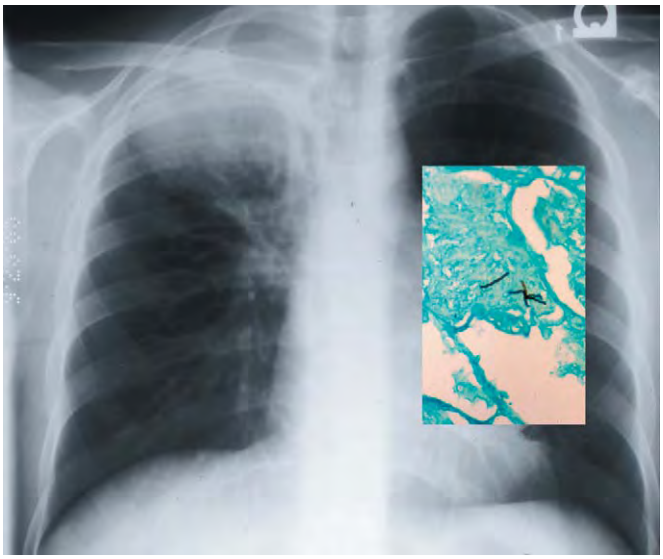
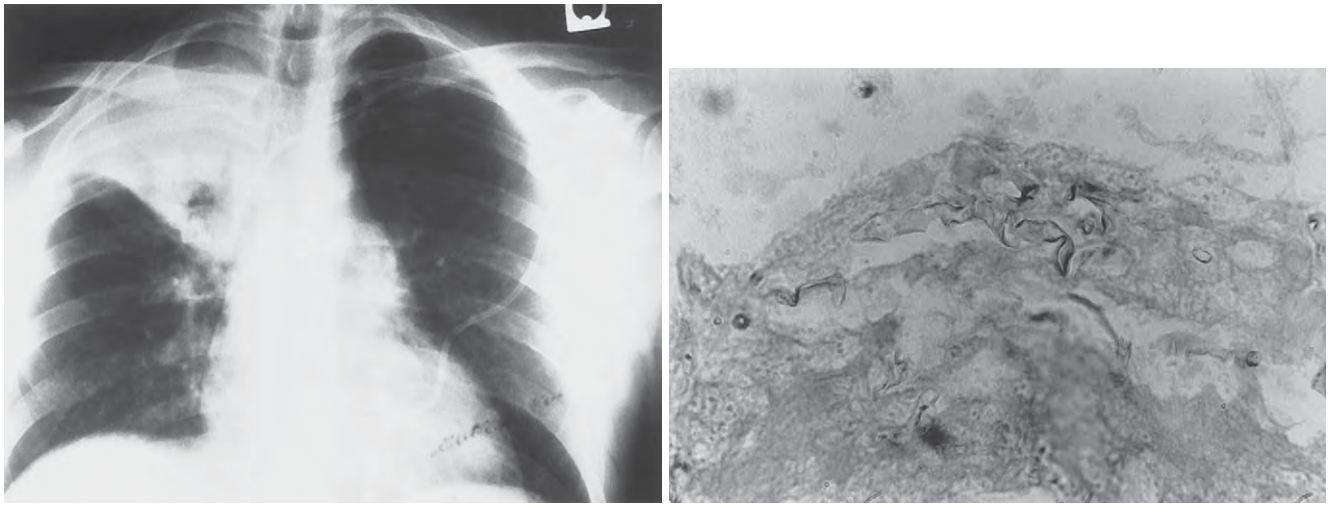


Figure 36-4 *Aspergillus* species: chest radiograph and histologic section (inset). (Grocott-Gomori methenamine-silver nitrate stain.)



A B

Figure 36-5 *Mucor* species: Chest radiograph showing a cavitary lesion in the right upper lobe **(A)** with histologic section **(B)**.

atric patients with malignancy and pulmonary fungal disease caused by *Aspergillus* species, two basic types of involvement were seen: multiple nodules and fluffy masses. Cavitation occurred in 6 of 14 patients.[45] Computed tomography is more sensitive than plain radiographs and can reveal early evidence of cavitation.

Diagnosis of *Aspergillus* pneumonia is generally made by tissue examination. *Aspergillus* organisms can be isolated from bronchoalveolar lavage fluid in approximately 50% of cases, and needle aspiration biopsy of suspected lesions can also demonstrate typical fungal lesions. Isolation of the organism from a nasal culture in a patient with typical clinical risk features (e.g., prolonged neutropenia, progressive nodular infiltrates, cavitary lesion) may be helpful, but negative cultures do not exclude *Aspergillus* infection.

Mucor, Rhizopus, *and* Cunninghamella *Species*. Mucormycosis includes fungal disease caused by a variety of species in the genera *Mucor, Rhizopus,* and *Cunninghamella*. In tissues, these organisms are differentiated from *Aspergillus* organisms by their broad, nonseptate hyphae that branch at angles up to 90 degrees and that have an appearance of twisted ribbons (Fig. 36-5B). *Rhizopus* organisms cause disease only in patients with underlying disease. In adults, it is associated with chronic acidosis states, such as diabetes mellitus with ketoacidosis. Most pediatric cases of pneumonia occur in the oncology population, in whom the organism is found in the same risk groups as *Aspergillus* species.

Pneumonia caused by *Rhizopus* organisms is usually an insidious segmental pneumonia that is slowly progressive despite antifungal therapy. Persistent fever, chest pain, hemoptysis, and weight loss are typical. Cavitation may occur, and dissemination to the brain and other sites occurs because of the propensity of the organism to invade the blood vessels (see Fig. 36-5). Death may occur suddenly and is caused by massive pulmonary hemorrhage, mediastinitis, or airway obstruction (Fig. 36-6). The specific diagnosis usually depends on demonstration of the organism in open, transbronchial, or needle aspiration lung biopsy specimens.

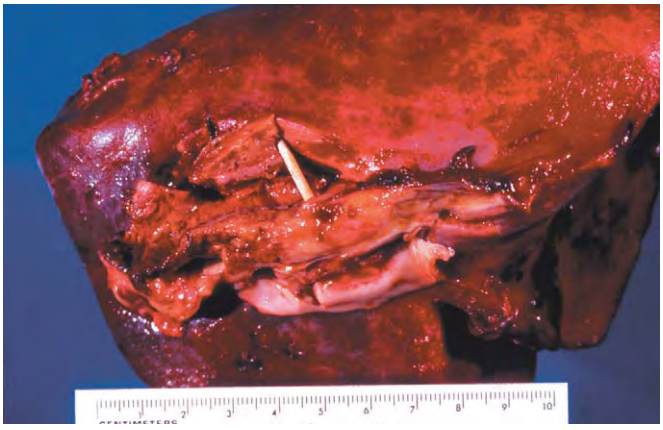


Figure 36-6 Fatal mucormycosis due to invasion of mediastinal vessels from primary pulmonary lesion.

Candida *Species*. Although important as a cause of fungal sepsis and secondary hematogenous pulmonary involvement, primary *Candida* pneumonia is unusual.[46] *Candida albicans* and *Candida tropicalis* are the most important causes of fungal sepsis and secondary pulmonary involvement.[47] Patients with HIV infection, primary immunodeficiencies, and prolonged neutropenia are at greatest risk, but other predisposing conditions include diabetes, corticosteroid administration, treatment with broad-spectrum antibiotics, intravenous hyperalimentation, and venous access devices. In tissue, silver stains show oval budding yeasts 2 to 6 μ in diameter with pseudohyphae. In primary *Candida* pneumonia, the prominent histologic features include bronchopneumonia, intra-alveolar exudates, and hemorrhage.

Histoplasma *and* Blastomyces *Species*. *Histoplasma capsulatum* and *Blastomyces dermatitidis* are ubiquitous soil fungi endemic to the eastern and southwestern United States. Histoplasmosis, a common infection, may be asymptomatic or lead to an acute pneumonia with fever, hilar adenopathy, and pulmonary infiltrates. Blastomycosis is a less common, more serious infection. Both can cause chronic granulomatous

pulmonary disease as well as disseminated disease. In the immunocompromised patient, including those with AIDS, the major risk factor is dissemination with pulmonary infiltrates, hepatosplenomegaly, fever, and adenopathy. Histoplasmosis is more common in the immunocompromised host than is blastomycosis.

Cryptococcus neoformans. *Cryptococcus neoformans* is a yeast that causes protean clinical manifestations in immunocompromised patients, particularly those with AIDS. The meninges, endocardium, skin, and lymph nodes are often involved. The lungs are the portal of entry for *C. neoformans*, and pulmonary involvement may be minimal if dissemination occurs quickly. Pneumonia is typically accompanied by chest pain, fever, and cough. Pulmonary disease with *Cryptococcus* organisms is rarer in pediatric patients with AIDS than in adults.

Rare Fungi. Non-*Candida* fungal infections are commonly seen after bone marrow transplantation with the respiratory tract being involved in 95% of single-organ infections and 84% of disseminated infections.[48] Several recent trends have been noted in fungal infections caused by rarer fungal pathogens, including saprophytic fungi[49] (Box 36-2). These fungi cause skin and soft tissue infections and occasionally invade the lungs and sinuses. They are often difficult to diagnose, and their response to therapy with amphotericin B may be very poor. Fungal infections that are associated with a high mortality rate include those caused by *Chrysosporium*, *Fusarium*, *Mucor*, and *Scopulariopsis*.

Pneumocystis jiroveci. *P. jiroveci* (formally *carinii;* some reserve *P. carinii* for the similar organism occurring in the immunosuppressed rat) has been an organism of uncertain taxonomy and was regarded as a parasite because of its resemblance to cystic spore-forming protozoa.[50-52] More recent studies using DNA hybridization methods place *P. jiroveci* as a fungus.[53,54] The organism exists in three forms in tissues: the trophozoite, the sporozoite, and the cyst (Fig. 36-7A). The trophozoites are 2 to 5 μ in diameter and stain best with Giemsa stains but are not visible with Grocott-Gomori methenamine-silver nitrate or toluidine blue O stains, which stain the 5- to 8-μ cyst forms. The cysts are spherical or cup shaped and often appear to contain up to eight 1- to 2-μ sporozoites within the cyst wall (see Fig. 36-7B). The organism cannot be cultured from routine clinical specimens and must be identified in tissue, sputum, or alveolar lavage fluid.

The organism is found primarily within the alveoli, although the extrapulmonary occurrence of organisms has been commonly reported in patients with AIDS. The trophozoites appear to attach to type I cells through surface glycoproteins related to lectins and there undergo encystation[55,56] (Fig. 36-8). This interaction directly or through soluble factors leads to cell injury. The alveoli of lungs infected with *P. jiroveci* are filled with trophozoites and protein-rich debris, and the altered permeability produced by the organism contributes to the development of pulmonary edema and surfactant abnormalities, which lead to stiff lungs.[57,58]

BOX 36-2 Unusual Fungal Infections with Pulmonary Involvement

Aspergillus, Candida, and *Mucor* are the primary pathogens.
Primary *Candida* pneumonia (as opposed to secondary pneumonia after septicemia) is rare.
Infection by *Candida* organisms other than *C. albicans* has become increasingly important (primarily fungemia with secondary pulmonary involvement); species include *C. tropicalis*, *C. parapsilosis, C. krusei,* and *C. glabrata* (formerly *Torulopsis glabrata*).
Emerging infections and their pathogens follow:
Phaeohyphomycoses
—*Curvularia* species: sinusitis
—*Bipolaris, Exserohilum, Alternaria* species: clinical presentation similar to that of *Aspergillus* species
Hyalohyphomycoses
—*Fusarium* species: sinusitis or rhinocerebral disease
—*Scopulariopsis* species
—*Pseudallescheria boydii*: sinusitis, pneumonia
—*Trichosporon* infection: risk factors similar to those of *Candida* species (primarily hematogenous)
—*Malassezia furfur:* hematogenous infection

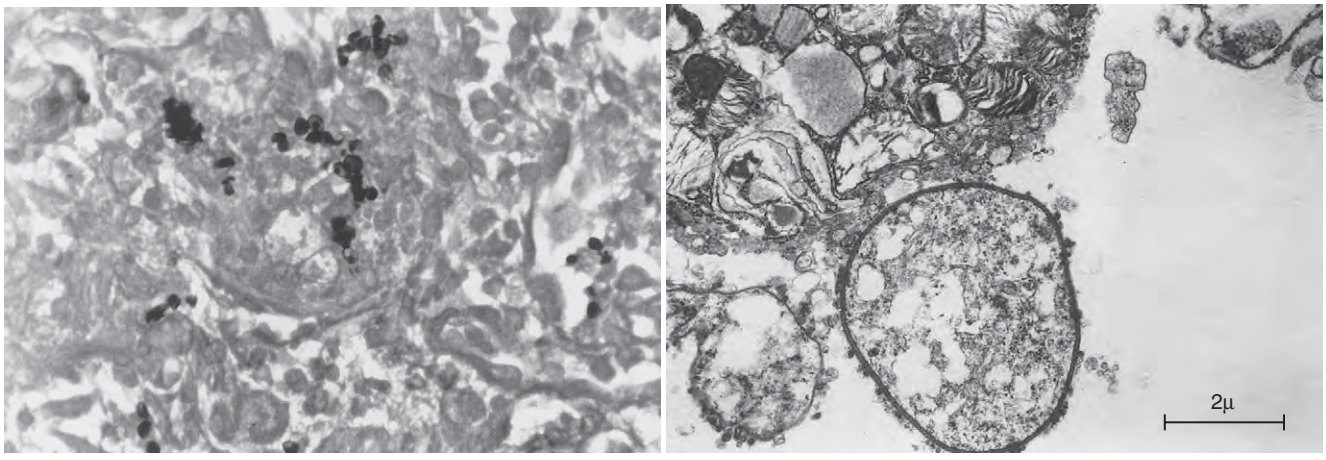


Figure 36-7 ***Pneumocystis jiroveci*. A,** Histologic section (Grocott-Gomori methenamine-silver nitrate stain). **B,** Electron microscopy.

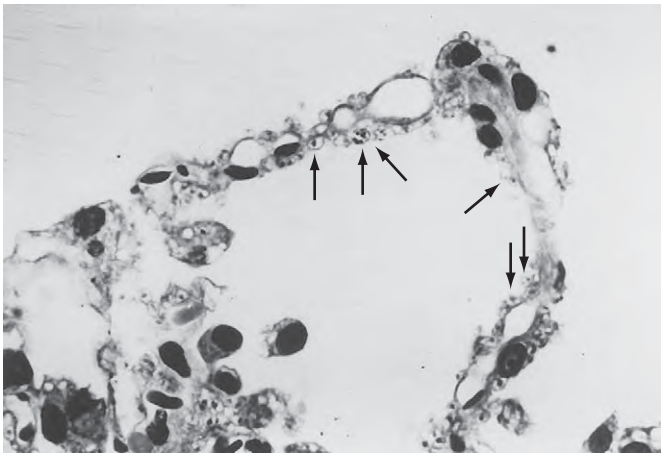


Figure 36-8 ***Pneumocystis jiroveci.*** Alveolar thin section showing cysts (*arrows*) lining the alveolar wall.

The earliest reports of PCP were in epidemics occurring in severely malnourished infants, a type rarely seen in developed countries. The majority of PCP cases occurs in infants and children with congenital or acquired immunodeficiencies. Latent infection with *P. jiroveci* was thought to be common because serologic studies indicated that 40% of children have antibodies to the organism. Based on this finding, disease was thought to be caused primarily by reactivation of a primary infection, but more recent studies using sensitive PCR and fluorescent antibody tests have failed to demonstrate *P. jiroveci* in autopsy or BAL fluid specimens from normal lungs. More likely, disease in immunocompromised patients originates from an environmental source, including other infected patients.[59]

In patients with congenital immunodeficiency or malignancy, the clinical features of PCP are nonspecific and include dyspnea, tachypnea, fever, and mild cough. Hypoxemia with a mild respiratory alkalosis is common, but cyanosis occurs later. The most common chest radiographic findings are diffuse bilateral infiltrates commencing in the perihilar regions.

Since 1980, the most common underlying host defect in patients with *P. jiroveci* is AIDS. The clinical features of PCP in the pediatric AIDS population differ from the pneumonias seen in other populations. In patients with AIDS, the duration of symptoms is typically longer, and the presentation is more insidious. Hypoxemia is less intense. Organisms appear to be abundant in patients with AIDS and can usually be identified in sputum, bronchoalveolar lavage fluid, or even gastric lavage samples. Other superinfections (such as CMV) and pulmonary complications are often present in patients with AIDS, however, and it may be difficult to know what role these infections play in the symptoms. In patients with AIDS, *P. jiroveci* is more likely to spread to the nodes, spleen, bone marrow, and other sites. These patients are more likely to have atypical radiographic images, including lobar pneumonias, unilateral disease, and solitary nodules, although atypical radiographic presentations can also occur in other host disorders.

Bacteria

The bacterial pathogens associated with pneumonia in immunocompromised hosts include those typically associated with pneumonia in children, including *Staphylococcus aureus*, *Haemophilus influenzae* type b, and *Streptococcus pneumoniae*. They may cause chronic suppurative lung disease and are discussed further in Chapter 35.

Gram-Positive Organisms. *Listeria monocytogenes* is a gram-positive rod that causes primarily septicemia with subsequent pulmonary involvement in immunocompromised patients. Corynebacteria (commonly called *diphtheroids*) are gram-positive bacilli or coccobacilli that exist as saprophytes on the mucous membranes and skin. C. *jeikeium*, a strain from this group, causes sepsis and pneumonia in oncology patients and recipients of bone marrow transplants.[60]

Gram-Negative Organisms. *Pseudomonas aeruginosa* is an important cause of pneumonia in immunocompromised children, particularly hospitalized patients. In a large series of 98 children with bacteremia caused by *P. aeruginosa*, 21% had evidence of pneumonia, and the overall mortality rate from *P. aeruginosa* infection was 27%. Significant risk factors included neutropenia and perineal skin lesions.[61] Other gram-negative organisms that cause pneumonia include *Legionella pneumophila* and *Capnocytophaga* species.

Mycobacteria

Until recent years, the incidence of pulmonary disease caused by *Mycobacterium tuberculosis* had been declining. With the onset of the AIDS epidemic, however, disease caused by *M. tuberculosis* and atypical strains such as *Mycobacterium avium-intracellulare* has increased.[62] A detailed discussion of mycobacterial infections in patients with AIDS is beyond the scope of this chapter but is covered in Chapters 37 and 39.

Parasites and Other Organisms

Toxoplasma gondii *and* Cryptosporidium parvum. *Toxoplasma gondii* and *Cryptosporidium parvum* are both parasites. *T. gondii* infects cats and other animals and secondarily infects man, causing congenital toxoplasmosis during intrauterine infection; primary infection later in life usually causes only lymphadenopathy and mild systemic symptoms. C. *parvum* infects a variety of hosts and often occurs with waterborne outbreaks.[63]

In patients with AIDS, *Toxoplasma* primarily causes central nervous system disease but can cause disseminated disease with secondary pulmonary involvement. C. *parvum* causes severe diarrhea, but disseminated disease with pulmonary involvement can occur.

CLINICAL FEATURES

Patterns of Pneumonia

Recurrent or Persistent Pneumonia. Often the first clue to an abnormal host disorder is the development of recurrent or persistent pneumonia. Patients usually have persistent or recurrent radiologic evidence of pneumonia that is associated with the typical signs of infection such as fever and tachypnea. It is important to note whether these infiltrates clear completely after therapy, whether they involve one lobe or more than one lobe, and whether they are associated with other radiologic findings such as hyperinflation or situs inversus. The differential diagnosis of recurrent or persistent pneumonia is extensive and includes many underlying causes other than immunodeficiency.[64]

Severe Pneumonia with Usual Infections. The patient with an abnormal ability to deal with infection often has an atypical course when that patient is infected with a "usual" childhood respiratory pathogen. Varicella, influenza, parainfluenza, measles, and respiratory syncytial virus (RSV) are all potentially devastating pulmonary infections in immunocompromised hosts.[65-67] Although adenovirus is capable of causing severe pneumonia in any child, it is particularly devastating in immunocompromised hosts and possibly exceeds VZV and *P. jiroveci* as a cause of fatal pneumonias in high-risk populations such as recipients of bone marrow transplants.[68] Suppurative bronchitis related to common bacterial pathogens *H. influenzae* and *S. pneumoniae* infection is common in immunoglobulin deficiency.

Opportunistic Pneumonias. The "opportunistic" pathogens are those typically not seen except in the patient with altered host defense. PCP is probably the best example of pulmonary infection caused by an opportunistic pathogen and occurs in a variety of immunocompromised patients, including those with AIDS, T cell disorders, and agammaglobulinemia, pediatric oncology patients; and patients receiving high doses of corticosteroids.

Pathogens and Underlying Host Disorder

Another useful way to consider the types of pulmonary infections that occur in immunocompromised hosts is by considering the underlying host disorder. Childhood cancer therapy, bone marrow transplant and organ transplants, primary immunodeficiencies, and AIDS are each associated with specific pathogen groups (Table 36-3).

CHILDHOOD CANCER

Patients with childhood cancer are at high risk for respiratory infections for a variety of reasons in addition to the immunosuppressive effects of chemotherapy and radiation (Box 36-3). Among childhood cancer groups, there are differing risks for various pathogens.

The major risk factor for pneumonia in patients with leukemia is chemotherapy-induced neutropenia. Because patients with nonlymphocytic leukemia undergo the most intensive chemotherapy, they are at greatest risk for developing pneumonia. Bacterial pneumonias are most common, but RSV, adenovirus, and enteroviruses are also significant causes of pneumonia in patients with leukemia. Fungal pneumonias occur in patients with prolonged neutropenia, hospitalization, and broad-spectrum antibiotic therapy. *Aspergillus* species and Zygomycetes (*Mucor*, *Rhizopus*, and *Cunninghamella* species) are the two most common fungal pulmonary patho-

BOX 36-3 Predisposition to Pneumonia in Childhood Malignancy

Granulocytopenia
Mucosal disruption: skin, gut, lung
Cellular immune dysfunction
Humoral defects
Splenectomy
Mechanical: catheters
Malnutrition
Radiation
Graft-versus-host disease
Administration of corticosteroids

Table 36-3
Typical Pulmonary Pathogens Associated with Immune Disorders

	Pathogens		
	Bacterial	**Fungal**	**Viral, Protozoal, or Other**
Neutropenia			
Chronic	*Haemophilus influenzae, Streptococcus pneumoniae, Staphylococcus aureus, Klebsiella* spp	—	—
Acute	*S. aureus*	—	—
Prolonged hospitalization	Gram-negative organisms, including *Pseudomonas* spp	*Candida* spp, *Aspergillus* spp, *Mucor* spp	—
Agammaglobulinemia, hypogammaglobulinemia	*S. pneumoniae, H. influenzae, Pseudomonas* spp	*Aspergillus* spp	*Pneumocystis jiroveci*
Congenital T cell disorders	*Legionella* spp, *Nocardia* spp, *Listeria* spp, Mycobacteria infections (including atypical strains), *Salmonella* spp	*Candida* spp, *Cryptococcus* spp	Cytomegalovirus (CMV), *P. jiroveci,* Varicella-zoster virus (VZV), herpes simplex virus (HSV)
AIDS	*Mycobacterium tuberculosis, Mycobacterium avium-intracellulare*	*Cryptococcus* spp	CMV, *P. jiroveci, Toxoplasma* spp
Complement deficiencies	Virulent encapsulated spp (e.g., *S. pneumoniae, H. influenzae*)	—	—
Immunosuppressive therapy (e.g., renal, liver, lung transplant)	*S. aureus, Listeria* spp, *Mycobacterium tuberculosis*	*Aspergillus* spp, *Mucor* spp, *Histoplasma* spp	CMV, *P. jiroveci,* VZV, *Toxoplasma* spp, HSV, *Cryptococcus* spp
Bone marrow transplant			
Early (<30 days)	*Pseudomonas* spp, other gram-negative and gram-positive spp	*Candida* spp	—
Late (>30 days)	*S. aureus*	*Aspergillus* spp	CMV, *Toxoplasma* spp, VZV, *P. jiroveci,* Epstein-Barr virus, adenovirus
Late (>100 days)	Encapsulated gram-positive (*H. influenzae, S. pneumoniae*)	—	VZV

Table 36-4
Pulmonary Complications after Bone Marrow Transplant

Pulmonary Host Defense	Association	Organisms	Other Pulmonary Disorders
Pretransplant	Neutropenia, chemotherapy, prolonged use of antibiotics, iatrogenic procedures	Bacteria, fungi	—
Early post-transplant (<1 mo)	Neutropenia, mucositis, use of antibiotics, radiation	Bacteria (particularly gram-negative), HSV, RSV, *Candida* spp, *Aspergillus* spp,	Pulmonary edema, ARDS
Later post-transplant (1-4 mo)	Acute GVHD, failed engraftment	CMV, adenovirus, PC, *Aspergillus* spp, *Mucor* spp, HHV-6, EBV	Interstitial pneumonia, lymphoproliferative syndromes
Late post-transplant (>4 mo)	Chronic GVHD, poor antibody response	VZV, encapsulated gram-positive bacteria, PC	Bronchiolitis obliterans, BOOP

ARDS, acute respiratory distress syndrome; BOOP, bronchiolitis obliterans–organizing pneumonia; CMV, cytomegalovirus; EBV, Epstein-Barr virus; GVHD, graft-versus-host-disease; HHV-6, human herpesvirus type 6; HSV, herpes simplex virus; PC, *Pneumocystis jiroveci;* RSV, respiratory syncytial virus; VZV, varicella-zoster virus.

gens Patients with lymphoma are at risk for pneumonia because of neutropenia during therapy and because of a variety of nonspecific immunologic defects, including anergy.[69,70] Patients with Hodgkin disease are often infected with *Toxoplasma gondii* and fungi such as C*ryptococcus neoformans*. The mediastinal adenopathy and lung nodules commonly seen in these children at diagnosis often require extensive evaluation to differentiate lymphoma from granulomatous pulmonary infections such as tuberculosis and histoplasmosis.

TISSUE TRANSPLANTATION: BONE MARROW AND SOLID ORGAN

The types of pulmonary complications in allogeneic bone marrow transplant vary with the period after transplantation (Table 36-4). Immediately after transplantation, patients are neutropenic and at risk for bacterial pneumonias caused by *P. aeruginosa* and *S. aureus*. As the transplant becomes established and the neutrophil count rises, acute GVHD becomes a serious concern. Immunosuppressive therapy for GVHD with corticosteroids or cyclosporine A adds to the risk of pneumonia caused by viral pathogens (CMV, herpes simplex virus [HSV], adenovirus) as well as *P. jiroveci* and other fungi.

If engraftment fails and prolonged neutropenia occurs, the risk of fungal pneumonia rises significantly. Idiopathic interstitial pneumonias also occur during this later time, possibly because of radiation or chemotherapy.[71] Late (more than 4 to 6 months after the transplantation) causes of pneumonia include *H. influenzae* and *S. pneumoniae* and are associated with persistent humoral immune deficits to these encapsulated organisms. A frequent cause of morbidity in the late transplant period is BOOP, which is thought to be an immunologic disorder related to chronic GVHD.[72-76] The frequency of this complication in pediatric recipients of bone marrow transplants is not clear, and it may be less common than in adult recipients.[74] Infection may play a role in provoking or exacerbating chronic lung damage caused by BOOP.[75,76]

CMV infection remains a major cause of morbidity and mortality in pediatric recipients of bone marrow transplants. CMV occurs more frequently in recipients of allogeneic bone marrow transplants than in those receiving antologous transplants (12.4% versus 3.3%) and in patients who are seropositive before transplant or who receive marrow from seropositive donors.[77] The incidence increases with age and is 1.3% from birth to 9 years of age and 2.1% from 10 to 19 years of age. The mortality rate of CMV pneumonitis was greater than 90% before the use of ganciclovir and immunoglobulin therapy, which must be started early to be effective. In one series, only 10 of 75 recipients of bone marrow transplants with CMV pneumonitis survived for a long time, and of these, 9 were ventilator independent at the initiation of therapy with ganciclovir and immunoglobulin.[78] Studies of risk groups for CMV pneumonitis in a group of 62 allogeneic pediatric and adult recipients of transplants confirmed a low incidence in seronegative recipients who received grafts from seronegative donors and screened blood products. T cell depletion to prevent GVHD in a CMV-seropositive recipient whose tissue was grafted from a nonimmune donor is associated with a high risk of CMV interstitial pneumonia.[79] Fungal infections, including invasive pulmonary disease, are another major cause of morbidity and mortality in the bone marrow transplant population. Prolonged neutropenia is a major risk factor for the development of fungal infections.

The development of pulmonary infections after renal and other solid organ transplants is attributable to chronic immunosuppression with cyclosporine A and corticosteroid therapy.[80] CMV is the most significant pulmonary infection in recipients of all transplants, and in recipients of heart-lung transplants, *P. jiroveci* and *Toxoplasma* infections are also quite common.[81,82] In pediatric recipients of 58 consecutive renal transplants who were followed for up to 72 months, CMV infection occurred in 40% and CMV disease in 15% (1 death).[83] The highest risk for CMV infection occurs in the first 12 weeks after the transplantation, and donor CMV seropositivity, regardless of recipient CMV serostatus, is significantly associated with CMV infection.

Gram-negative and fungal infections are the most common pulmonary complications in recipients of liver transplants. They occur primarily in the first month after transplantation.[84]

PRIMARY IMMUNODEFICIENCY

In patients with common variable immunodeficiency and X-linked agammaglobulinemia, repeated bacterial pneumonias are most common, and *P. jiroveci* is occasionally seen in patients with hypogammaglobulinemia.[85-88] Patients with

congenital T cell disorders, including severe combined immunodeficiency, are at risk for most of the same opportunistic pathogens as patients with AIDS, including PCP.

Fungi, primarily *Aspergillus* species, and *S. aureus* are the most common lung infections in children with chronic granulomatous disease. Extensive lung destruction and hilar adenopathy are common in these patients.[89-91] Patients with chronic mucocutaneous candidiasis, a T cell disorder, have persistent and recurrent *Candida albicans* infection of the mucous membranes and skin but 50% have recurrent bacterial pneumonias, and they are at risk for infections caused by other opportunistic pathogens, including *P. jiroveci*, *Nocardia*, and varicella-zoster virus pneumonias. Pulmonary complications, including bronchiectasis, empyema, and lung abscess, frequently occur.[91]

AIDS

The extensive list of pulmonary infections associated with AIDS includes *P. jiroveci*, CMV, bacteria, and atypical mycobacteria as major causes of pneumonia in this group[92] (Fig. 36-9).

Radiographic Presentation

Pneumonias in this population can be classified by the general appearance of the radiograph. Findings include diffuse alveolar and interstitial pneumonias, localized alveolar lobar or lobular pneumonias (which may involve more than one lobe), and nodular infiltrates (which may be cavitary or progress to frank lung abscess). The common causes of these general radiographic patterns are listed in Box 36-4, but it must be emphasized that radiographic appearances are often deceptive in immunocompromised hosts and are usually not helpful in making a specific etiologic diagnosis. The value of CT over plain radiography in this population is also clear. In neutropenic patients with unexplained fever and normal chest radiography, CT scans of the chest are frequently abnormal before plain radiographs and CT scans also can show early changes such as peripheral halo effects that can suggest a specific diagnosis (*Aspergillus* or similar fungi).

P. jiroveci is the prototypical organism associated with the radiographic pattern of diffuse interstitial and alveolar pneumonias (Fig. 36-10). Although the incidence of *P. jiroveci*

BOX 36-4 Causes of Radiologic Presentations

Diffuse Interstitial and Alveolar

Pneumocystis jiroveci pneumonia (PCP)
Cytomegalovirus (CMV)
Cryptococcus neoformans
Viruses (e.g., adenovirus)
Aspergillus species (rare)
Candida species (rare)

Lobar or Lobular

Bacteria
Nocardia species
C. neoformans
Aspergillus species
Mucor species
Mycobacteria
Viruses
Legionella species

Nodules, Cavities, or Lung Abscess

Bacteria (*S. aureus*, anaerobes)
C. neoformans
Mycobacteria
Nocardia species
Aspergillus species: "halo sign": nodules surrounded by a halo of ground glass attenuation of the lung, suggesting invasive fungal disease involving blood vessels
Legionella species
PCP (rare except in HIV)
Lymphocytic interstitial pneumonitis (reticulonodular)

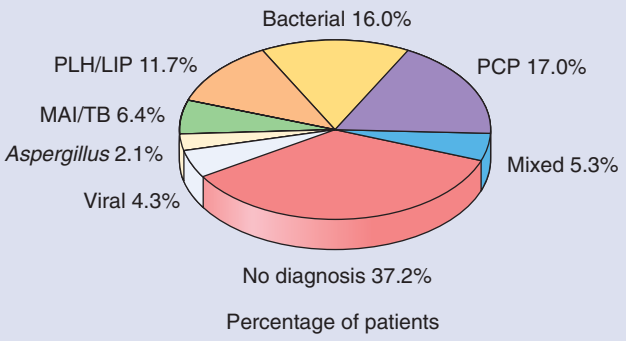


Figure 36-9 Causes of pneumonia in AIDS. LIP, lymphocytic interstitial pneumonia; MAI, *Mycobacterium avium intracellulare*; PCP, *Pneumocystis jiroveci* (*carinii*) pneumonia; PLH, pulmonary lymphoid hyperplasia. (From Marolda J, Pace B, Bonforte RJ, et al: Pediatr Pulmonol 10:231-235, 1991.)

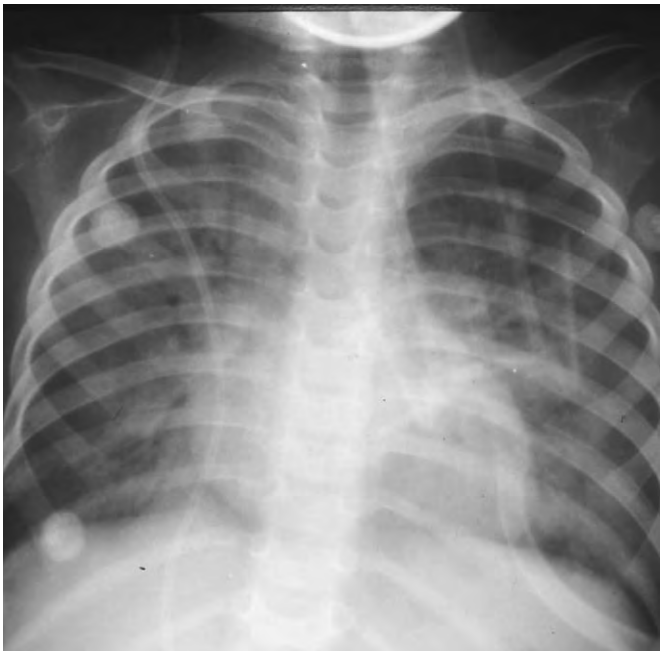


Figure 36-10 Chest radiograph of *Pneumocystis jiroveci* pneumonia.

infection has declined significantly in patient populations receiving prophylaxis, PCP remains the major pathogen associated with AIDS, and atypical radiographic appearances of *P. jiroveci* are common and include normal radiographs; radiographs showing cystic, unilateral, and granulomatous changes; and radiographs showing associated pleural disease.[92-95] The use of aerosolized pentamidine for PCP prophylaxis in AIDS may alter the radiographic presentation more toward upper lobe disease. This was thought to occur because of the preferential distribution of the medication to the lower lobes, but studies of drug levels suggest that other factors may be involved because medication levels are similar in both upper and lower lung zones despite larger numbers of organisms in the upper lung zones.[96] CMV is also associated with diffuse pneumonia in immunocompromised patients and is frequently seen in association with other infectious agents. Viral infections, including adenovirus and influenza, are also important causes of diffuse pneumonia.

Bronchopneumonias and lobar consolidation can occur in immunocompromised patients and are caused by the usual pathogens, such as *S. pneumoniae*, *H. influenzae*, and *S. aureus*. However, because the radiographic pathology is a product of the host's response to the organism, patients with abnormal host defenses often have an altered initial radiographic pattern.

Solitary pulmonary nodules, either unilateral or bilateral, are less common presentations of infection in most immunocompromised patients but do occur frequently in pediatric oncology patients. Although these most often represent fungal pneumonias, infections of other organisms, including *Nocardia* species, can also manifest as pulmonary nodules. The development of a lung abscess generally indicates a degree of host immunity sufficient to localize an infection. The most common cause of cavitary lesions in pediatric patients with cancer is fungal infection, especially with *Aspergillus* species. Both PCP and mycobacterial infections can be associated with cavitary disease in patients with AIDS.[94,95]

DIAGNOSIS

General Approach to Immunocompromised Children with Pneumonia

Although clinical information such as the general association of certain types of pulmonary pathogens with certain at-risk groups and general radiographic patterns may be useful, both approaches have limitations in the immunocompromised patient with pneumonia. Many noninfectious pulmonary processes also occur in this group, and the list of organisms causing pneumonia is extensive. Generally, empirical broad-spectrum antibiotic therapy must be started in patients with known immunodeficiency at the first sign of fever and often before the development of overt pneumonia. This often complicates subsequent diagnostic studies. The laboratory diagnosis of opportunistic pulmonary infections is a complicated and evolving field and the choice of diagnostic tests depends on the experience and skill of the clinical laboratory.[97]

Indirect Diagnostic Tests

The utility of various respiratory specimens for direct detection or culture of opportunistic infections is shown in Tables 36-5 through 36-8 and Box 36-5.

SPUTUM EXAMINATION AND CULTURE

Sputum samples are difficult to obtain in children younger than 10 years of age and when obtained, must be interpreted cautiously. Analysis of sputum produced by cough induced with the inhalation of hypertonic saline aerosols has been useful in diagnosing infection in older children with AIDS and PCP.[98] Gastric aspirates can be used in the younger child and are particularly helpful when the pathogen being consid-

Table 36-5
Specimens for Optimal Diagnosis of Pulmonary Infections

	Preferred Specimens for Direct Detection or Culture								
Specimen Type	**Bacteria**	***Legionella* species**	***Chlamydia* species***	***Mycoplasma* species***	***Nocardia* species**	**Fungi**	***Mycobacteria* species**	***Pneumocystis jiroveci***	**Viruses**
Expectorated sputum	++	+	–	+	+	+	++	–	+
NaCl-induced sputum	–	–	–	–	+	–	++	++	0–
Nasopharyngeal washes or swabs	–	–	+	+	–	–	–	–	++
Bronchoalveolar lavage, brushings, biopsies	++	++	++	++	++	++	++	++	++
Percutaneous needle aspirate, open lung biopsy	++	++	++	++	++	++	++	++	++

*Culture not generally available.
–, not recommended or undocumented utility; +, acceptable; ++, preferred.
From Shelhamer JH, Gill VJ, Quinn TC, et al: The laboratory evaluation of opportunistic pulmonary infections. Ann Intern Med 24:585-599, 1996.

Table 36-6
Significance of Respiratory Virus Detection in the Presence of Pneumonia in Patients Receiving Bone Marrow and Solid Organ Transplant

Site	Virus	Significance for Pneumonia
Urine	CMV, HSV, adenovirus	Suggestive
Blood	CMV, HSV	Highly suggestive
Nasopharynx	CMV, HSV, adenovirus	Highly suggestive
	RSV, parainfluenza, influenza	Highly suggestive with upper respiratory infection symptoms
Bronchoalveolar lavage fluid	CMV, HSV, adenovirus	Presumptive cause
	RSV, parainfluenza, influenza	Presumptive cause
Lung tissue	CMV, HSV, adenovirus	Diagnostic
	RSV, parainfluenza, influenza	Diagnostic

CMV, cytomegalovirus; HSV, herpes simplex virus; RSV, respiratory syncytial virus.
From Shelhamer JH, Gill VJ, Quinn TC, et al: The laboratory evaluation of opportunistic pulmonary infections. Ann Intern Med 24:585-599, 1996.

BOX 36-5 Diagnostic Techniques for *Pneumocystis jiroveci* Pneumonia (PCP)

Technique	Yield (%)
Routine sputum	Poor
Induced sputum	30-55
Induced sputum with immunofluorescent-antibody staining	60-97
Bronchoalveolar lavage	80-95
Bronchoalveolar lavage and transbronchial biopsy	>95
Open-lung biopsy	>95

Table 36-7
Utility of Diagnostic Tests for Fungal Pneumonia

Organism	Sputum or Bronchoalveolar Lavage Wet Mount	Sputum or Bronchoalveolar Lavage Culture	Blood Culture	Antigen Determination	Serology
Aspergillus species	++	++	–	–	–
Zygomycetes species	++	++	–	–	–
Fusarium species	++	++	++	–	–
Cryptococcus species	++	++	+	++ (blood)	–
Histoplasma species	++	++	+	++ (blood/urine)	+
Coccidioides species	++	++	+	–	+
Candida species	–	–	+/–	–	–

–, test is not helpful or is not available; +, test is suggestive of a causative agent if positive; ++, test is frequently helpful.
From Shelhamer JH, Gill VJ, Quinn TC, et al: The laboratory evaluation of opportunistic pulmonary infections. Ann Intern Med 24:585-599, 1996.

Table 36-8
Direct Stains,* Direct Tests, and Culture Available for Common Pulmonary Pathogens†

Organism	Direct Stain	Antigen or Nucleic Acid	Culture	Incubation Duration
Routine bacteria	Gram stain	Not available	Routine methods	3-4 d
Legionella species	Direct fluorescent antibody	PCR,† urine antigen (RIA)	Special *Legionella* media (BCYE)	2-7 d
Fungi	Wet mount or calcofluor white	Serum cryptococcal antigen Serum histoplasma antigen	Mycologic media (e.g., Sabouraud, BHI agar)	6-8 wk
Mycobacterium species	Acid-fast stain	PCR‡	Mycobacterial media (Middlebrook 7H 10/11)	≥8 wk
Nocardia species	Modified acid-fast stain	Not available	Blood agar, Sabouraud	4-6 wk
Pneumocystis species	Fluorescent antibody, Giemsa, toluidine blue O	PCR‡	Noncultivable organism	
Viruses	Fluorescent antibody for specific viruses§	EIA‡ for RSV, influenza A FAB for CMV, VZV, HSV	Traditional tissue culture Shell vial culture‖	≥2 wk 2-5 d
Chlamydia species	None¶	PCR‡	HL or HEp-2 cells	3-5 d
Mycoplasma species	None	PCR‡	Selective media	7-10 d

*These stains usually done by microbiology laboratories on sputum, bronchoscopic, or biopsy specimens.
†The PCR assay is available in a few diagnostic laboratories but is not generally available.
‡Research technique.
§Direct fluorescent antibody and EIA are available only for some viruses (see text).
‖Influenza A and B; parainfluenza 1, 2, and 3; RSV, CMV, HSV, and VZV are commonly available.
¶None for *Chlamydia pneumoniae*.
BCYE, buffered charcoal yeast extract; BHI, brain-heart infusion; CMV, cytomegalovirus; EIA, enzyme immunoassay; FAB, fluorescent antibody; HSV, herpes simplex virus; PCR, polymerase chain reaction; RIA, radioimmunoassay; RSV, respiratory syncytial virus; VZV, varicella-zoster virus.

ered is not a usual colonizing organism of the upper airway (e.g., pathogen causing tuberculosis).

ENDOTRACHEAL TUBE ASPIRATES

If the child requires endotracheal intubation for respiratory distress, endotracheal aspirates are easy to obtain. The diagnostic yield in complex immunocompromised patients is improved by using wax-protected microbiological brushes or nonbronchoscopic bronchoalveolar lavage.[99,100]

BLOOD CULTURES

Although blood culture should be obtained in all immunocompromised children suspected of having bacterial or fungal pneumonia, positive cultures are unusual, although generally highly specific.

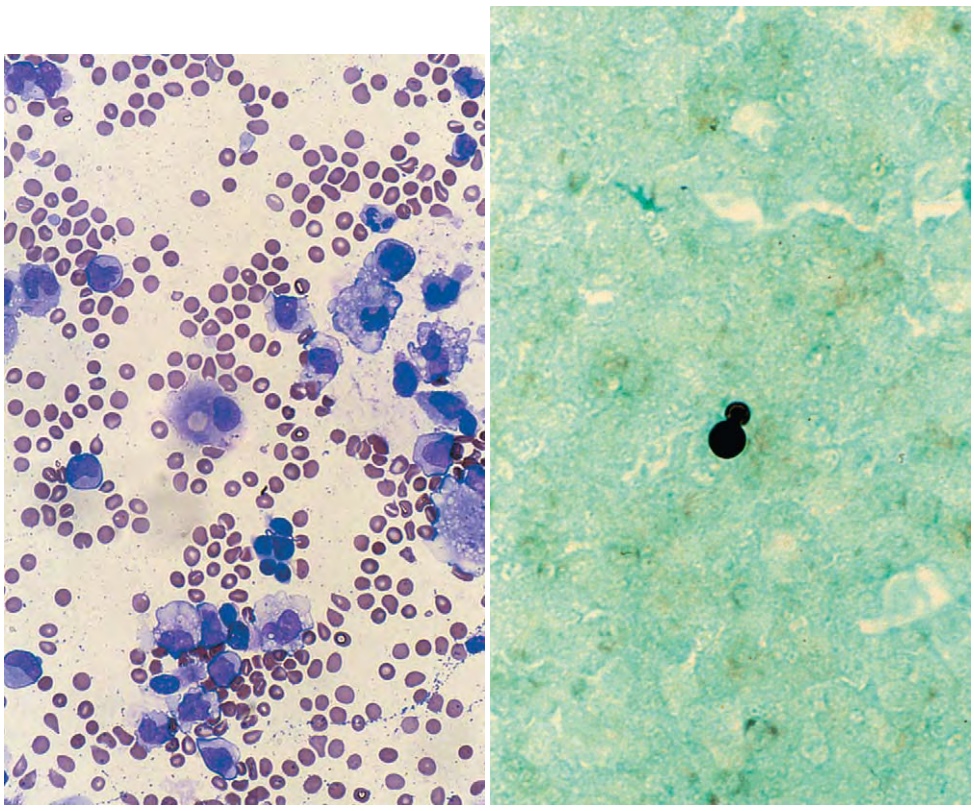
ANTIGEN AND ANTIBODY DETECTION METHODS

The rapid diagnosis of RSV, influenza A virus, parainfluenza virus, and *Chlamydia* infections by enzyme-linked immunosorbent assay and direct immunofluorescence is now available routinely. The sensitivities of these tests depend partly on the adequacy of the sample provided to the laboratory. Viral cultures are generally available, and the shell vial technique for the rapid identification of CMV and other viral pathogens has proved very useful, although the significance of viral isolates depends on the virus and the site from which it is isolated (see Table 36-6). Although *Mycoplasma pneumoniae* can be cultured on enriched media, this usually takes several weeks, and the diagnosis is usually based on serologic conversion. Genetic probes for detecting *Legionella* species, *Mycobacterium* species, and *M. pneumoniae* are now commercially available. Fungal infections can also be identified from a variety of specimens. A number of tests for the direct detection of fungal antigens have been described, but none is in widespread clinical use with the exception of *Cryptococcus* antigen.

Flexible Bronchoscopy

Flexible bronchoscopy is safe in experienced hands and provides excellent culture material in the immunocompromised child with pneumonia.[101-108] Indications in children with pneumonia include (1) failure of the pneumonia or fever to clear with appropriate antibiotic therapy; (2) suspicion of endobronchial obstruction by an infection or a tumor; (3) recurrent pneumonia in a lobe or segment; and (4) suspicion of unusual organisms such as *P. jiroveci*, fungi, and the pathogen that causes tuberculosis. Although the yield of gastric aspiration is probably superior to that of bronchoscopy for tuberculosis, bronchoscopy can also be useful to evaluate for endobronchial disease or bronchial compression.

The bronchoscope suction channel is contaminated by organisms of the upper airway, and simple washings obtained through the bronchoscope channel are generally useless for culture. Several techniques, including the use of a double-sheath, wax-protected sterile brush and quantitative cultures of bronchoalveolar lavage fluid, have been developed to avoid this problem. Bronchoalveolar lavage is the most useful technique for diagnosing infection in the immunocompromised host, and a variety of infectious and noninfectious diagnoses, including hemorrhage and pulmonary involvement with leukemia (Fig. 36-11), can be made using it. Bronchoalveolar lavage is generally safe even in patients with reduced numbers of platelets. Brushings obtained through the bronchoscope can be used for cytologic examination and viral cultures, but the yield is usually low.



A B

Figure 36-11 Diagnosis of conditions from specimens obtained from bronchoalveolar lavage. **A,** Monocytic leukemia. **B,** Blastomycosis.

Although the safety and usefulness of bronchoscopy are well documented in this population, it is important for the clinician to recognize the limitations of bronchoscopy. In patients on empirical broad-spectrum antibiotic therapy, the yield of bacterial pathogens is likely to be low. In oncology patients and other non-AIDS immunocompromised patients, the number of *P. jiroveci* organisms is usually low compared to the number obtained from patients with AIDS, so the results may be falsely negative. In populations receiving prophylaxis for this infection, the yield for PCP is likely to be low, reducing the overall yield of bronchoscopy for treatable infections. CMV can also be diagnosed rapidly by bronchoscopy, but patients may have other complicating infections, such as those caused by fungi and CMV, that are more easily missed by bronchoscopy. Infections caused by *Aspergillus* and other fungi are often difficult to diagnose by bronchoscopy, particularly early in the infection when therapy is most likely to be effective.

Transbronchial biopsies (TBB) can also be taken through the bronchoscope. Although safe in older patients, transbronchial lung biopsies yield an unacceptable number of false-negative results in immunosuppressed patients and are most useful when organisms such as *P. jiroveci* or granulomatous lesions are likely. Reported experience in pediatric patients is limited, but transbronchial biopsy has a significant role in monitoring rejection and infections in the pediatric patient after lung transplantation.[109]

Transthoracic Needle Aspiration Biopsy

Needle aspiration of the lung is useful for the diagnosis of PCP in pediatric patients with cancer and for the diagnosis of localized infections in other immunosuppressed patients.[110,111] Pneumothorax was a complication in 37% of the needle aspirates done for PCP, and this risk must be considered. Hemorrhage is more serious but less common. The use of computed tomography or fluoroscopic guidance greatly improves the yield and safety of this procedure, and it is the procedure of choice for many children with suspected peripheral fungal lesions that can safely be aspirated.

Open Lung Biopsy

Open lung biopsy is the standard by which other diagnostic modalities are judged. Because it uses current surgical techniques, open lung biopsy is generally a procedure with a low morbidity that can be done rapidly and allows the surgeon to obtain the optimal tissue for culture and microscopic examination. "Minithoracotomy" and lingular biopsy may be all that are necessary in patients with diffuse pulmonary processes. Biopsy using fiberoptic pleuroscopy may be adequate for pleural-based lesions and reduces the morbidity associated with open biopsy.

TREATMENT

Early treatment is necessary for the immunocompromised patient with pneumonia, and empirical antibiotic therapy is generally started at the first sign of clinical pneumonia. In many patients (e.g., the febrile, neutropenic patient), empirical antibiotic therapy may already have started before the pneumonia becomes clinically or radiographically apparent. Antibiotic therapy is typically broad spectrum, aimed at both gram-positive and gram-negative bacterial infections (e.g., vancomycin-aminoglycoside or semisynthetic penicillin, third-generation cephalosporin). If a patient has new diffuse, bilateral pneumonia with respiratory distress and hypoxemia, the clinician must make a rapid decision about whether to proceed to bronchoscopy or open lung biopsy before the patient's condition progresses to respiratory failure and any procedure becomes more hazardous. Empirical therapy is usually guided by the underlying disorder and the radiographic and clinical features of the pneumonia and would usually include TMP/SMX for PCP as well as erythromycin for *Mycoplasma* and *Legionella* infection. Amphotericin B is often started in the febrile neutropenic patient who develops a new pulmonary infiltrate while on antibiotics. Because of its low morbidity, flexible bronchoscopy should be considered early in the course of the pneumonia. If bronchoscopy is negative, the risks and benefits of open lung biopsy must be weighed in each patient, particularly if the pneumonia progresses despite appropriate antimicrobial therapy. A good response to empirical antibiotic therapy indicates that it should be continued for a minimum of 2 weeks, but in the case of antifungal therapy, treatment may be required for much longer periods.

Viral Infections

CYTOMEGALOVIRUS

Immunoglobulin enriched for anti-CMV activity has been used intravenously for prophylaxis in high-risk populations without clear benefit. However, when CMV-IVIG (intravenous immunoglobulin) is combined with the antiviral medication ganciclovir, the mortality rate in CMV pneumonitis in recipients of bone marrow transplants is reduced. At present, ganciclovir and CMV-IVIG are the primary therapies for CMV pneumonitis in immunocompromised patients.

HERPES SIMPLEX VIRUS/VARICELLA

VZIG can modify or prevent varicella in high-risk hosts exposed to the infection if administered within 48 to 72 hours of exposure. Acyclovir and VZIG have been the major factors accounting for the reduced incidence of serious VZV pneumonias in immunocompromised hosts.

HHV-6

No specific treatment is available.

ADENOVIRUS

Supportive therapy includes the administration of oxygen, treatment of bacterial superinfections, IVIG, and assisted ventilation. Cidofovir, a nucleotide analog with broad antiviral activity against DNA viruses, including adenovirus, was safe and effective in treatment of adenoviral infection in pediatric stem cell transplant patients.[112]

Fungal Infections

ASPERGILLUS *AND* CANDIDA *SPECIES*

The treatment of *Aspergillus* pneumonia includes amphotericin B, given at a dose of 1 to 1.5 mg/kg. Sometimes, flucy-

tosine or rifampin is also administered. The surgical excision of *Aspergillus* lesions is somewhat controversial.[113-116] Invasive pulmonary aspergillosis during treatment of hematologic malignancy is generally considered a contraindication to subsequent bone marrow transplantation, but adults treated with amphotericin B and surgery have survived without disease and without reactivation of *Aspergillus* infection after bone marrow transplantation.[117] The outcome of *Aspergillus* pneumonia depends primarily on host factors, the degree of immunosuppression, and the return of neutrophil counts to normal levels. Amphotericin B has been the treatment of choice for invasive candidal infections; flucytosine is used if synergism is desired. The imidazole antifungal agents, including ketoconazole, fluconazole, and itraconazole, have activity against *Candida* species and have been used successfully. Use of the imidazole antifungal agents for prophylaxis has helped kill more resistant fungal organisms in high-risk populations. These newer antifungal therapies have replaced conventional amphotericin B in the treatment of aspergillosis and candidiasis, including voriconazole for invasive aspergillosis and caspofungin for invasive candidiasis.[118,119]

MUCOR

As with *Aspergillus* organisms, treatment with amphotericin B and possibly surgical resection as early as possible is critical to achieving a cure. Correction of chronic acidosis if present also appears to be important in some forms of this infection.

HISTOPLASMOSIS AND BLASTOMYCOSIS

Amphotericin B is indicated for both histoplasmosis and blastomycosis in immunocompromised hosts. Itraconazole is also effective for histoplasmosis and moderate blastomycosis without central nervous system involvement.

CRYPTOCOCCUS NEOFORMANS

Treatment includes intravenous amphotericin B and oral fluconazole.

PNEUMOCYSTIS

All patients at known risk for *P. jiroveci* infection should receive prophylaxis (Box 36-6). For pediatric oncology and immunocompromised patients, oral TMP/SMX given 3 days a week is effective. However, if patients or parents are noncompliant, there is a risk of breakthrough pneumonias. For most patients, TMP/SMX remains the drug of choice, but other prophylactic regimens have been used, particularly in patients with AIDS; these include aerosolized and intravenous pentamidine and dapsone. Intravenous pentamidine may be associated with a higher risk of failure. Although there is extensive experience with aerosolized pentamidine in adults, there is less information on its use in infants and children.

PCP can be treated using several medications. The earliest medication available for PCP was pentamidine, which appears to work by inhibiting dihydrofolate reductase. Pentamidine was initially given by the intramuscular route, but subsequent studies showed that dosages of 4.0 mg/kg/day by the intravenous route are as safe as those given via the intramuscular route, although both are associated with high rates of immediate reaction, such as hypotension, tachycardia, and nausea. Hypoglycemia and nephrotoxicity are the most serious side effects of parenteral pentamidine. Pentamidine is also given by the aerosol route for the treatment of mild to moderate pulmonary disease in patients with AIDS, but its effectiveness is highly dependent on the delivery system used, and the aerosol route may predispose patients to extrapulmonary disease with *P. jiroveci*. TMP/SMX is as effective as pentamidine (approximately 70%) with fewer side effects. Some 60% of patients who do not have AIDS and in whom TMP/SMX therapy fails respond to treatment with pentamidine. In addition to pentamidine and TMP/SMX, a number of other medications are effective for the treatment of PCP; these include dapsone and trimetrexate. Patients with AIDS have a high incidence of reactions to many types of medications, including TMP/SMX.

Supportive therapy is a major part of the treatment for PCP. Oxygen, continuous positive airway pressure, continuous negative pressure, and assisted ventilation have all been used effectively in PCP. Trials in patients with AIDS indicate that corticosteroid administration during therapy improves outcome.[120-123] Typically, 4 to 6 days pass before improvement occurs with either pentamidine or TMP/SMX, and failure to improve warrants consideration of other infections and a change to another anti-*Pneumocystis* drug.

BOX 36-6 Indications for the Use of Anti-*Pneumocystis* Prophylaxis

- Solid-organ transplant recipients and allogeneic hematopoietic stem cell transplant or bone marrow transplant recipients with institutional incidence of 5% or in high-risk patients:
  - —History of PCP or frequent opportunistic infections
  - —With invasive cytomegalovirus (CMV) infection or at high risk for CMV disease
  - —During intensified immune suppression for acute allograft rejection or graft-versus-host disease (GVHD)
- Individuals receiving anti–T cell therapies
- Autologous bone marrow transplant recipients with leukemia or lymphoma, undergoing intensive conditioning or graft manipulation, or after fludarabine or 2-CDA administration
- Individuals with prolonged neutropenia (if marrow suppression is tolerable)
- Individuals with corticosteroid doses of >20 mg of prednisone per day for >2-3 wk

Bacterial Infections

Listeria infection is treated using ampicillin plus an aminoglycoside. Significantly, newer cephalosporins are not active against this species. C. *jeikeium* is resistant to most antibiotics except vancomycin. In most immunocompromised patients with pneumonia, vancomycin should be included in the treatment regimen to cover methicillin-resistant S. *aureus* and C. *jeikeium* when suspected.

TOXOPLASMA GONDII *AND* CRYPTOSPORIDIUM PARVUM

Treatment of *T. gondii* includes pyrimethamine-sulfadiazine. Treatment of C. *parvum* is with azithromycin.

CLINICAL COURSE AND PROGNOSIS

The clinical course and prognosis for immunocompromised patients with pulmonary infections are highly variable and depends on a number of factors including the underlying host disorder, the infectious agent, and how early effective treatment is started (Box 36-7). The clinical course may also be altered by the degree of residual host immunity. For example, corticosteroid therapy accelerates the resolution of *P. jiroveci* infection in patients with AIDS, suggesting that the residual host inflammatory response to this organism is important in the pathogenesis of respiratory dysfunction with PCP, even in profoundly immunosuppressed patients—a finding supported by reports of development of respiratory failure during reversal of immunosuppression in non-HIV patients.[124]

Fungal pulmonary infections in patients with chemotherapy-induced neutropenia often result in mild clinical symptoms and radiographic findings until a rise in the neutrophil counts results in significant inflammation, lung destruction and cavitation, and clinical deterioration. Because it is a relatively common opportunistic infection, the prognosis for invasive aspergillosis is well characterized. In solid organ transplants the incidence of infection ranges from 1% in renal transplant recipients to 7% to 9% in lung and bone marrow transplantation. Mortality rate for these populations ranges from 55% to 92% and depends significantly on early diagnosis.[125]

Adult and pediatric recipients of bone marrow transplants who were treated with recombinant human macrophage colony-stimulating factor had greater overall survival rate (27% versus 5% because of a 50% survival rate in patients with *Candida* infections)—although the survival rate in patients who developed *Aspergillus* infection remained poor.[126]

BOX 36-7 Common Clinical Scenarios in Immunocompromised Patients

Slow Progression, Absent (or Mild) Fever, Diffuse Pulmonary Opacity

Likely causes: pulmonary edema, pulmonary involvement with primary disease, drug or radiation injury
Evaluations: CT, bronchoscopy with bronchoalveolar lavage (BAL), cardiac ECHO

Rapidly Progressive, Fever, Diffuse Opacity

Likely causes: opportunistic infection, drug-induced
Evaluation: early bronchoscopy with BAL

Pneumonia and Sepsis/ARDS

Likely causes: bacterial
Evaluation: blood cultures, BAL, early empirical antibiotic therapy

Moderate Progression, Fever, Nodular/Round Density Progressing toward Cavitation

Likely causes: fungal, *Legionella, Nocardia*
Evaluation: CT, bronchoscopy, CT-guided aspiration biopsy

PITFALLS AND CONTROVERSIES

The major difficulty with immunocompromised patients is balancing institution of early empirical therapy (based on expected pathogens) with invasive diagnostic studies such as bronchoscopy (with or without transbronchial biopsy), CT-guided needle aspiration biopsy, and open lung biopsy (see Box 36-5).

Although bronchoscopy is generally the initial procedure of choice for pneumonia that has not responded to empirical therapy, there are several limitations to bronchoscopy for some types of infection (Box 36-8).

In immunocompromised patients, it is difficult to make generalizations about open lung biopsy, and much depends on local factors such as the availability of flexible bronchoscopy, the age of the child, the underlying conditions, complications such as thrombocytopenia and coagulopathies, and prior antibiotic or antifungal therapy. Some studies have questioned how often the results of open lung biopsy have led to a change in therapy if patients with nonspecific histologic findings and organisms treated by empirical therapy (e.g., *P. jiroveci*) are excluded. Published results in immunocompromised pediatric patients have indicated yields that range from 36% to 94% for a specific diagnosis.

Although open lung biopsy is the procedure of choice for obtaining definitive diagnostic information in immunosuppressed patients with pulmonary infiltrates, the timing of the biopsy is difficult. The clinician does not want to perform the procedure too early, especially if empirical therapy appears to be working and the patient is in good condition. On the other hand, when therapy is marginally successful, the surgeon does not want to wait so long that the patient's condition deteriorates and the risk of biopsy significantly increases. The authors generally suggest relatively early biopsy in immunosuppressed patients with pneumonia (see Fig. 36-10). Any patient with a condition not clearly responding to therapy chosen on the basis of other diagnostic techniques (including bronchoscopy) or therapy chosen empirically would usually benefit from a specific diagnosis by biopsy. In most medical centers, this is a relatively safe procedure, especially when performed before the patient has the need for respiratory support. The risks increase only when the biopsy is delayed until the patient has become critically ill. When the technique is used for the diagnosis of diffuse disease, only a limited thoracotomy with a superficial subsegmental resection is necessary. In localized disease typical of fungal infections, a more extensive procedure may be required to obtain an adequate specimen.

In specific patient groups such as recipients of bone marrow transplants and patients with AIDS, the use and timing of open biopsy may be different. In patients with AIDS, open lung biopsy is rarely necessary because a specific diagnosis can usually be made by using the results of bronchoalveolar lavage or transbronchial lung biopsy (see Fig. 36-11). If the disease progresses despite apparently adequate therapy or bronchoscopy is not diagnostic, open lung biopsy

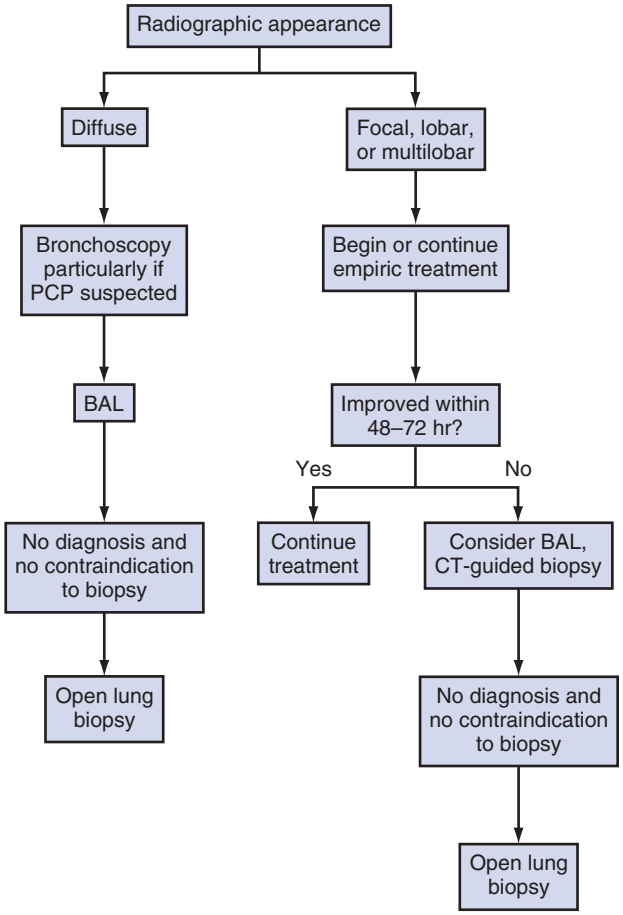


Figure 36-12 Flow diagram for the diagnosis of pneumonia in immunocompromised hosts. BAL, bronchoalveolar lavage; CT, computed tomography.

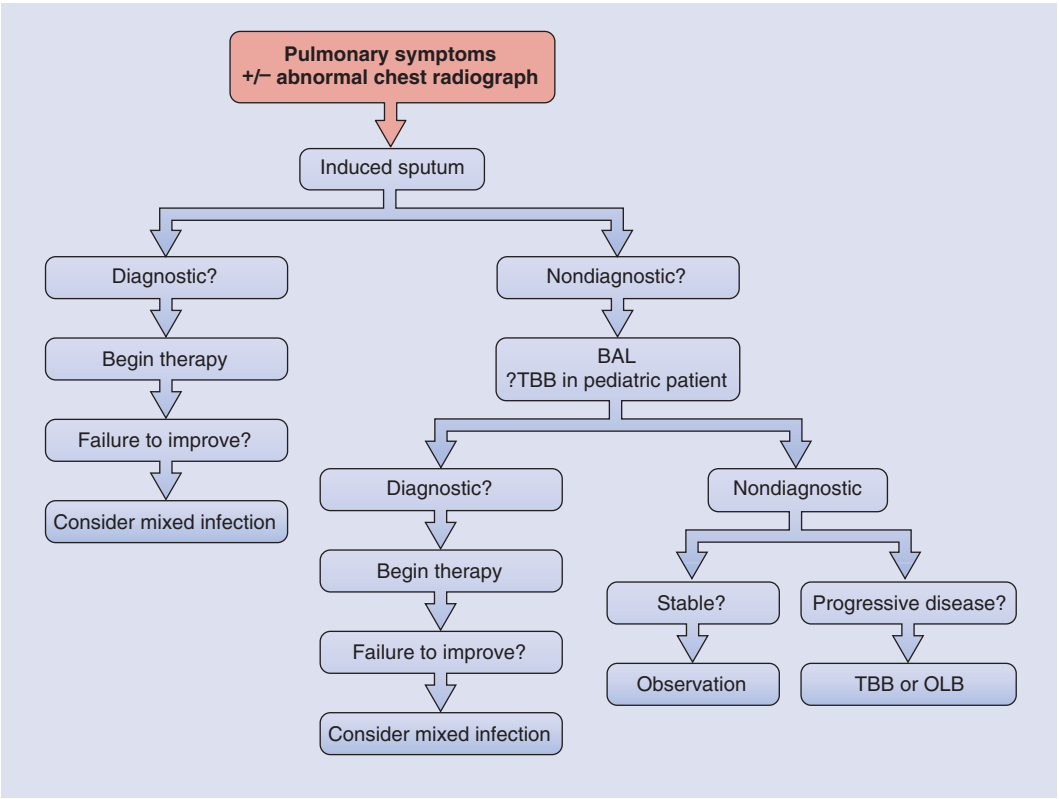


Figure 36-13 Flow diagram for the diagnosis of pulmonary disease in patients with AIDS. BAL, bronchoalveolar lavage; TBB, transbronchial biopsy; OLB, open lung biopsy. (From Dichter J, Levine SJ, Shelhamer JH: Hematol Oncol Clin North Am 7:887-912, 1993.)

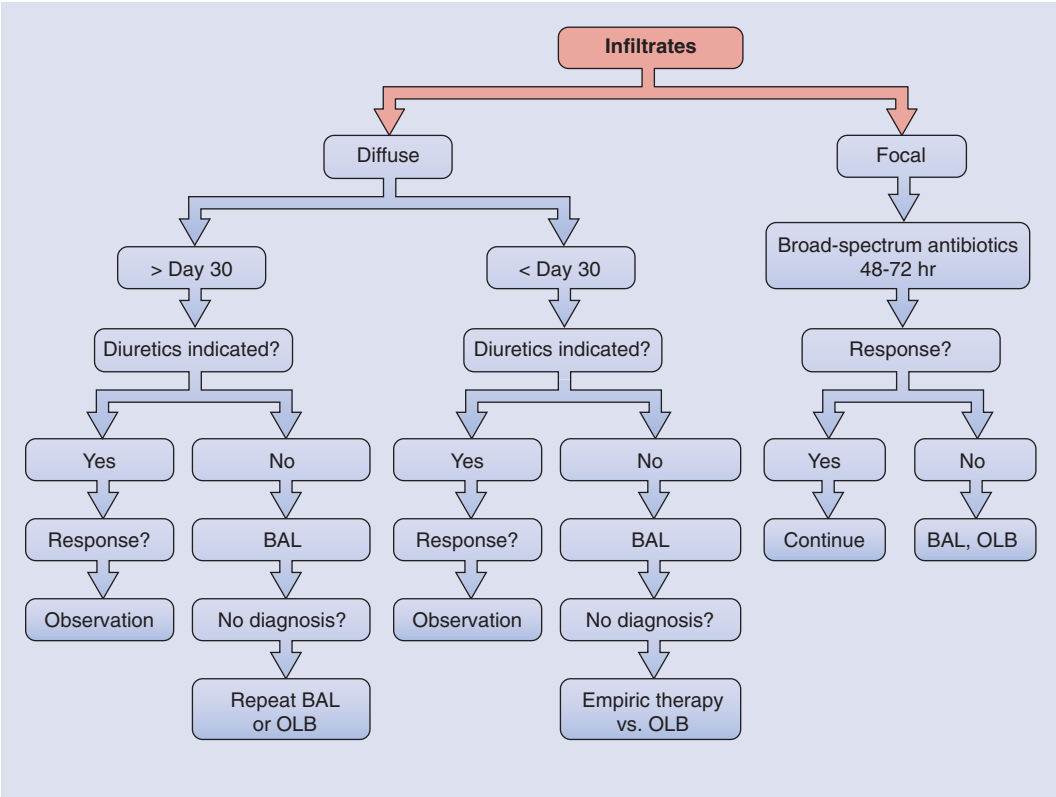


Figure 36-14 Flow diagram for the diagnosis of pulmonary disease in recipients of bone marrow transplants. BAL, bronchoalveolar lavage; OLB, open-liver biopsy. (From Dichter J, Levine SJ, Shelhamer JH: Hematol Oncol Clin North Am 7:887-912, 1993.)

BOX 36-8 Limitations of Bronchoscopy in Immunocompromised Patients

FALSE POSITIVES: *Candida* spp., cytomegalovirus (CMV) (particularly in bone marrow transplant patients)
FALSE NEGATIVES: aspergillosis and other fungal pathogens (particularly early), tuberculosis, *Nocardia,* tumor or involvement with hematologic malignancy

should be considered to rule out other co-pathogens (Figs. 36-12 and 36-13). In recipients of bone marrow transplants the approach may be modified to allow therapy of common noninfectious complications such as pulmonary edema before embarking on invasive diagnostic studies (Fig. 36-14).

Another area of relative controversy is the role of aggressive lung resection for fungal pneumonias. Patients with invasive aspergillosis and *Mucor* have a significant risk of death from pulmonary hemorrhage, and organisms may persist even after neutropenia has resolved, predisposing to recurrent infection with additional chemotherapy. It has been suggested that wedge resection or lobectomy may reduce the risk in these clinical situations.

For the immunocompromised patient who develops respiratory failure secondary to pulmonary complications, the outcome in the past has been poor, with very high mortality rates. Advances in treatments and supportive care have improved the outcome considerably for many patient groups, but these patients continue to present very challenging management and ethical dilemmas.[127-129]

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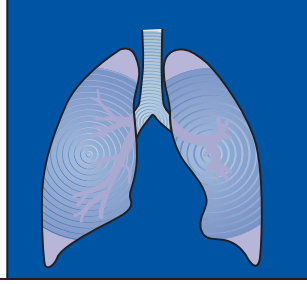


CHAPTER 37 Human Immunodeficiency Virus Infection

Heather J. Zar and Michael R. Bye

TEACHING POINTS

- Respiratory illness is the predominant cause of mortality and morbidity in HIV-infected children.
- Severe pneumonia is often caused by co-infection with more than one pathogen.
- *Streptococcus pneumoniae* is the major bacterial pathogen causing pneumonia.
- Viral respiratory infections account for a lower incidence of pneumonia in HIV-infected compared with HIV-negative children, but are associated with more severe disease and a higher case fatality rate.
- *Pneumocystis jiroveci* (formerly *Pneumocystis carinii* pneumonia, hence [PCP]) is frequently the manifesting illness in infants undiagnosed with HIV; HIV-exposed infants are also at risk of PCP.
- With use of highly active antiretroviral therapy (HAART), the rate of opportunistic and respiratory infections has declined substantially.
- Cotrimoxazole prophylaxis may reduce mortality and morbidity in HIV-infected children of all ages, who are not taking HAART.
- The incidence of chronic lung disease increases with longer survival of HIV-infected children.

A changing pattern in the epidemiology of pediatric HIV and HIV-associated lung disease has emerged in developed countries over the last decade. In these countries, programs to prevent mother-to-child HIV transmission (MTCT), early diagnosis of HIV infection in infants, and use of *Pneumocystis* prophylaxis and highly active antiretroviral therapy (HAART) have led to a substantial decline in the incidence of pediatric HIV and HIV-associated respiratory infections. Concomitantly, with improved survival of HIV-infected children on HAART, the incidence of HIV-associated chronic lung disease has increased. In contrast, in developing countries, particularly those in sub-Saharan Africa, the HIV epidemic has escalated with a rise in acute and chronic HIV-associated pulmonary diseases. This has been compounded by poor access and unavailability of preventive strategies and of HAART for HIV-infected children. As a result, HIV-associated lung disease is a major cause of childhood morbidity and mortality in developing countries.

EPIDEMIOLOGY

The total number of pediatric AIDS cases has declined substantially in developed countries in the last decade owing to a dramatic reduction in perinatal HIV transmission. New cases of HIV infection in children in developed countries occur predominantly in adolescents owing to sexual transmission, but most adolescents will remain asymptomatic until adulthood.[1] However, globally there are approximately 2.3 million HIV-infected children, most of whom live in sub-Saharan Africa.[2] Approximately 540,000 children are infected with HIV annually; approximately 470,000 of these cases occur in developing countries.[2]

In the absence of HAART, up to 90% of HIV-infected children will develop a serious respiratory illness sometime in the course of their HIV disease, resulting in a large increase in the incidence and severity of childhood respiratory illness in developing countries and an exponential increase in infant and under-5 mortality rates.[3] Mortality rates among HIV-infected African children are much higher than those for developed countries; 26% to 59% of HIV-infected African children die within the first year of life and under-5 mortality rates exceed 60% in some countries.[4,5] Respiratory disease, principally pneumonia, is the predominant cause of childhood mortality in children in developing countries—accounting for approximately 2 million deaths annually in children younger than 5 years.[6] Pneumonia is also the most common cause of hospitalization in African HIV-infected children. Pneumonia-specific mortality rates are higher in HIV-infected children with case fatality rates consistently reported as three to six times those of HIV-negative patients.[7] In a U.S. cohort of HIV-infected children in the pre-HAART era followed longitudinally, respiratory infection was the most common cause of death in children under 6 years of age, with 32% caused by pulmonary infection.[8] The frequency of pulmonary disease as the underlying cause of death decreased significantly with increasing age, with 56% of respiratory-related deaths occurring within the first year of life.[8]

Clinical Features

HIV-associated respiratory involvement may manifest as acute or chronic disease, involving the upper and/or lower respiratory tract. Infections, especially pneumonia, are the major cause of acute lung disease whereas chronic disease

may manifest as chronic infection, bronchiectasis, or lymphocytic interstitial pneumonia (LIP).

INFECTIOUS DISEASES

The rate of acute respiratory infections has decreased dramatically with the use of HAART.[9] In the pre-HAART era, the most common opportunistic infection in children in the United States was serious bacterial infection, principally pneumonia.[10] Other common opportunistic infections (event rates >1 per 100 child-years) involving the respiratory tract were PCP, disseminated *Mycobacterium avium* complex (MAC) and tracheobronchial candidiasis.[10] Less commonly (event rates <1 per 100 child-years) tuberculosis (TB), cytomegalovirus (CMV) disease, and systemic fungal infections occurred.[10]

In the HAART era, the number of opportunistic infections has declined substantially, although the relative prevalence of AIDS-defining infections has remained constant.[11] In children not taking HAART or those resistant to antiretroviral therapy, acute respiratory infections are common and may be severe. Infection of the upper airways may produce sinusitis, ear disease, supraglottitis, epiglottitis, or laryngotracheobronchitis. More severe acute infection may involve the lower airways and manifest as pneumonia, pleural effusion, bronchiolitis, a lung abscess or localized parenchymal disease. A number of bacteria, viruses, or fungi may cause respiratory infections in HIV-infected children (Box 37-1); mixed infections also occur commonly.

Bacterial Infections

Pre-HAART, bacterial pneumonia was the most common serious bacterial infection, with an event rate of 11 per 100 child-years[12]; this has declined to a rate of 2.2 in the HAART era.[9] Bacterial pneumonia is still a major cause of hospitalization and mortality in HIV-infected children who are unable to access HAART, particularly in developing countries.[3,13] The clinical signs of pneumonia are similar in HIV-infected and uninfected children but bacteremic illness is more common in HIV-infected children, occurring in approximately 15% to 20%, and the case fatality rate is higher.[14,15]

The etiology of bacterial pneumonia is similar to that in HIV-uninfected children (see Chapter 35), with *S. pneumoniae* the most common cause and accounting for more than 50% of associated bacteremic illness.[14-19] The risk of pneumococcal infection or invasive disease is significantly higher in HIV-infected than uninfected children.[14,19] The incidence of *Staphylococcus aureus* respiratory infection is increasing in HIV-infected children and may manifest as an empyema, pneumatocele, or lung abscess.[20] *S. aureus* is the most common pathogen occurring in catheter-associated bacteremia.[21] In addition, gram-negative pathogens such as *Klebsiella pneumoniae, Pseudomonas aeruginosa, Haemophilus influenzae,* non-typhoid *Salmonella* and *Escherichia coli* may cause pneumonia with or without bacteremia in HIV-infected children.[14,15,22,23]

HIV infection has been associated with an increase in the antimicrobial resistance patterns of bacterial pathogens causing pneumonia, with implications for empirical antibiotic therapy.[14] Methicillin-resistant *S. aureus* has increasingly emerged as a pathogen in HIV-infected children. There are variable data on the prevalence of penicillin-resistant pneumococcal infection in HIV-infected children but no clear differences in clinical outcome for susceptible and resistant strains have been shown, except for isolates with high level resistance.[24]

Immunization with the pneumococcal conjugate vaccine reduces the incidence of pneumonia and invasive disease.[25-27] In HIV-infected children, immunization reduces the incidence of invasive disease due to vaccine strains by 65% and also prevents 13% of radiologically confirmed pneumonia.[25] Although the efficacy is lower than that in HIV-uninfected children, vaccination still offers protection to a substantial proportion of HIV-infected children. Moreover, immunization reduced the incidence of infection with drug-resistant pneumococcal strains.[25] Immunization also reduces the incidence of hospitalization for viral-associated pneumonia, suggesting that more severe pneumonia requiring hospitalization may occur due to viral and *S. pneumoniae* coinfection.[28]

BOX 37-1 Etiology of Pneumonia in HIV-Infected Children

Bacteria

Streptococcus pneumoniae
Haemophilus influenzae
Staphylococcus aureus
Mycobacterium tuberculosis
Non-tuberculous *Mycobacteria*
Non-typhoid *Salmonella*
Klebsiella pneumoniae
Streptococcus milleri
Escherichia coli
Moraxella catarrhalis

Atypical Bacteria

Mycoplasma pneumoniae
Chlamydia trachomatis
Chlamydia pneumoniae

Viruses

Respiratory syncytial virus
Cytomegalovirus
Human meta-pneumovirus
Parainfluenza virus types 1 and 3
Adenovirus
Influenza virus A or B
Measles virus
Varicella-zoster virus
Human papillomavirus type 6 or 11

***Pneumocystis* and Fungi**

Pneumocystis jiroveci (previously *Pneumocystis carinii*)
Candida species
Aspergillus species
Histoplasma capsulatum
Cryptococcus neoformans
Coccidioides immitis

Mycobacterial Infections

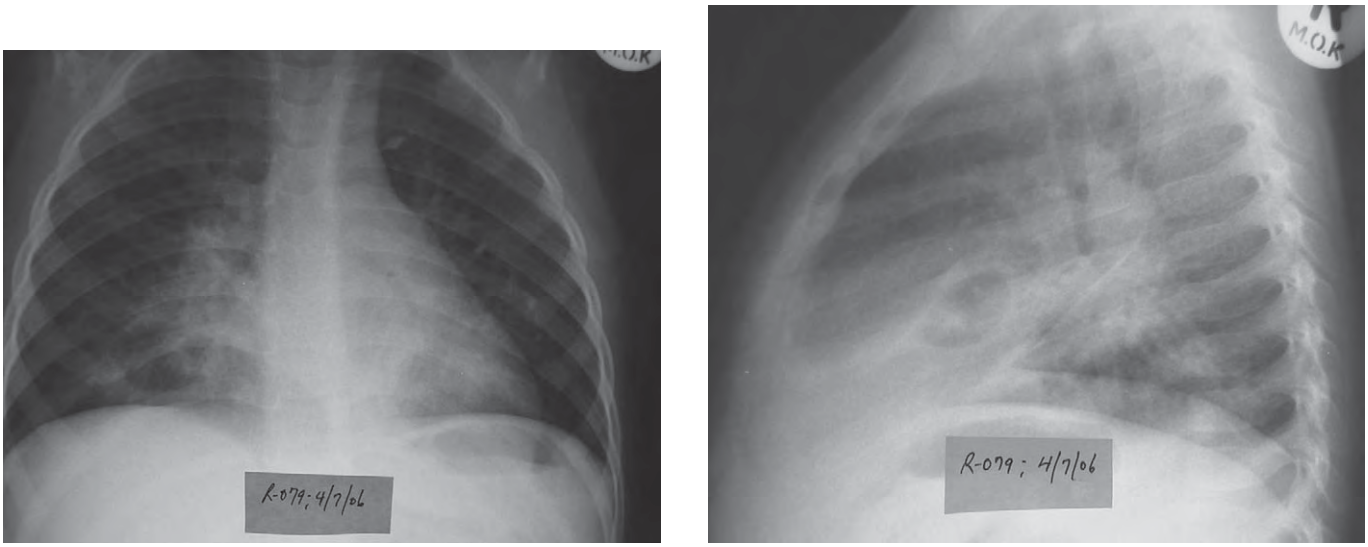
Mycobacterium tuberculosis is an important cause of acute pneumonia in HIV-infected children living in high TB prevalence areas, with culture-confirmed pulmonary tuberculosis occurring in approximately 8% of children hospitalized with pneumonia.[14,15,29] Pediatric TB infection is usually acquired from an infectious adult contact (see Chapter 39). The incidence of TB and risk of disease are higher in HIV-infected compared to immunocompetent children.[29-31] Primary infection rather than reactivation disease is usual in children.[32] Co-infection with *M. tuberculosis* and HIV results in more rapid deterioration of immune dysfunction, viral replication, and HIV progression and more frequent and severe other infections.[33-36]

HIV-infected children with TB may present with nonspecific signs including weight loss, failure to thrive, and fever or with signs and symptoms of acute pneumonia or airway obstruction.[29,33-36] Pulmonary TB may also manifest as chronic, persistent respiratory symptoms and failure to thrive (see Chapter 39). The clinical presentation is similar in HIV-infected and uninfected children, although more severe disease, cavitary disease, and more rapid progression may occur in HIV-positive children (Fig. 37-1).[29,33-36] Extrapulmonary and miliary disease (Fig. 37-2) occur more commonly and progression to death is more rapid than in HIV-negative children.[29,33-36] Multidrug resistant (MDR) TB is increasingly prevalent in TB-endemic areas; the clinical features are similar to drug susceptible TB, although the prognosis is poorer.[37] In the United States, MDR TB, reported in 2.8% of foreign-born and 1.4% of U.S.-born children with TB, is uncommon.[32]

Localized or disseminated *Mycobacterium bovis* infection including pneumonia has been reported in HIV-infected children who received bacille Calmette-Guérin (BCG) immunization; this may occur weeks to years after vaccination.[38-40] Ulceration at the site of vaccination and localized lymphadenopathy are not uncommon in HIV-infected children; systemic dissemination occurs more rarely.[38-40] The risk of disseminated BCG disease is increased several hundred-fold in HIV-infected infants compared to HIV-uninfected infants.[38] The clinical presentation of disseminated *M. bovis* may be indistinguishable from *M. tuberculosis* infection.[40] Disseminated *M. bovis* infection has a poor prognosis with a case fatality rate of approximately 50%.[40]

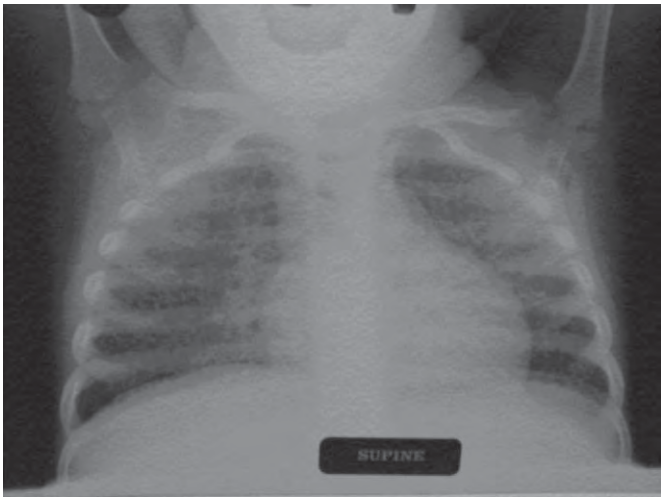
Non-tuberculous mycobacteria (NTM), particularly MAC, may cause disseminated disease including pulmonary infection in severely immunosuppressed HIV-infected children; isolated pulmonary disease is rare.[10,41] Children with pulmonary disease are at high risk for developing dissemination; up to 72% develop systemic disease within 8 months.[10] Disseminated MAC appears to be more common in children who have transfusion-acquired HIV than perinatal acquisition.[42] Epidemiologically, disease occurs in adults with CD4 counts less than 50 cells/μL but the threshold has been less well established in young children.[43] Primary and secondary prophylaxis is, therefore, recommended for severely immunosuppressed children based on CD4 counts.[43,44] The incidence of NTM disease has declined significantly with successful use of HAART from a rate of 1.8 per 100 child-years pre-HAART to 0.1 post-HAART.[9,12]

With increasing use of HAART, an immune reconstitution syndrome (IRIS) associated with mycobacterial infection has been reported.[45] Immune reconstitution syndrome may occur weeks to months after initiation of HAART therapy and may result either from unrecognized mycobacterial infection or from a florid immune response directed against a mycobacterial antigen in those already on therapy for mycobacterial infection.[45] IRIS has been described with different mycobacterial species including *M. tuberculosis*, *M. bovis*, or MAC infection.[46-48] Most cases of IRIS with *M. tuberculosis* have been described in HIV-infected adults,[49-50] but this is increasingly being recognized in HIV-infected children from high TB-prevalent areas.[51] Clinically, IRIS is characterized by a seemingly paradoxical worsening in signs with increasing lymphadenopathy, new clinical and radiological respiratory signs, and fever (Fig. 37-3).[47,48,50,51] The tuberculin skin test may become positive and chest radiographs may show devel-



A B

Figure 37-1 Anteroposterior **(A)** and lateral **(B)** chest radiographs of a young child with cavitary tuberculosis.



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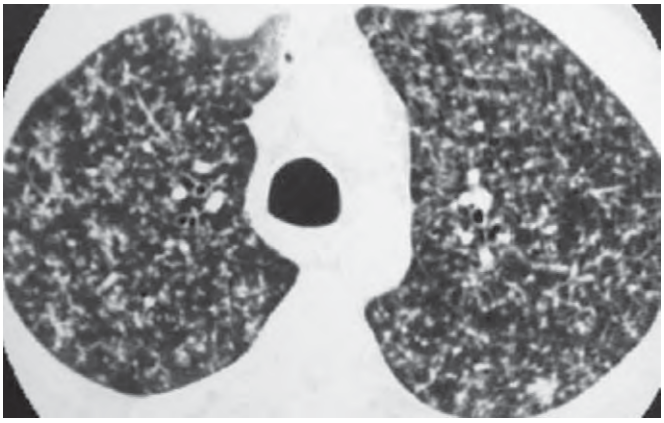


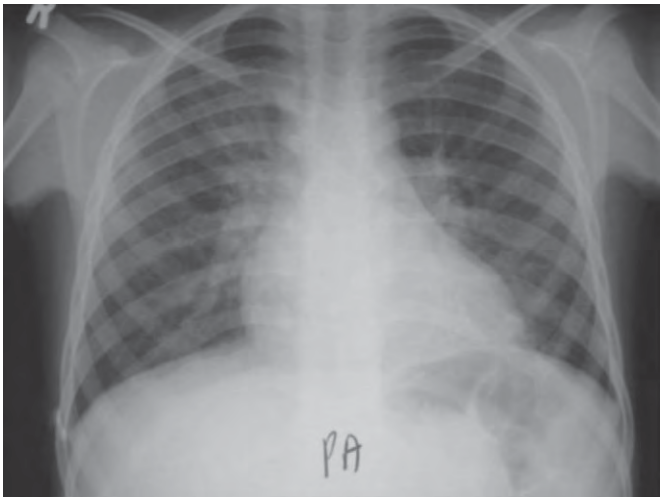
B

Figure 37-2 Chest radiograph **(A)** and chest CT scan **(B)** of a child with miliary tuberculosis showing multiple diffuse small nodules.

opment of lymphadenopathy or new infiltrates.[50,51] IRIS must be distinguished from other infections, multidrug resistant TB, or non-response to TB therapy because of noncompliance.[50] To minimize the risk of IRIS, HIV-infected children with confirmed or probable TB should be treated with antituberculous drugs for 1 to 2 months before commencing HAART.[50] When IRIS develops in a child who was not known to have TB, therapy for TB should be initiated. If lymphadenopathy or respiratory signs are particularly severe, oral corticosteroids may be beneficial, although there are no controlled trials in children.[50]

Viral Infection

Viral respiratory infection, although accounting for less pneumonia in HIV-infected compared with HIV-negative children, is associated with more severe disease and a higher case fatality rate.[52] The presence of wheezing suggests a viral etiology; however, HIV-infected children with viral lower respiratory infection are more likely to develop pneumonia rather than wheezing.[52] Respiratory syncytial virus (RSV) is the most common cause of viral pneumonia, especially in the first 3 years of life (see Chapter 33). Concurrent bacterial infection has been reported in 30% to 50% of children hospitalized with viral pneumonia. Human meta-pneumovirus (hMPV),



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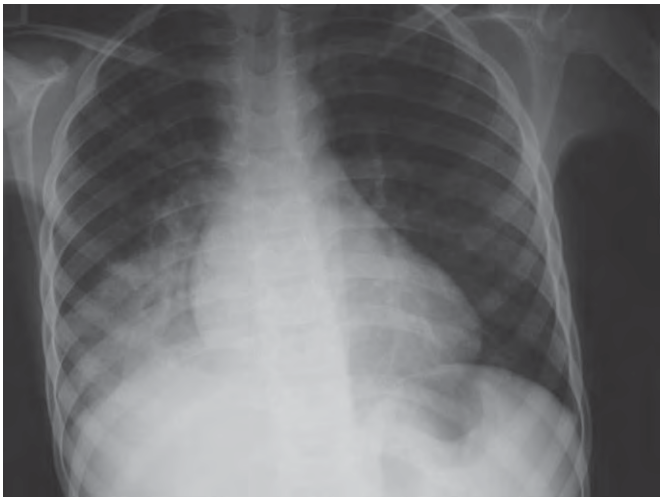

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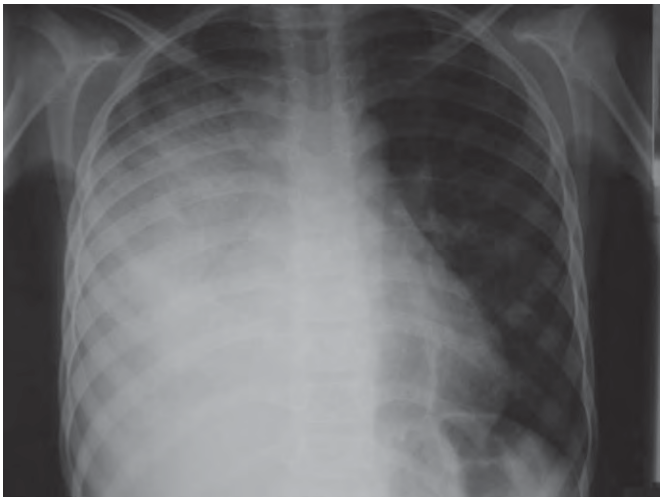


C

Figure 37-3 Immune reconstitution in a child with undiagnosed tuberculosis (TB) started on HAART. **A,** Chest radiograph prior to HAART initiation when a TB work-up was negative. **B,** Chest radiograph 1 month into HAART therapy showing development of right-sided disease. **C,** Chest radiograph 2 months into HAART therapy showing extensive right-sided disease and compression of the right bronchus. A gastric lavage culture obtained prior to initiating HAART then grew *Mycobacterium tuberculosis* and the tuberculin skin test became positive.

is emerging as an important respiratory pathogen in HIV-infected children and produces a similar spectrum of disease to RSV.[53] Other respiratory viruses that may produce lower respiratory tract infection include parainfluenza virus types 1 and 3, adenovirus and influenza A or B virus (see Box 37-1).[52]

Cytomegalovirus (CMV) may produce severe, disseminated disease including pneumonia in HIV-infected children.[10] CMV can cause primary pneumonitis or may be found in association with other pathogens, especially *Pneumocystis*. Co-infection with CMV and HIV results in more rapid progression of HIV disease.[54] Therefore, CMV prophylaxis should be provided for severely immunosuppressed children or those with a history of CMV disease. The incidence of CMV infection has decreased with the use of HAART.[9]

Herpesvirus infections may involve the respiratory tract in HIV-infected children. Oral herpes-simplex virus lesions may spread to involve the larynx and upper airways resulting in croup[55]; disseminated disease including pneumonia may also occur. Pneumonia may occur as a complication of varicella-zoster virus infection.[56] Measles virus infection may result in severe pneumonia; in HIV-infected children infection may occur without a typical skin rash, making diagnosis particularly difficult.[57]

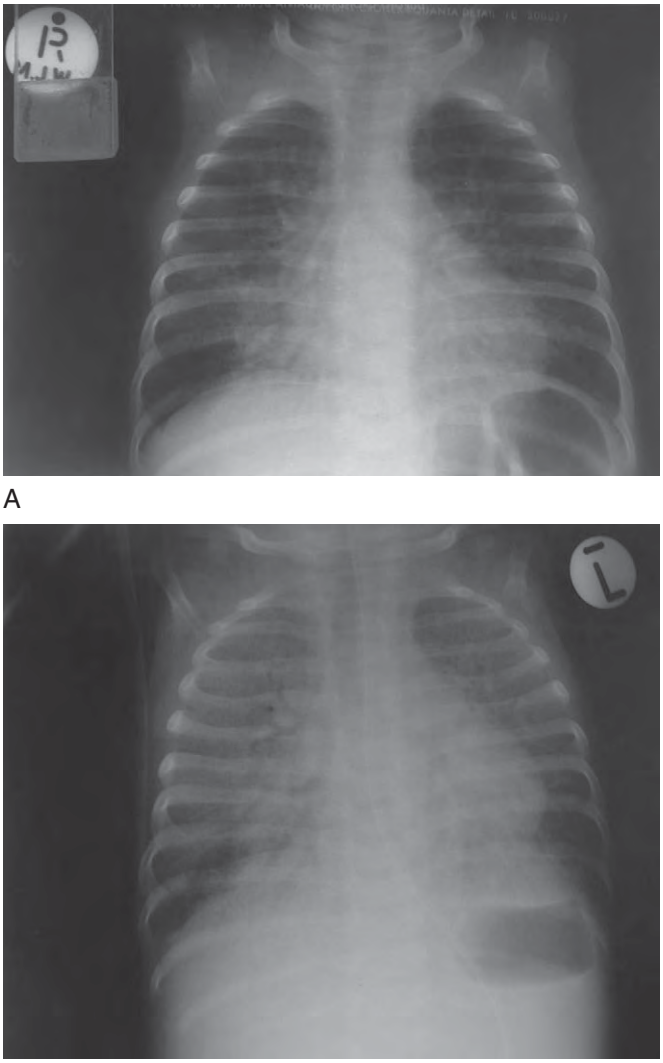
Human papillomavirus (HPV) type 6 or type 11 may produce lesions in the oral cavity, pharynx, larynx, and rarely in the lower airways or lungs; the disease has a tendency to recur.[58] Clinically, disease may manifest as progressive hoarseness, stridor, airway obstruction, and respiratory distress.[59] Rarely lung nodules, cysts, recurrent pneumonia, emphysema, or atelectasis have been described in immunocompetent children.[58,59] Little is known about the epidemiologic risk of disease in HIV-infected children. An increased prevalence of HPV in HIV-infected compared with HIV-uninfected women has been reported; however, the rate of HPV transmission to children has not been associated with the HIV status of the mother or child.[60,61]

PNEUMOCYSTIS *INFECTION*

Pneumocystis jiroveci pneumonia (PCP) was the most common opportunistic infection in HIV-infected infants prior to widespread prenatal HIV screening, trimethoprim-sulfamethoxazole (TMP-SMX) prophylaxis, and HAART.[12] The incidence of PCP has declined significantly in developed countries following these advances; the rate of PCP was 1.3 per 100 child years pre-HAART, declining to 0.1 with HAART.[9,12] PCP remains the most common AIDS indicator of disease among HIV-infected children, accounting for 57% of AIDS-defining conditions among those younger than 1 year of age.[10] PCP may frequently be the initial clinical presentation of HIV infection in infants; in developed countries, PCP occurs most commonly in infants born to women with unrecognized HIV infection.[62] In developing countries, PCP is a major cause of severe pneumonia and death in HIV-infected children, with the peak incidence at 3 to 6 months of age.[63-65] In these countries, the incidence of PCP varies from 8% to 49% among HIV-infected children hospitalized for pneumonia—depending on the patient population and the methods used for diagnosis.[63-65] PCP is the most common cause of death in African HIV-infected infants younger than 6 months, accounting for approximately 50% of respiratory related deaths.[13] Increasingly PCP has also been reported in older HIV-infected children; 25% of cases in a Zambian postmortem study occurred in those older than 6 months.[13]

Symptoms of PCP include tachypnea, fever, dyspnea, and cough.[66] HIV-infected infants under 6 months of age are especially at risk for PCP and have an acute, severe illness characterized by prominent and progressive hypoxia and increasing respiratory difficulty.[67] Auscultation of the lungs is usually normal, although crepitations or wheezing may occur. No specific clinical features can reliably distinguish children with PCP from those with other lower respiratory tract infections; however, disease is characterized by severe, progressive, clinical and radiologic signs and hypoxia (Fig. 37-4). Clinical signs may be compounded by co-infection with bacterial or viral co-pathogens.[68,69] Less commonly, PCP has also been reported to manifest with a pneumothorax, cyst, pneumatocele, or a bronchiolitis-like picture.[70,71]

PCP is associated with mortality rates ranging from 35% to 87% with higher rates in children with acute respiratory failure.[63-65,72,73] Timely anti-*Pneumocystis* therapy may



A

B

Figure 37-4 Radiologic progression of *Pneumocystis jiroveci* pneumonia (PCP) in an HIV-infected infant. **A,** initial radiograph and **B,** rapid progression of opacification within 24 hours.

improve outcome as suggested by historical comparisons and adult studies in which early use of corticosteroids for PCP has been associated with better survival.[74-76] Mutations in *P. jiroveci* dihydropteroate synthase genes (a key enzyme target of TMP-SMX) have been described in HIV-infected patients with PCP—especially with widespread use of TMP-SMX as prophylaxis.[74] However, the clinical importance of mutant strains is unclear and the response to TMP-SMX treatment is variable.[74]

HIV-exposed but uninfected children may also be at increased risk of PCP compared to HIV unexposed children. Probable transmission of *P. jiroveci* from an HIV-infected mother to her HIV-uninfected infant has been reported in a few cases.[77-79] HIV-exposed children may be at risk for PCP owing to close and early exposure to the organism from the mother, reduced passage of functional maternal antibody, impaired cell-mediated immunity, or concomitant malnutrition.

Fungal Infections

Chronic *Candida* infection is common in HIV-infected children and may produce oropharyngeal, laryngeal, or esophageal candidiasis and promote the development of gastroesophageal reflux disease.[10,80] Infection of the upper airways may result in *Candida* supraglottitis, epiglottitis, and a croup-like picture.[81,82] Laryngeal candidiasis may manifest as severe acute airways obstruction.[82] Pulmonary disease may also occur in the context of severe disseminated disease. Other fungal infections including aspergillosis, histoplasmosis, cryptococcosis, and coccidioidomycosis may produce respiratory illness usually in the context of severe immunosuppression and disseminated disease.[10] Pulmonary cryptococcosis without dissemination may manifest with fever, intrathoracic adenopathy, and pulmonary infiltrates.[10] Occasionally, pulmonary cryptococcosis may be asymptomatic and manifest on routine chest radiographs as pulmonary nodules.[10] Pulmonary coccidioidomycosis may produce diffuse reticulonodular infiltrates associated with fungemia and systemic disease.[10] Other pulmonary manifestations include nodules or cavities.

DIAGNOSIS

Diagnosis of the etiology of respiratory infection is difficult because signs are nonspecific and co-infection with more than one organism occurs frequently. For bacterial pneumonia, blood culture may be useful because HIV-infected children have higher rates of bacteremic pneumonia than do HIV-uninfected children; approximately 15% of HIV-infected children hospitalized for pneumonia have a positive blood culture.[14] Current evidence suggests that no radiologic or laboratory findings can distinguish the etiology of pneumonia with sufficient sensitivity or specificity.

Diagnosis of pulmonary tuberculosis is particularly difficult in HIV-infected children for whom clinical scoring systems have not been developed and in whom anergy may reduce the reliability of the tuberculin skin test (see Chapter 39). Diagnosis is frequently based on a combination of epidemiologic history of a TB contact and suggestive clinical and radiologic findings. A tuberculin skin test of 5 mm or more of induration is regarded as positive.[10] Tests of T lymphocyte γ-interferon production are promising. A study of African children with suspected TB reported that the T cell–based enzyme-linked immunospot assay (ELISPOT) had a higher sensitivity than the tuberculin skin test, particularly in HIV-infected children in whom the ELISPOT sensitivity was 73% compared with 36% for the skin test.[83] Definitive diagnosis requires culture confirmation of *M. tuberculosis* from sputum, bronchoalveolar lavage (BAL), gastric lavage, or lung or lymph node biopsy. A concerted effort should be made to obtain diagnostic specimens in children in whom TB is suspected because this may provide diagnostic confirmation and drug susceptibility.[84] Recently, induced sputum examination has been reported to be effective and safe for culture confirmation in infants and children; approximately 25% of HIV-infected children hospitalized with suspected pulmonary TB were culture-positive from sputum.[85] The yield from a single induced sputum sample was equivalent to that obtained from three gastric lavages.[85] Therefore, a single induced sputum sample should be the primary diagnostic procedure in a child with suspected pulmonary TB. In contrast, the culture yield from a single BAL is lower than that from three properly performed consecutive gastric lavages.[86] The efficacy of polymerase chain reaction (PCR) has been disappointing with sensitivity on gastric aspirates varying from 45% to 83% in HIV uninfected children.[84]

Definitive diagnosis of *Mycobacterium bovis* or MAC relies on isolation of the organism from the blood or from biopsy specimens from normally sterile sites.[10] If lymphadenopathy is present, an aspirate and culture can be diagnostic. Multiple mycobacterial blood cultures may be necessary to improve the yield.[10] Culture is essential to differentiate nontuberculous mycobacteria from *M. tuberculosis* and to determine the drug susceptibilities.

Diagnosis of PCP should be based on the clinical presentation and empirical treatment initiated.[67] PCP should be suspected in any infant presenting with acute, severe pneumonia who has signs of HIV infection or who comes from an area of high HIV prevalence, particularly if *Pneumocystis* prophylaxis is not being given. In such infants, a presumptive diagnosis of PCP should be based on a history of acute respiratory decompensation, lack of auscultatory signs, and hypoxemia. In HIV-infected children not taking HAART, four clinical variables have been reported to be associated with PCP—age less than 6 months, a respiratory rate >59 breaths per minute, arterial hemoglobin saturation less than 92%, and absence of a history of vomiting.[67] Most children have significant hypoxemia with an alveolar-arterial oxygen gradient >30 mm Hg. Serum lactate dehydrogenase (LDH) may be markedly elevated (>1000 IU/L) but this is nonspecific and may reflect the extent of lung involvement.[87,88] The chest radiograph usually shows a diffuse interstitial pattern which progresses to alveolar opacification; however, hyperinflation, focal infiltrates, cavities, a miliary pattern, pneumothoraces, pleural effusion, or a normal appearance may also occur.[70,71,89]

Definitive diagnosis requires identification of *P. jiroveci* from lower respiratory tract secretions including BAL, lung biopsy, or induced sputum tests.[74] Bronchoscopy with BAL is the diagnostic procedure of choice in young children, with reported sensitivity ranging from 55% to 97%.[10] Transbronchial biopsy is not recommended unless BAL is nondiagnos-

tic.[10] Transbronchial biopsy may be positive up to 10 days after starting therapy; the sensitivity of biopsy is 87% to 95%.[10] Induced sputum analysis using hypertonic nebulized saline may be useful; a positive yield has been described in infants as young as 1 month of age.[64] Nasopharyngeal secretions may also yield *P. jiroveci* in cases of severe infection.[63,65] Induced sputum in combination with nasopharyngeal aspiration (NPA) may provide a higher yield than either specimen alone; the sensitivity and specificity for induced sputum and NPA for diagnosis of PCP compared to the yield on autopsy have been reported to be 75% and 80%, respectively.[65]

As *P. jiroveci* cannot be cultured, identification of the organism requires special stains.[66] Silver methenamine, toluidine-blue or calcofluor white are useful for staining cyst forms, whereas Giemsa, modified Wright-Giemsa, or modified Papanicolaou stains identify trophozoites.[66,74] Fluorescein-conjugated monoclonal antibodies provide greater sensitivity, detecting both the cyst and trophozoite forms.[74] Polymerase chain reaction techniques, with a high sensitivity and specificity and potential to improve diagnostic accuracy, are not widely available and are currently mainly a research tool.[74] Nasopharyngeal secretions may be useful for detection of respiratory viruses or atypical organisms such as *Chlamydia trachomatis*.

TREATMENT (Table 37-1)

Bacterial Infections

Empirical antibiotic therapy for pneumonia should be broad spectrum and consider the local prevalence of antimicrobial resistance and recent use of prophylactic or therapeutic antibiotics.[10] A combination of a β-lactam with an aminoglycoside antibiotic or a second or third generation cephalosporin alone is appropriate empirical therapy. The choice of antimicrobial agent should be modified according to culture results and susceptibility testing.

Table 37-1
Recommended Therapy of Lower Respiratory Infections in HIV-Infected Children by Etiology

Infection	First Line Therapy
Bacterial pneumonia	Broad-spectrum antibiotic—β-lactam with an aminoglycoside *or* a second or third generation cephalosporin Add methicillin or vancomycin if *Staphylococcus aureus* is suspected
PCP	Trimethoprim-sulfamethoxazole Corticosteroids if hypoxic
Mycobacterial infections	
Mycobacterium tuberculosis	INH, rifampicin, pyrazinamide as induction for 2 months (add 4th drug if suspected drug resistance or severe disease); then maintenance with INH, rifampicin for at least 7 months for pulmonary TB Corticosteroids if endobronchial disease or airway compression
Mycobacterium bovis	Surgical excision of localized disease; four-drug therapy for disseminated disease (INH, rifampicin, ethambutol, ofloxacin, or ciprofloxacin) Clarithromycin plus ethambutol
Cytomegalovirus	Ganciclovir

INH, isoniazid; PCP, *Pneumocystis jiroveci* pneumonia (formerly *Pneumocystis carinii* pneumonia); TB, tuberculosis.

MYCOBACTERIAL INFECTIONS

Treatment of pulmonary TB is similar to that in HIV uninfected children although the response to standard therapy in HIV-positive children is poorer than in HIV-negative children with lower cure rates and higher mortality.[36,37] Mortality is particularly high within the first 2 months of treatment. Optimal therapy for HIV-infected children with TB has not been tested in well-designed studies. Empirical therapy for pulmonary TB in HIV-infected children should include three drugs (isoniazid [INH], rifampicin, and pyrazinamide) daily for a 2-month induction period; a fourth drug (either ethambutol, ethionamide, or streptomycin) should be added if drug resistance is suspected or for severe disease.[10,35,90] Following a 2-month induction phase, therapy with two drugs (INH, rifampicin) should be continued either daily or three times a week in drug susceptible isolates. Directly observed therapy (DOT) is advised to promote adherence and reduce the rate of treatment relapse or failure; for the induction phase DOT should be administered daily, whereas for the continuation phase, two to three times weekly is sufficient.[91] However, children with severe immunosuppression should receive therapy daily or three times weekly during the continuation phase because less intense regimens have been associated with the acquisition of resistance in adults with CD4 counts <100 cells/μL.[92] High rates of treatment failure have occurred in children treated for 6 months; therefore, a minimum of 9 months of therapy is advised.[10,93,94] For extrapulmonary TB, the duration of therapy should be at least 12 months.[10] Therapy for drug resistant TB should be individualized, using a minimum of three drugs, at least two of which are bactericidal (see Chapter 39).[10] Adjunctive corticosteroids may be beneficial for children with an endobronchial lesion and airway compression; a suggested regimen is 1 to 2 mg/kg/day prednisone tapered over 6 to 8 weeks.[10]

For children on HAART, the antiretroviral regimen should be reviewed to ensure optimal TB and HIV therapy and minimize potential toxicity and drug interactions.[35] Rifampicin induces hepatic cytochrome P450 enzymes and may, therefore, reduce levels of antiretroviral agents, particularly the protease inhibitors (PIs) and non-nucleoside reverse transcriptase inhibitors (NNRTI). Therefore, rifampicin should not be used in conjunction with single protease inhibitors except for ritonavir.[10] Alternatively rifampicin may be used in conjunction with ritonavir-boosted saquinavir, provided that high-dose ritonavir boosting is used.[10] Concurrent rifampicin with the NNRTI delavirdine is not recommended; however, use with efavirenz is possible. Use with nevirapine is recommended only when there are no other options because of the potential decrease in nevirapine levels.[10] Rifabutin is a less potent inducer of the P450 enzymes and is, therefore, a suitable alternative to rifampicin, but there is limited experience of its use in children.[10] Adjustments in dosage of rifabutin and co-administered antiretroviral drugs may be necessary because some drugs (e.g., efavirenz) lower rifabutin levels, whereas others (e.g., the PIs, ritonavir, indinavir, nelfinavir, ritonavir-boosted saquinavir) increase levels.[10] For antiretroviral-naïve children, TB therapy should be given for 4 to 8 weeks before

starting HAART to minimize the risk of immune reconstitution syndrome, optimize adherence, and differentiate potential side effects due to TB or antiretroviral drugs.[48-51]

Monitoring of HIV-infected children on TB treatment should include regular evaluation of clinical response, monitoring for drug adverse effects and liver enzyme measurements (at baseline and monthly for the first few months), particularly in the initial months of therapy owing to the potential for hepatotoxicity.[10,91] Elevations of transaminase levels of two to three times normal do not require discontinuation of drugs. A chest radiograph should be done at baseline and repeated 2 to 3 months into therapy to evaluate response; however, the chest radiograph may remain abnormal for months to years and a normal chest radiograph is not a criterion for discontinuing therapy.

Management of BCG disease is difficult. Treatment is complicated by the inherent resistance of *M. bovis* to pyrazinamide, inherent intermediate resistance of some BCG strains to isoniazid, and the emergence of resistance during inappropriate therapy.[95] In immunocompetent children, localized BCG disease is usually self-limiting. However, in HIV-infected children, treatment is warranted because of the risk of dissemination and poor outcome.[40] Surgical excision of localized lymphadenopathy is one strategy. Alternatively, medical therapy with four drugs (INH, rifampicin, ethambutol, ofloxacin or ciprofloxacin) in high doses is recommended.[40] The optimal duration of therapy is not known but at least 9 months of treatment is recommended, based on adult experience.[96]

Treatment of MAC should comprise combination therapy with a minimum of two drugs because monotherapy with a macrolide leads to rapid evolution of resistance.[10] Initial recommended therapy is clarithromycin or azithromycin plus ethambutol.[10] Rifabutin may be added as a third drug in patients with severe disseminated infection; addition of ciprofloxacin, amikacin, or streptomycin may be considered depending on the severity of illness.[10]

Viral Infections

Treatment of CMV disease focuses on preventing disease progression and not on cure. Ganciclovir is most widely used, with drug dosing separated into induction and maintenance dosage (see Chapter 33). Other possible agents include valganciclovir, foscarnet, or cidofovir.[10] These drugs may produce significant side effects including bone marrow depression and renal toxicity. For children with CMV disease who have sustained immune reconstitution on HAART, there are no data on when maintenance therapy may be safely discontinued; this should be considered on an individual basis.

Laryngeal HPV lesions are difficult to treat. Therapy is directed at maintaining airway patency, so obstructing papillomas should be removed. Adjuvant therapy using intralesional cidofovir has been reported to result in regression and reduced need for surgery in HIV-uninfected children.[97]

Pneumocystis and Fungal Infections

Empirical therapy for *Pneumocystis* should be given to any child with suspected PCP because untreated infection is usually fatal.[66] The most effective therapy is TMP-SMX (15 mg/kg/day TMP) intravenously three to four times a day for 21 days (Table 37-2).[10,66,74] Oral treatment can be used if intravenous therapy is not feasible, if disease is mild or when clinical improvement occurs. The response to therapy may be slow with clinical improvement occurring only after 3 to 5 days.[66] Adverse reactions to TMP-SMX occur in approximately 15% of cases, but treatment should be discontinued only if reactions are severe—such as neutropenia or a

Table 37-2
Treatment of PCP in Children

Drug	Dose	Route	Comments
Trimethoprim-sulfamethoxazole (TMP-SMX)	15-20 mg/kg TMP with 75-100 mg/kg SMX per day given q6h	Intravenous *or* oral	First choice Oral therapy only if mild disease or when clinical improvement occurs
Pentamidine	4 mg/kg daily	Intravenous	In those who cannot tolerate TMP-SMX or where no response after 5 to 7 days High incidence of side effects. Should not be administered with didanosine due to risk of pancreatitis
Atovaquone	30 to 45 mg/kg/day	Oral	Limited experience in children
Trimetrexate glucuronate with leucovorin	No studies of established doses in children Adult dose 45 mg/m^2/day trimetrexate glucuronate with leucovorin 20 mg/m^2 q6h	Intravenous	Limited experience in children
Dapsone and trimethoprim (TMP)	No studies of established doses in children Adult dose is 100 mg dapsone daily (pediatric equivalent 2 mg/kg) and 15 mg/kg TMP	Oral	Limited experience in children
Primaquine and clindamycin	No studies of established doses in children Primaquine adult dose is 30 mg daily orally Pediatric equivalent is 0.3 mg/kg daily orally Clindamycin adult dose is 600 mg intravenously q6h for 10 days; then 300-450 mg orally q6h for 11 days. Pediatric equivalent is 10 mg/kg q6h orally or intravenously	Oral/intravenous	Limited experience in children Most effective alternate therapy for adults with PCP unresponsive to primary therapy

Corticosteroids should be added in moderate or severe *Pneumocystis jiroveci* pneumonia. PCP, *Pneumocystis jirovecii.*

severe dermatologic reaction.[66,98] Intravenous pentamidine (4 mg/kg) may be an alternative drug for children who cannot tolerate TMP-SMX or who have not responded after 5 to 7 days of TMP-SMX (see Table 37-2).[10] Pentamidine is associated with a high incidence of adverse reactions including pancreatitis, alterations in blood glucose, renal dysfunction, cardiac dysrhythmias, fever, neutropenia, and hypotension.[99] Patients who show clinical improvement after 7 to 10 days of intravenous pentamidine may be switched to an oral drug to complete 21 days of therapy. Other alternative anti-*Pneumocystis* agents include atovaquone, dapsone with trimethoprim, trimetrexate glucuronate with leucovorin and clindamycin with primaquine, but there is little information on the efficacy or tolerability of these regimens in children (see Table 37-2).[10,91]

Corticosteroids are recommended in hypoxic children with moderate to severe PCP. Although no controlled trials on the use of corticosteroids in children have been performed, use has been reported to reduce the need for mechanical ventilation and to improve survival compared with historical controls.[75,76,100] Data from adult studies has found that corticosteroids are beneficial, improving oxygenation and reducing the incidence of respiratory failure when used within 72 hours of commencing anti-*Pneumocystis* therapy in hypoxic HIV-infected adults.[74] Corticosteroids are, therefore, recommended for a PaO_2 < 70 mm Hg or an alveolar-arterial oxygen gradient of >35 mm Hg.[10] The optimal dose and duration have not been determined, but a recommended regimen is prednisone 2 mg/kg for 5 to 7 days with tapering doses over the next 10 to 14 days.[75]

A few case reports have described use of surfactant to improve pulmonary function in children with severe PCP.[101,102] Children with PCP may be co-infected with bacterial or viral pathogens[68,69]; additional antimicrobial therapy for these should be used when appropriate. Specifically, CMV co-infection has been associated with more severe disease requiring mechanical ventilation and a poor outcome. The effect of corticosteroid therapy for PCP on CMV pneumonitis is unclear.

Uncomplicated oropharyngeal candidiasis can be treated with topical therapy.[103] Oral fluconazole, itraconazole, or ketoconazole are effective alternative agents.[10,104] For esophageal disease fluconazole or itraconazole is recommended.[10] Children with severe pulmonary cryptococcosis should be treated with amphotericin B; maintenance therapy with fluconazole or itraconazole can be substituted when improvement has occurred.[10] Mild or moderate pulmonary cryptococcosis can be treated with oral fluconazole or itraconazole.[10] Life-long suppressive therapy with fluconazole or itraconazole is necessary to prevent relapse.[10] There are little data on treatment of pulmonary coccidioidomycosis in children and recommendations are based on adult data with amphotericin B recommended for the acute illness followed by chronic suppressive therapy with fluconazole or itraconazole.[105] Alternatively, in mild disease, therapy may be initiated with fluconazole or itraconazole.[10]

PREVENTION

Prevention of HIV-associated lung disease is an important goal. Although the efficacy of preventive measures such as immunization is reduced in HIV-infected children, efficacy may depend on the degree of immunosuppression and use of antiretroviral therapy. General and specific preventive measures (Table 37-3) are discussed subsequently.

General Measures

General preventive strategies such as avoidance of passive smoke exposure, preventing exposure to indoor biomass fuels, and improved nutrition and growth may reduce the incidence and severity of respiratory infections.[106] Micronutrient supplementation, particularly the use of vitamin A to prevent measles-associated pneumonia and daily prophylactic elemental zinc (10 mg to infants, 20 mg to older children) may substantially reduce the incidence of pneumonia, particularly in malnourished children.[106,107]

CHEMOPROPHYLAXIS

Prevention of Pneumocystis jirovecii *Pneumonia*

Prophylaxis against *Pneumocystis* infection is very effective if initiated in HIV-exposed infants within the first few months of life. The most effective prophylactic agent is oral TMP-SMX, a widely available, well tolerated, and inexpensive drug. A randomized controlled study of TMP-SMX prophylaxis in HIV-infected Zambian children reported that this treatment reduced mortality by 43% and morbidity, including hospitalization, by 23%.[108] The impact on mortality occurred in children of all ages.[108] Although most children were not investigated for *P. jiroveci* or other pathogens, the authors hypothesize that the effect of TMP-SMX prophylaxis may also provide protection against bacterial infection.

Current recommendations for PCP prophylaxis include (Table 37-4):[91,109]

1. All infants born to HIV-infected mothers from 6 weeks of age until HIV infection has been excluded in the child and the mother is no longer breastfeeding
2. All HIV-infected children from 6 weeks until 1 year of age. HIV-infected children older than 1 year should receive prophylaxis if their CD4 counts are less than 15% of lymphocytes or if they have symptomatic HIV disease. However, a higher CD4 threshold for providing prophylaxis may be applicable in developing countries, as evidenced by a trial in Zambia where prophylaxis reduced mortality in children even in those with higher CD4 counts.[108,109] Prophylaxis should be continued indefinitely irrespective of age or CD4 counts when HAART is unavailable.[109]
3. Prophylaxis should be continued in children taking HAART for at least 6 months. There is little information on the safety of discontinuing prophylaxis once immune reconstitution has occurred. Discontinuation of prophylaxis may be considered in those with confirmed immune restoration for 6 months or more as indicated by two measurements of CD4 > 25% at least 3 to 6 months apart in children 2 to 6 years of age.[110]
4. Lifelong prophylaxis should be given to all children who have had an episode of PCP; the safety of discontinuing secondary prophylaxis in the context of immune reconstitution has not been established.

Table 37-3
Preventive Measures and Indications

Intervention	Indications
General	
Vitamin A	Malnourished children
	Measles-associated pneumonia
Zinc	Malnourished children
Avoidance of passive smoke exposure	All
Adequate nutrition	All
Immunization	
Routine EPI immunizations (DPT, inactivated poliovirus, measles, HiB)	All
Pneumococcal conjugate	All
Influenza vaccine	All
Measles, mumps, rubella vaccine (MMR)	Mild or moderately immunocompromised children (CDC immune category 1 or 2)
Varicella vaccine	Asymptomatic or mildly symptomatic children without immunosuppression (CDC category N1 or A1)
Chemoprophylaxis	
TMP-SMX	PCP prophylaxis in all infants and in children >1 year with moderate or severe immunosuppression or if clinically symptomatic
	Secondary prophylaxis in children with prior PCP
INH prophylaxis	Children exposed to a close contact with TB once TB disease has been excluded in the child
	Tuberculin skin test–positive children
Azithromycin/clarithromycin	Prophylaxis for nontuberculous mycobacteria in severely immunosuppressed children
	Lifelong secondary prophylaxis in children with prior infection
Ganciclovir	Prophylaxis for CMV in severely immunosuppressed children
	Lifelong secondary prophylaxis in children with prior CMV disease
Immune Prophylaxis	
Intravenous immunoglobulin (IVIG)	Consider to prevent bacterial infections in children with hypogammaglobulinemia *or* recurrent, severe infections *or* inability to form antibodies to common antigens
Varicella-zoster globulin	Children exposed to varicella or zoster without a prior history of varicella infection or immunization within 2 weeks of exposure
Measles immunoglobulin	Children exposed to measles
RSV immunoglobulin	Children at risk for severe RSV (premature infants, those <2 years with chronic lung disease, or severely immunosuppressed children) monthly for the duration of the RSV season
HAART	At appropriate stage of immune suppression

CDC, Centers for Disease Control and Prevention; CMV, cytomegalovirus; DPT, diphtheria pertussis tetanus; HAART, highly active antiretroviral therapy; INH, isoniazid; RSV, respiratory syncytial virus; TMP/SMX, trimethoprim sulfamethoxazole.

Table 37-4
Indications for PCP Prophylaxis in HIV-Infected Children

Age	*CD4 T-Lymphocyte Count
†4-6 weeks to 12 months	All patients irrespective of CD4 count
1-5 years	<500/mm^3 *or* if percentage is less than 15%
>5 years	<200/mm^3 *or* if percentage is less than 15%

*If CD4 measurements are unavailable, then prophylaxis should be given to all symptomatic children indefinitely.[109]
†HIV-exposed children should receive prophylaxis from 4-6 weeks to 4 months; thereafter prophylaxis may be discontinued if HIV infection has been excluded and the mother is not breastfeeding.
PCP, *Pneumocystis jiroveci* pneumonia.

TMP-SMX prophylaxis (150 mg/m^2/day of TMP) may be given three times a week (single dose on 3 consecutive days, or two divided doses on consecutive or alternate days or 7 divided doses each dag for a week).[91] If TMP/SMX is not tolerated or cannot be used, alternatives include dapsone (2 mg/kg once daily), atovaquone (30-45 mg/kg once daily) or aerosolized pentamidine (300 mg via Respigard II inhaler every 4 weeks) if the child is older than 5 years of age.[91,111-114] Safety and efficacy concerns regarding aerosolized pentamidine preclude its use in young children. A study of the safety of inhaled pentamidine in young children reported cough, wheeze, or oxygen desaturation in five of seven infants.[114]

Prevention of Mycobacterial Disease

INH prophylaxis is currently not routinely recommended for HIV-infected children, except if a child has been exposed to a household contact with TB (see Chapter 39), when INH prophylaxis (5-10 mg/kg) should be given daily for 6 to 9 months once active tuberculosis disease has been excluded (see Table 37-3). Prophylaxis should also be given to HIV-infected children with TB infection (tuberculin skin test >5 mm induration) but not disease. A recent study in a high TB prevalence area reported that INH prophylaxis given to HIV-infected children, irrespective of tuberculin skin reactivity or a household TB contact, substantially reduced mortality and TB incidence; however, further studies are needed before this can be widely recommended.[115]

Primary prophylaxis for NTM with azithromycin or clarithromycin should be considered for severely immunosuppressed children (see Table 37-3) as follows: for children younger than 1 year, CD4 < 750/uL; children 1 to 2 years CD4 < 500/uL; children 2 to 6 years, CD4 < 75/uL; children 6 years or older CD4 < 50/uL.[91] Rifabutin may be an alternative agent in children older than 6 years.[91] Secondary prophylaxis should be given to children with a history of dis-

seminated MAC to prevent recurrence.[91] Lifelong prophylaxis is indicated; the safety of discontinuing secondary prophylaxis in the context of sustained immune restoration following HAART has not been well studied in children.

Prevention of Cytomegalovirus Infection

Oral ganciclovir or valganciclovir may be used for primary prophylaxis in severely immunosuppressed HIV-infected children as reflected by a CD4 count less than 50 cells/μL (see Table 37-3).[116] Secondary lifelong prophylaxis should be given to children with a history of disseminated CMV disease to prevent recurrence; there are little data on the safety of discontinuing prophylaxis once sustained immune reconstitution on HAART has occurred.

Immunization

The nature and degree of immunosuppression determine the safety and efficacy of vaccination in HIV-infected children. The efficacy of immunization may be substantially reduced in symptomatic HIV-infected subjects who are not on HAART. Immunization with inactivated vaccines (diphtheria, pertussis, tetanus toxoids; inactivated poliovirus, *H. influenzae b*, hepatitis B, and pneumococcal conjugate vaccine) should be given to HIV-infected children at the usual recommended age as for uninfected children (see Table 37-3).[91] Although the pneumococcal conjugate vaccine has lower efficacy in HIV-infected children who are not on HAART compared with HIV-uninfected children, it reduces the incidence of invasive disease and pneumonia in a substantial proportion of HIV-infected children. In a large South African study, the nine valent vaccine prevented 13% of radiologically diagnosed pneumonia and 65% of invasive pneumococcal disease in HIV-infected children.[25] A booster dose of the vaccine may be required during the second year in HIV-infected children.

Measles, mumps, rubella vaccine (MMR), a live attenuated vaccine, should be given to HIV-infected children at 12 months of age, unless they are severely immunocompromised.[91] Varicella vaccine should be considered at 12 to 15 months for asymptomatic or mildly symptomatic HIV-infected children without immunosuppression (CDC categories N1 and A1); vaccine should not be administered to symptomatic immunosuppressed children due to the potential for disseminated disease.[91] Influenza vaccine should be given annually to all HIV-infected children at the start of the influenza season.[91] BCG vaccine is not recommended in HIV infected infants due to the risk of disseminated disease.

Immune Prophylaxis

PREVENTION OF BACTERIAL INFECTIONS

Intravenous immunoglobulin (IVIG) for prevention of bacterial infections including pneumonia may be indicated for HIV-infected children who have hypogammaglobulinemia (IgG < 4 g/L) *or* recurrent, severe infections (two or more bacterial infections including pneumonia in 1 year) *or* inability to form antibodies to common antigens.[16,17,91,117] However, IVIG may not offer additional protection if children are taking TMP-SMX prophylaxis.[17] Moreover, there is no evidence to suggest that immunoglobulin offers additional protection in children taking HAART. Children with bronchiectasis may benefit from monthly immunoglobulin.[91] Immunoglobulin is usually given as a monthly injection.

PREVENTION OF VARICELLA

Administration of varicella-zoster globulin should be considered for HIV-infected children exposed to varicella or zoster who have no history of varicella infection or immunization and who have not received immunoglobulin within 2 weeks of exposure.[91]

PREVENTION OF MEASLES

HIV-infected children exposed to measles should receive a dose of intramuscular immunoglobulin irrespective of immunization status.[91]

PREVENTION OF RESPIRATORY SYNCYTIAL VIRUS

The efficacy of the humanized monoclonal specific antibody against RSV (palivizumab) or RSV immune globulin (RSV-IVIG) has not been well studied in HIV-infected children. Nevertheless, those at risk for severe RSV infection such as premature HIV-infected infants, those under 2 years of age with chronic lung disease, or severely immunosuppressed children may benefit from prophylaxis.[91] A dose should be given monthly for the duration of the RSV season.[91]

CHRONIC LUNG DISEASE

Chronic lung radiologic changes are common among HIV-infected children with increasing age[118,119]; a longitudinal birth cohort study reported that the cumulative incidence of chronic radiographic lung changes in HIV-infected children was 33% by 4 years old.[118] The most common chronic radiologic changes are increased bronchovascular markings, reticular densities, or bronchiectasis.[118,119] Chronic changes are associated with lower CD4 cell counts and higher viral loads; radiologic resolution of these may reflect declining immunity.[118] The spectrum of chronic HIV-associated lung disease includes lymphocytic interstitial pneumonia (LIP), chronic infections, bronchiectasis, malignancies, bronchiolitis obliterans, and interstitial pneumonitis.

Lymphocytic Interstitial Pneumonia and Pulmonary Lymphoid Hyperplasia

Lymphocytic interstitial pneumonia (LIP) and pulmonary lymphoid hyperplasia (PLH) represent a spectrum of chronic lymphocytic infiltrative diseases of the lungs, occurring commonly in HIV-infected children. The etiology is unknown; evidence suggests that infection with Epstein-Barr virus may initiate a lymphoproliferative response in the presence of HIV infection.[120] Clinically children develop insidious, chronic respiratory symptoms—principally cough and mild tachypnea.[121] Lymphoproliferation, occurring in other organs, may produce associated generalized lymphadenopathy, digital clubbing, bilateral nontender parotid enlargement and hepatosplenomegaly.[121-123] Hypoxemia, if present, is usually mild. Children may survive for years with a course characterized by recurrent episodes of acute lower respiratory tract infections.[124] Long-term cor pulmonale or bronchiectasis may develop.[125]

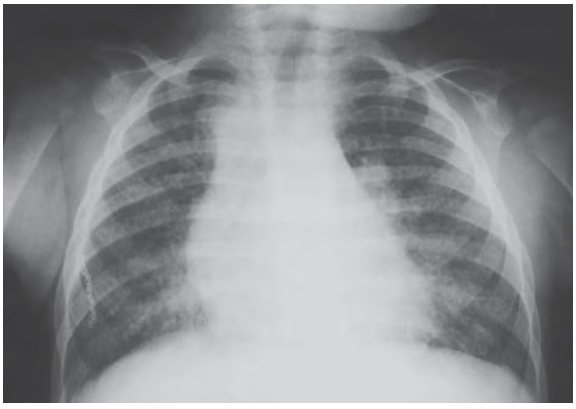
Children with LIP have moderately elevated serum IgG and LDH levels and titers to viral capsid antigen of Epstein-Barr virus.[120] Chest radiographs often show a diffuse reticulonodular pattern, more pronounced centrally (Fig. 37-5A) and bilateral hilar adenopathy which may be difficult to distinguish from pulmonary or miliary TB.[123] Clinically, relatively mild respiratory illness, the presence of parotid enlargement, and a reticulonodular pattern on chest radiograph or CT scan may help to distinguish children with LIP from those with miliary TB.[123] Peribronchiolar thickening alone or normal chest radiographs may also occur.[122,123] Radiographic lesions may resolve in association with worsening immune status.[126,127] Respiratory status may improve with the use of HAART[127]; among HIV-infected adults with LIP, HAART has been reported to result in resolution of radiographic abnormalities.[128]

High-resolution CT may improve diagnostic certainty; typical features include micronodules of 1 to 3 mm in diameter, with a perilymphatic distribution and subpleural nodules (see Fig. 37-5B).[129] The role of nuclear scanning in confirming the diagnosis has not been well studied, but diffuse pulmonary gallium uptake has been reported in an HIV-infected child with LIP.[130]

Children with LIP have marked BAL lymphocytosis, but this is nonspecific. Definitive diagnosis requires open lung biopsy.[122] Lung biopsies revealed collections of lymphoid aggregates, often with germinal centers, surrounding the airways and a significant interstitial infiltrate composed primarily of lymphocytes (Fig. 37-6).

Treatment is symptomatic, including antibiotics for acute infections and inhaled bronchodilators. Although there are no trials of efficacy, case reports indicate a response to systemic corticosteroids.[131-133] Oral corticosteroids are, therefore, recommended for children with hypoxemia.[133] A suggested regimen is prednisone, 2 mg/kg/day for 2 to 4 weeks, until the partial pressure of oxygen increases. Corticosteroids are then tapered to 0.5 to 0.75 mg/kg alternate days provided that the partial pressure remains adequate.[133] Further tapering may be possible as long as adequate oxygenation is maintained. No data exist on the use of inhaled corticosteroids.

LIP is categorized as a World Health Organization (WHO) stage 3 AIDS-defining illness and is thus an indication for initiating HAART in children who are not yet taking antiretroviral therapy.[134]



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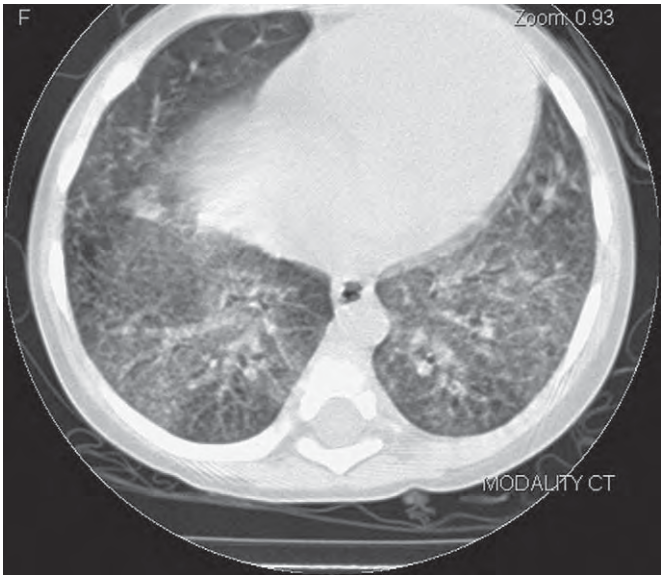

B

Figure 37-5 **A,** Chest radiograph of a child with lymphocytic interstitial pneumonia (LIP) with multiple nodular densities throughout all lung fields. The nodules are larger centrally than peripherally. Also noted are hilar adenopathy and widening of the mediastinum. **B,** High resolution chest CT scan of a child with LIP showing a diffuse micronodular pattern. (**A,** Courtesy Henry Pritzker, Bronx, NY.)

Chronic Pulmonary Infections

Chronic infection resulting from recurrent or persistent pneumonia may produce chronic lung disease. Infectious causes of chronic lung disease include many of the bacterial, viral, or fungal pathogens in Box 37-1. Infection with *M. tuberculosis* is a particularly important and prevalent cause of chronic lung disease in developing countries.[29,30,33-36,123] Distinguishing pulmonary or miliary *M. tuberculosis* from LIP may be difficult; in general, children with LIP are older and less severely ill, enlarged parotid glands may occur, and chest radiology demonstrates a reticulonodular pattern.[123] A few case reports have described chronic *Pneumocystis jiroveci* infection occurring in HIV-infected children, usually manifesting with cystic disease or with pneumatocele formation.[71,135]

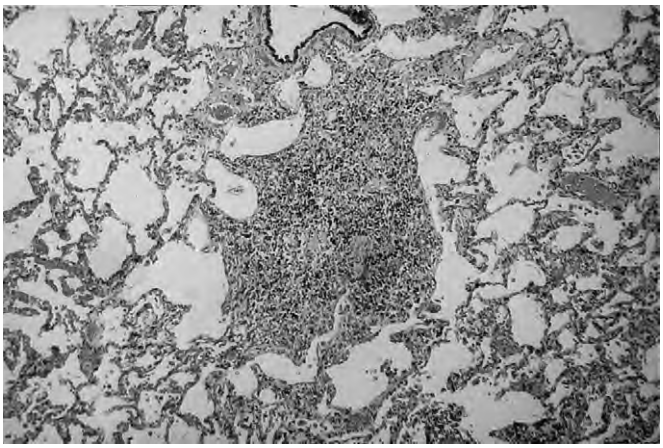

Figure 37-6 Lung biopsy specimen of a patient with lymphocytic interstitial pneumonia. There is a diffuse lymphocytic infiltrate present throughout. An aggregate of cells into a germinal center is also seen in the center of the field. (Courtesy Sumi Mitsudo, Bronx, NY.)

BRONCHIECTASIS

Bronchiectasis may occur following recurrent bacterial infection, secondary to chronic infection including *M. tuberculosis* and as a consequence of LIP.[125,136] The clinical presentation is similar in HIV-infected and uninfected children (see Chapter 69). Clinical features include sputum production, halitosis, digital clubbing, and abnormalities on chest auscultation. Development of bronchiectasis may be associated with the degree of immunosuppression; among 23 HIV-infected children (median age of 7.5 years) with bronchiectasis, all had CD4 T cell counts less than 100 cells/mm^3.[136] Therapy includes physiotherapy and aggressive treatment of intercurrent infections.

MALIGNANCY

Children with HIV have an increased risk of malignancy, which is reported in 2.5% of children with AIDS in the United States.[137] The most common malignancy is non-Hodgkin lymphoma (NHL) followed by Kaposi sarcoma (KS), leiomyosarcoma, and Hodgkin lymphoma.[137,138] Infection with EBV virus has been associated with the development of NHL in HIV-infected children—including those with mild immunosuppression.[138] Primary NHL may arise in a lymph node or be extranodal.[137,138] AIDS-related NHL may occur in almost any extranodal site including the lungs; in addition, pulmonary disease may result from dissemination from a primary focus.

In African HIV-infected children, KS is the most common AIDS-defining malignancy.[139] The epidemiology of childhood HIV-associated KS is probably related to the prevalence of human herpes virus-8 infection, which may be transmitted from an infected mother.[139-141] The most common clinical presentation is that of violaceous plaques on the skin.[142] Pulmonary dissemination may produce chronic progressive dyspnea, cough, and fever. Kaposi sarcoma may also produce upper airway obstruction. Hemoptysis may occur with endobronchial lesions.[140,142] Chest radiograph abnormalities include bilateral adenopathy, perihilar infiltrates, pleural effusion, or combinations of interstitial, alveolar, or nodular patterns. The finding of poorly marginated discrete lesions on CT scan may be specific for KS.[143] Thoracentesis may reveal serosanguineous or hemorrhagic exudates, but is nonspecific for KS. The diagnosis is best made by open lung biopsy. The outcome is generally poor.

MISCELLANEOUS

Desquamative interstitial pneumonitis, bronchiolitis obliterans, and nonspecific interstitial pneumonitis occur in children with AIDS. The manifestations are progressive dyspnea, hypoxemia, cough, and sometimes fever; radiographs reveal interstitial pneumonitis. These conditions may be difficult to distinguish from LIP or miliary TB without open lung biopsy,[123] which is required for definitive diagnosis.

PITFALLS AND CONTROVERSIES

- HIV-infected children are at higher risk for pneumococcal pneumonia or bacteremia than HIV-uninfected children; but the efficacy of the pneumococcal conjugate vaccine is lower in HIV-infected children.
- Diagnosis of TB in HIV-infected children is difficult owing to anergy, nonspecific signs and radiologic changes, and difficulty in obtaining microbiologic confirmation.
- An immune reconstitution inflammatory syndrome (IRIS) characterized by a paradoxical worsening in clinical signs occurs with mycobacterial infections and is difficult to distinguish from other infections, multidrug resistant mycobacterial infections, or nonresponse to mycobacterial therapy.
- The use of corticosteroids in PCP has not been tested in any randomized trials in children but historical comparisons and adult studies report efficacy. However, the impact of corticosteroids on CMV pneumonitis, which may coexist with PCP, is unclear.
- Chronic pulmonary TB or miliary TB may be difficult to distinguish clinically or radiologically from LIP.

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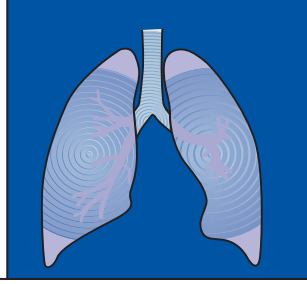

CHAPTER 38 Pertussis

Ziad M. Shehab

TEACHING POINTS

- The most severe morbidity and essentially all the mortality from pertussis occur in infants under 6 months of age, who cannot be protected by immunization.
- Reports of pertussis continue to increase sharply, especially among adolescents and adults as immunity to pertussis wanes with time. Natural disease results in protection for about 15 years, while vaccination is protective for about 6 years.
- Pertussis in older children and adults may be manifested by chronic cough. Up to 25% of adults with coughing illnesses of more than 1 week's duration have serologic evidence of pertussis.
- Older children, adolescents, and adults are a major source of exposure of young infants. Routine immunization of children 11 to 12 years of age is now recommended with a vaccine with reduced dose diphtheria and tetanus toxoids and acellular pertussis vaccine (Tdap). These vaccines were licensed in the United States in 2005. Appropriate immunization of all household members of infants under 1 year of age is critical in their protection from exposure to pertussis.
- Treatment and prophylaxis of pertussis are best achieved with a 5-day course of azithromycin.

Pertussis is a serious respiratory illness caused by the bacterium *Bordetella pertussis*. The disease was described as early as the fifteenth century, and the first report of an epidemic is credited to Guillaume de Baillou for his description of the 1578 epidemic in Paris.[1] The organism was first identified and cultured by Jules Bordet and Octave Gengou at the Pasteur Institute in 1906.[2] The name *pertussis*, meaning "violent cough," was coined by Sydenham in 1679.[3] This prolonged tussive illness is fittingly described by the Chinese as the "100-day cough."

The illness is characterized by paroxysmal bouts of coughing followed by the classic whoop in an afebrile or a mildly febrile person. Not all infected individuals with the infection develop these symptoms; neonates sometimes present with apnea without coughing spells.[2-6] Pertussis is the cause of significant morbidity and mortality in infants under 1 year of age, especially in preterm infants and those born to young mothers.[7,8] About one fourth of children and adults with a coughing illness lasting longer than 7 days have serological evidence of pertussis. Prevention of pertussis disease has been largely accomplished by immunization, first with the whole cell vaccine and, more recently, with the acellular pertussis vaccines. The infection that remains endemic in adolescents and adults, where it is underrecognized, is responsible for the persistence of the epidemics that are seen in young infants approximately every 3 years.[9] Over the past 25 years, a better understanding of the epidemiology and biology of pertussis is leading to efforts toward the control and perhaps eradication of pertussis.

EPIDEMIOLOGY, RISK FACTORS, AND PATHOGENESIS

Pertussis is highly contagious and is distributed worldwide, resulting in an estimated burden of 42.7 million cases in 2002 and leading to the death of about 293,699 people, essentially all infants under 4 years of age,[10] with 90% of cases occurring in developing countries.[11] In the United States, pertussis was responsible for 270,000 cases of severe tussive illness and 10,000 deaths each year in the prevaccine era.[12] After the introduction of the whole cell vaccines in the 1940s, there was a sharp decline in the number of cases, with a nadir of 1010 cases reported in 1976, followed by a steady rise to record levels of 25,827 in 2004[13] (Fig. 38-1). Most of this increase comes from reports in adolescents and adults, with a significant component coming from improved recognition of the disease such as was seen in Massachusetts in 1989 through 1998[14] and Wisconsin in 2000 through 2004.[13] Even though the rate of pertussis has decreased by 150-fold with the introduction of pertussis immunization, epidemics of disease continue to occur in 2- to 5-year cycles, and the infection remains endemic in adolescents and adults. Pertussis remains largely underreported in the United States and worldwide, with only 5% to 25% of cases being reported in developing countries.[9,11]

Patients are most infectious during the first week of illness. Infectivity decreases during the 2 weeks that follow. Transmission occurs by droplet nuclei, especially from individuals with cough. Although no long-term carrier state has been identified, asymptomatic "transient carriers" have been described but their role in transmission of the organism is thought to be minimal.[15] Silent carriage is infrequent, is transient, and is most likely unimportant in the epidemiology of the disease.[16]

Fomites are not a factor in transmission, and there is no known animal reservoir for pertussis. Attack rates among susceptibles are very high, ranging from 50% to 100% depending on the nature of the exposure.[17] The risk of transmission

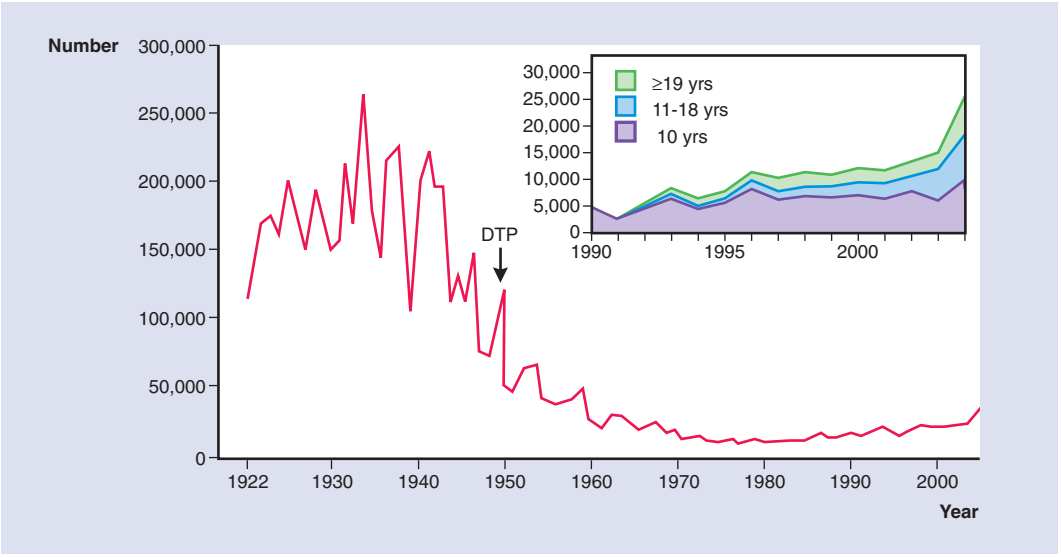

Figure 38-1 Number of pertussis cases per year: 1922-2004, United States. (Reprinted from Centers for Disease Control and Prevention: Preventing tetanus, diphtheria, and pertussis among adolescents: Use of tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccines. Recommendations of the Advisory Committee on Immunization Practices. MMWR 55(RR-3):1-43, 2006.)

is related to the closeness of contact to the index case. Attack rates have ranged from 25% to 50% among unimmunized school contacts and 70% to 100% in households. Natural disease provides almost complete protection during childhood, whereas vaccine-induced immunity is less complete, with an incidence rate of 10% to 20% in fully immunized children and up to 50% in household settings.[18] Natural disease confers protection for about 15 years, whereas vaccine-induced immunity lasts up to 6 years.[19]

Immunity secondary to natural disease is not complete. In such adults and children, reinfection may result in a typical pertussis syndrome; a short, atypical illness; or it may be asymptomatic. The rate of infection in adolescents and adults with a history of pertussis or serologic evidence of prior immunity ranges from 5% to 20%.[13,20] These infections may be important in boosting immunity.

Vaccine-related immunity also wanes with time. During an epidemic, Lambert[17] demonstrated a household attack rate of 20% for recipients of whole cell vaccine in those immunized within 3 years, whereas the attack rate was 95% for those immunized 12 or more years earlier. Jenkinson[21] showed a decline in protective efficacy in young infants from 100% in the first year after immunization to 52% four years later, highlighting the need for a preschool booster immunization. Asymptomatic infection is now more common in preschoolers than in school-aged children, and the attack rate of laboratory-confirmed pertussis increases with the age of the child. The protection provided by the vaccine is therefore short lived, and immunization of school children, adolescents, and adults is necessary.[9,13,22] Pertussis has a moderate seasonality with a higher incidence in the summer and autumn.

The epidemiology of pertussis is changing since the introduction of pertussis vaccines. In areas of low vaccine penetration pertussis affects mostly children in the 2- to 6-year-old age group; approximately half of unimmunized children develop pertussis by age 5, and essentially all were infected by age 15, with about three fourths experiencing symptomatic infection. It is mostly a disease of young children and less so of young infants who were partially protected by transplacental maternal antibody. Repeated exposures during epidemics resulted in high levels of protection by the time these children reached adulthood. Whole cell pertussis vaccine is responsible for a major reduction in the number of cases of pertussis and has caused a significant shift in the peak age of disease. Thus, children are protected well during childhood, but because of the limited duration of vaccine-induced protection and the decrease in opportunities for reexposure, adults become susceptible again, and newborns and young infants are no longer protected by maternally derived antibody.[23] As a result, the disease becomes most prevalent among young infants who are at highest risk for high morbidity and mortality from this disease.[24] Although the size of the epidemics has been reduced, the interval between epidemics has not significantly changed since the introduction of the vaccine.[9] In Canada, a change of the epidemiology was observed in the outbreak of 2000; namely, a decrease in pertussis in children less than 5 years of age and a significant rise in infections in preteens and teens. The drop in pertussis among infants and preschoolers may be the result of the introduction and widespread use of five-component acellular pertussis vaccine since 1996 or may be the result of the use of a relatively ineffective whole cell vaccine in Canada in the 1980s and early 1990s.[25]

After a nadir in 1976, the reported incidence of pertussis has been increasing in all age groups, with a disproportionate increase in preadolescents, adolescents, and adults. Over the past 15 years, there was an 18.8-fold increase in reported cases in 10- to 19-year-olds and a 15.5-fold increase in adults, compared to a 1- to 5-fold increase in younger age groups. Thus, in 2004, adults accounted for 29% of reported cases, 11- to 18-year-olds for 34%, those younger than 12 months for 13%, and 1- to 10-year-olds for 21%. The incidence outside of the first year of life is highest for those 10 to 19 years old.[7,26]

Adults and adolescents have been recognized as a source of exposure of infants for over 25 years. Nelson[27] and other investigators have demonstrated that pertussis in adults is often atypical and asymptomatic and occurs in individuals with a history of prior immunization and even prior disease.[28-32] Endemic infection in adults may act as a reservoir from which infection is spread.[33] A recent study involving surveillance in four states shows that in 75% of the cases, the source of exposure is in the household and is typically an adolescent or adult.[34,35]

Indeed, antibody levels to pertussis antigens are often undetectable in the serum of adolescents and adults.[36] *B. pertussis* is a gram-negative, faintly staining, pleomorphic, nonmotile coccobacillus whose only reservoir is human. It is transmitted by the inhalation of aerosols of *B. pertussis* produced by a patient in the catarrhal or paroxysmal phase of the illness. Patients who have had symptoms for 4 weeks or longer are generally noninfectious.

The genus *Bordetella* includes nine species, of which four are closely related and cause disease in humans. *B. pertussis* is the major cause of the pertussis syndrome, while pertussis associated with *B. parapertussis* is less severe and lacks the typical lymphocytosis. *B. bronchiseptica,* the cause of canine distemper, can result in coughing illnesses in humans. *B. holmesii* has been associated with septicemia and some respiratory infections.[37] Infections with members of the genus *Bordetella* other than *B. pertussis* are not preventable by pertussis vaccines.

Pertussis is not an invasive infection of the respiratory tract. The illness is mediated by the effect of the toxins of *B. pertussis* on respiratory epithelial cells. Attachment to these cells is the first step in the pathogenesis of this infection and is mediated by a number of adhesins such as filamentous hemagglutinin (FHA), fimbriae (FIM), pertussis toxin (PT, also known as lymphocytosis promoting factor), lipopolysaccharide (LPS), and pertactin (PRN), resulting in redundancy in the adhesion function. In vitro, FHA is the major adhesin; however, its role in attachment does not seem to be critical in the presence of other adhesins. Vaccine studies point to pertactin as the most important vaccine antigen with regards to protection. The second step in pathogenesis, cell evasion from the immune system, is facilitated by PT, which inhibits migration of lymphocytes and macrophages to areas of infection, and adenyl cyclase, which impairs phagocytosis by excessive production of cAMP by the cell. Local tissue damage to ciliated epithelial cells is mediated by tracheal cytotoxin, dermonecrotic toxin, and perhaps adenyl cyclase, and may be responsible for the paroxysmal cough. The nature of the toxin and the identity of the cell that triggers the cough are not known.[37,38] The systemic manifestations of the toxins that are most easily recognized are leukocytosis and lymphocytosis seen in young infants and is the result of PT. It is also responsible for the hyperinsulinemia that may manifest as hypoglycemia in some young infants. Encephalopathy is likely related to anoxia associated with paroxysms of cough.[39]

CLINICAL FEATURES, COURSE, AND PROGNOSIS

> It comes only by degrees, and is at first dry, but when it has continued ten or twelve days, it turns humid, and the matter which is then coughed up looks ripe; nevertheless it increases more and more, leaving long intervals; the fits return at certain hours, but continue at each time with such violence and for so long a time, that the child grows blue in the face, its eyes look as if they were forced out, and they run besides, and a bleeding of the nose is sometimes brought on; it coughs till it is quite out of breath, that one is in apprehension of its being choaked [sic]; for if the patient now and then is capable of drawing some breath, it is with a sounding which very much indicates with what difficulty the lungs can admit air. The coughing continues, and does not leave off for that time, till the child vomits up a quantity of slime.
>
> ROSEN VON ROSENSTEIN (1776)[40]

The incubation period of pertussis is usually 7 to 10 days with a range of 4 to 21 days. However, in household settings, one fifth of the cases occur more than 4 weeks after onset of symptoms in the primary case.[41] *B. pertussis* attaches to the mucosa of the nasopharynx, trachea, bronchi, and bronchioles, increasing the secretion of mucus, which is initially thin and later viscid and tenacious. The classic disease, most often seen in unimmunized children, lasts 6 to 12 weeks and is divided clinically into three stages: catarrhal, paroxysmal, and convalescent.[42,43] The catarrhal phase, which lasts for 1 to 2 weeks, starts with symptoms that are indistinguishable from those of an upper respiratory tract infection and include rhinorrhea, conjunctival injection, sneezing, anorexia, listlessness, and a hacking nocturnal cough that gradually becomes diurnal. The cough is usually not associated with fever and gradually increases in severity and intensity to become explosive and paroxysmal in the second week after the onset of symptoms (Fig. 38-2). The patient is most infectious during the catarrhal phase, and infectivity decreases during the paroxysmal phase.

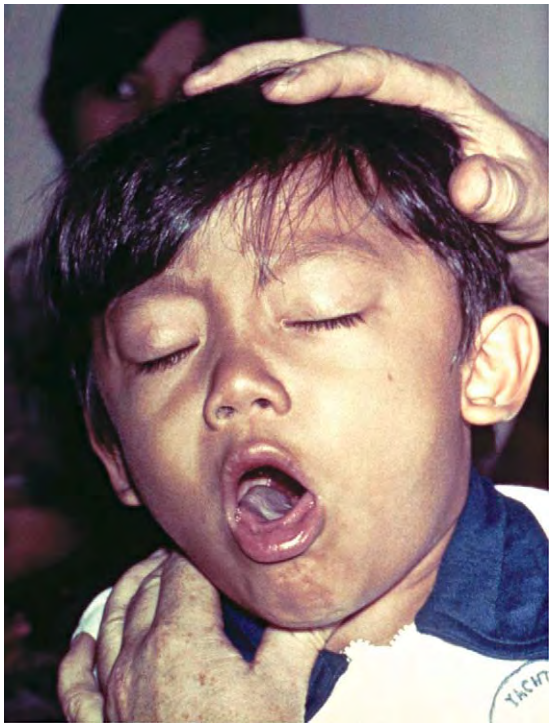

Figure 38-2 Child with cough due to pertussis. (Image at http://phil.cdc.gov/phil/quicksearch.asp ID# 6378; courtesy of Centers for Disease Control and Prevention.)

The paroxysmal phase persists for 1 to 4 weeks and is dominated by severe coughing that can occur in paroxysms characterized by five or more short coughs *without an inspiration* followed by a deep inspiratory effort, which may result in the characteristic whoop. During these episodes, large amounts of mucus are expelled, often causing vomiting and, in young infants, choking spells and cyanosis. The child may be exhausted after a paroxysm. The paroxysmal episodes can occur in rapid succession and may be triggered by stimuli such as feeding, sucking, or crying. Weight loss can be seen as a result of frequent vomiting or the refusal of the child to eat. Apneic spells may occur in infants under 6 months of age, in whom paroxysmal spells are sometimes not seen. Infants with pertussis have a higher frequency of apneic pauses and hypoxemia along with ventilation-perfusion mismatch, resulting in the rapid onset of hypoxia.[44] Whoops may not be present in atypical cases, in young infants, in immunized individuals, and in children with pneumonia. Immunized children can develop subclinical infections.[45] Unfortunately, even in the presence of classic symptoms, the diagnosis is often missed.[46]

The convalescent phase usually starts 4 to 6 weeks after the onset of disease and is characterized by a gradual decrease in the frequency and severity of the episodes. A nonparoxysmal cough may persist for many months. The duration of the illness in uncomplicated cases is 6 to 20 weeks.[43]

In the neonate, initial symptoms consist of poor feeding, tachypnea, and cough. The catarrhal phase may be short or absent, and many neonates do not develop a paroxysmal cough. Apnea, gagging, cyanosis, and bradycardia may be the first manifestations and are sometimes not initially associated with cough. Their symptoms often start at about 1 week of age and these young infants often require hospitalization, typically at 2 to 3 weeks of age, and sometimes require endotracheal intubation and mechanical ventilation.[4-6]

Pertussis in adults may be similar to that in young infants. Severe disease is unusual in this age group; however, the illness is often long lasting[47] and is unrecognized.[48] In their study of 664 adolescents and adults with pertussis, De Serres and colleagues found that 97% of patients had coughing illness lasting longer than 3 weeks, and 52%, longer than 9 weeks. The paroxysmal episodes lasted 3 weeks or longer in 73%, and 69% had a whoop. Complications were more frequent in adults (28%) than in adolescents (16%), as was cyanosis (9% and 6%, respectively) and hospitalization (3.5% and 1.4%, respectively). Pneumonia occurred in 2% of individuals under 30 years of age and 5% to 9% of those over 30.[49] Milder disease may present as an illness with a nonspecific cough; indeed, prolonged coughing may be the only manifestation of pertussis among immunized individuals. Household contacts of individuals with primary pertussis experience a high rate of infection, many of which are subclinical; in this setting, the infection rates were 46% in those contacts who remained well, 43% of those with mild disease, and 80% in those with pertussis.[50] During outbreaks, a coughing illness of 7 or more days is associated with serologic evidence of pertussis in 17% to 52% of adolescents and adults.[51-56] Post-tussive vomiting occurs in 17% to 50%. Thirty-eight percent of adolescents with pertussis reported in Massachusetts in 1989 through 2004 had already been coughing for more than one month at the time of diagnosis.[13] Other manifestations include pharyngeal symptoms in one third of adults, and sweating in 40% to 50% of persons over 30 years of age. Recurrences of a pertussis-like illness can occur after upper or lower respiratory tract infections.

Major complications are most commonly respiratory in nature, such as pneumonia (which may be primary or the result of secondary infection), apnea, asphyxia, bronchopneumonia, atelectasis, bronchiectasis, interstitial and subcutaneous emphysema, and pneumothorax.[32,43] Central nervous system complications have been reported in up to 14% of cases.[17] Acute encephalitis can progress to coma, stupor, or convulsions. Cerebral edema and hemorrhage can be seen. Long-term sequelae include spastic paralysis, mental retardation, and other permanent neurologic sequelae. In the recent U.S. experience, isolated seizures occurred in 2.2% of cases and encephalopathy in 0.7%.[39] Patients may also develop ulceration or laceration of the frenulum of the tongue, epistaxis, melena, subconjunctival hemorrhage, diaphragmatic rupture, hernias, rectal prolapse, apnea, or rib fractures.[37]

Severe complications of pertussis occur primarily in infants younger than 6 months.[57,58] They have the highest rates of hospitalization (63%), pneumonia (12%), seizures (1.4%), and encephalopathy (0.2%). These rates are even higher in infants under 2 months of age. Most deaths secondary to pertussis occur in young infants, especially those under 2 months of age.[59,60]

Nutritional deficiencies are the direct result of the infant's inability to eat because of the paroxysms associated with feeding. The malnutrition that follows, combined with the disease, can lead to death.

The case-fatality rate is 1.3% in children younger than 1 month and 0.3% in those aged 2 to 11 months old.[43,61] The mortality rate among infants in the United States is 2.4 per million, and 90% of all pertussis fatalities occur in infants under 6 months of age. Marked leukocytosis and the presence of pneumonia tend to predict poor outcomes.[24,62]

After pertussis, there is a decrease in forced expiratory flow at low lung volumes, reflecting obstruction of the more peripheral airways, and a lower mixing index, indicating a maldistribution of ventilation, findings consistent with the diffuse pulmonary inflammation and inspissated mucus seen in this disease. These decreases in pulmonary function persist into later childhood.[41] Other studies fail to show differences in respiratory symptoms or asthma in adolescents with a history of a pertussis-like illness in childhood.[63] There is no effect on lung function or bronchial reactivity in adults who had pertussis in childhood. The only observed association is with a reduction of forced vital capacity (FVC) in men, a finding that is difficult to interpret.[64]

DIAGNOSIS

Successful detection of *B. pertussis* depends largely on the quality of specimen collection and transport to the laboratory, stage of the disease, prior antimicrobial therapy, and immunization status. The preferred specimens are posterior nasopharyngeal (NP) swabs or aspirates. Throat swabs are not appropriate. The nature of the swab material for culture isolation should consist of Dacron or calcium alginate. Dacron swabs are recommended for PCR testing; calcium alginate swabs should not be used for PCR detection because of

inhibitory factors in the fiber. Transport systems include the Regan-Lowe (RL) transport medium, 1% acid-hydrolyzed casein, and Amies medium with charcoal. The latter two have a stability of less than 24 hours. Direct plating of NP specimens onto agar plates provides optimal sensitivity. The medium of choice for culture of the organism is charcoal agar (RL agar) supplemented with 10% horse serum. Bordet-Gengou agar is also used but the medium must be freshly made, making it less practical than charcoal agar, which has a shelf-life of 8 weeks.[37]

Detection of the organism is accomplished by direct fluorescent antibody (DFA) testing, nucleic acid detection, or culture methods. The DFA sensitivity ranges from 30% to 71% compared to culture, and the specificity is highly variable. PCR has been shown to be more sensitive than DFA or culture and remains positive longer in the course of the disease or following antibiotic exposure, presumably because of its ability to detect dead organisms. PCR also demonstrates higher sensitivity in people with mild or atypical symptoms and in older persons.[65-67]

The culture has a specificity of 100%. While the sensitivity of cultures could be as high as 80% to 90%, it typically ranges from 30% to 60% in the field. The yield drops rapidly after 2 weeks of coughing illness, after antimicrobial therapy, or prior vaccination. Culture has a sensitivity of only 1% to 3% after 3 weeks of cough.[13,68] Serologic assays, typically enzyme immunoassays, have been used to measure IgG, IgM, and IgA antibodies to PT, FHA, pertactin, and fimbriae. In general, a 2-fold increase in IgG and IgA to PT or FHA is considered a reliable indicator of infection with 90% of infected persons developing an IgG response to PT and FHA. An IgG response to PT is specific for *B. pertussis*, because no other member of the genus *Bordetella* expresses PT.[41]

The white blood cell count is usually moderately elevated to between 15,000 and 20,000/mm^3 but may be normal or may be as high as 60,000/mm^3, usually with 60% to 80% lymphocytes. Marked leukocytosis, with white blood cell counts of more than 25,000/mm^3, is seen in approximately 40% of children. Young infants under 6 months of age are less likely to have marked leukocytosis.[43] The disease caused by *B. parapertussis* resembles that caused by *B. pertussis* except for its milder nature and the absence of lymphocytosis.[69]

The differential diagnosis of atypical pertussis includes bronchitis and upper respiratory infections secondary to adenoviruses, parainfluenza and respiratory syncytial viruses, *Mycoplasma pneumoniae*, and *Chlamydophila pneumoniae*.[70,71] These agents may represent coinfections with *B. pertussis*.[72,73] Other causes of chronic cough, such as asthma, gastroesophageal reflux, postviral cough, chronic sinusitis with postnasal drip, tuberculosis, other chronic lung diseases, and malignancies, should also be considered in the differential diagnosis.[24] *Bordetella parapertussis* accounts for about 5% of pertussis illnesses and occurs in small local epidemics.

TREATMENT

Oral erythromycin, in a dosage of 40 to 50 mg/kg/day in 4 divided doses for 14 days, has been the mainstay of antimicrobial therapy. Given during the catarrhal stage, it may shorten the clinical illness and results in eradication of the organism within 5 days. It is generally thought that therapy after onset of symptoms has no effect on the clinical course. However, recent studies suggest that treatment early in the paroxysmal stage results in a decrease in the number of whoops.[74,75] Erythromycin is not indicated for neonates under 1 month of age because of the complication of hypertrophic pyloric stenosis. The erythromycin dose for adults is 1 to 2 g/day and is associated with a high rate of gastrointestinal side effects. *B. pertussis* is nearly always susceptible to the macrolides, with only three erythromycin-resistant isolates described to date. A 7-day regimen has been shown to be equivalent to the 14-day regimen[76] (Table 38-1).

The newer macrolides, azithromycin and clarithromycin, are also effective in eradicating *B. pertussis* and are better tolerated than erythromycin.[77-80] The dose of azithromycin is 10 mg/kg on days 1 to 5 for infants under 6 months of age and 10 mg/kg as a single dose on day 1 followed by 5 mg/kg on days 2 to 5 for children 6 months old and older, with a maximum dose of 500 mg on day 1 followed by 250 mg on days 2 to 5 for adults. The clarithromycin dose is 15 mg/kg/day in two divided doses for 7 days for children over 1 month of age; the dose for adults is 1 g/day in two divided doses for 7 days. Roxithromycin has similar pharmacokinetics and mechanism of action as azithromycin and clarithromycin and could be used for treatment or prophylaxis; however, no studies have been conducted with this agent.[81]

Trimethoprim-sulfamethoxazole (TMP-SMZ) can be used for those who cannot tolerate a macrolide or in the rare instances of macrolide resistance. The dose of TMP-SMZ is 8 mg/kg/day of trimethoprim and 40 mg/kg/day of sulfamethoxazole divided into two doses for 14 days. The dose for adults is 320 mg of trimethoprim and 1600 mg of sulfamethoxazole a day divided into two doses for 14 days. Ampicillin, amoxicillin, and cephalosporins have no activity and should not be used for prophylaxis or treatment.[82]

The same agents and administration regimens are used for prophylaxis of persons with direct exposure to patients with active pertussis. Prophylaxis is initiated only if the contact with the index case occurred 3 or fewer weeks from the onset of the cough in the index case except in high-risk patients (e.g., neonates), where it should be considered for the first 6 weeks from onset of symptoms.

Salbutamol is ineffective in ameliorating the symptoms of pertussis.[83-85] The benefits of the use of steroids have not been established.[86-88] Cough suppressants are not useful in the symptomatic management of pertussis, nor is diphenhydramine. Supportive therapy is a critical component of the care of infants with pertussis, including a quiet environment and gentle suctioning of respiratory secretions, which are important in preventing attacks or paroxysmal coughing. Administration of oxygen may be needed during paroxysms of cough to prevent hypoxia. Rarely, infants need to be intubated, paralyzed, and ventilated to allow for proper oxygenation. High-frequency jet ventilation is sometimes necessary. Maintenance of nutrition is essential during the acute phase of the illness. Small frequent feeds or nutrition via a nasogastric tube may be needed. Rarely, careful attention to hydration and nutrition has to be maintained with intravenous fluids. Intensive care measures may be needed in severe cases. Infants younger than 6 months or those with cyanosis or excessive vomiting during paroxysms may initially be admitted to the hospital.

Table 38-1
Recommended Antimicrobial Treatment and Postexposure Prophylaxis for Pertussis, by Age Group

Age Group	Primary Agents			Alternate agent
	Azithromycin	Erythromycin	Clarithromycin	TMP-SMZ
<1 month	Recommended 10 mg/kg/day as a single dose for 5 days	Associated with pyloric stenosis Use if azithromycin unavailable 40-50 mg/kg/day in 4 divided doses for 14 days	Not recommended	Contraindicated in <2 months (risk of kernicterus)
1-5 months	10 mg/kg/day as a single dose for 5 days	40-50 mg/kg/day in 4 divided doses for 14 days	15 mg/kg/day in 2 divided doses for 7 days	Contraindicated in <2 months TMP 8 mg/kg/day, SMZ 40 mg/kg/day in 2 divided doses for 14 days
Infants (≥6 months) and children	10 mg/kg/day in a single dose on day 1 then 5 mg/kg/day (max 250 mg) on days 2-5	40-50 mg/kg/day (max 2 g/day) in 4 divided doses for 14 days	15 mg/kg/day in 2 divided doses (max 1 g/day) for 7 days	TMP 8 mg/kg/day, SMZ 40 mg/kg/day in 2 divided doses for 14 days
Adults	500 mg in a single dose on day 1 then 250 mg/day on days 2-5	2 g/day in 4 divided doses for 14 days	1 g/day in 2 divided doses for 7 days	TMP 320 mg/day, SMZ 1600 mg/day in 2 divided doses for 14 days

From Aoyama T, Sunakawa K, Iwata S, et al: Efficacy of short-term treatment of pertussis with clarithromycin and azithromycin. J Pediatr 129:761-764, 1996; and Centers for Disease Control and Prevention: Recommended antimicrobial agents for treatment and postexposure prophylaxis of pertussis—2005 CDC guidelines. MMWR Morb Mortal Wkly Rep 54(RR-14):1-17, 2005.

Respiratory isolation should be instituted and continued until the patient has received macrolide therapy for 5 days or, in the absence of macrolide therapy, is at least 3 weeks from the onset of paroxysms.[89] Children with suspected pertussis who attend child care facilities should not be admitted to the facility until their disease is evaluated. They can return after the administration of a macrolide for 5 days. Contacts who have immunization delays should be immunized, as should infants under 4 years of age whose last vaccination was given 6 months or longer before the exposure. A macrolide may be given to household contacts irrespective of immunization status.

PREVENTION

Universal immunization of infants and children at 2, 4, 6, and 12 to 18 months and 4 to 6 years of age has been the mainstay of prevention of pertussis. Vaccines consisting of a combination of diphtheria and tetanus toxoids with whole cell pertussis vaccines consisting of killed organisms (DTP) are used worldwide in children under 7 years of age and are highly effective. They are associated, however, with frequent local and systemic reactions. Multiple uncontrolled series have implicated DTP in neurological events following vaccination. Data from the National Childhood Encephalopathy Study, a prospective case-control study in England and Wales, and subsequent studies in the United States, Denmark, and Canada show no evidence for a causal relationship between DTP and encephalopathy, epilepsy, or sudden infant death syndrome.[37]

DTP vaccines were used in the United States from the 1940s to the late 1990s, when they were replaced by acellular pertussis vaccines (DTaP) containing one or more pertussis antigens along with diphtheria and tetanus toxoids. These vaccines are immunogenic and are associated with fewer side effects than whole cell vaccines. The immunization program has been effective in reducing the incidence of pertussis from a rate of 157 per 100,000 population in the prevaccine era to less than 1 per 100,000 in the 1970s.[23] In the setting of household exposure of children 1 to 4 years of age, the efficacy is 59% to 97% depending on the case definition. The efficacy was 64% for any cough illness.[90] Vaccine efficacy depends on the number of vaccine doses and is 18%, 48%, 58%, and 68%, respectively, after one, two, three, or four DTP doses. Whole cell pertussis vaccines demonstrated excellent efficacy (89% to 96% for typical pertussis and 81% to 83% for mild or atypical pertussis), with the exception of the Connaught vaccine, which was poorly immunogenic, whereas the three- and five-component acellular vaccines now used in the United States had an efficacy of 84% and 85% against classic pertussis.[41,91,92] After a 150-fold drop in the incidence of pertussis, there has been a gradual increase in the number of reported pertussis cases in the United States, which may be explained partly by better recognition of the disease and by the use of a less effective DTP vaccine in the period from 1985 to 1992.

Acellular pertussis (DTaP) vaccines lack LPS and are less reactogenic.[93] They result in significantly fewer episodes of persistent crying, fevers of higher than 40.5° C, hypotonic-hyporesponsive episodes, and febrile seizures than do DTP vaccines. Seven trials in the 1990s have evaluated the efficacy of eight acellular vaccines. In general, vaccines that contain one, two, or three antigens (PRN, FIM) in addition to FHA and PT have better efficacy against both mild and typical pertussis than vaccines that contain only PT or PT and FHA.[41]

However, despite routine pertussis immunization in childhood, the infection remains endemic in the adolescent and adult populations and results in epidemics in young children every 2 to 5 years.[9] In order to control the circulation of *B. pertussis*, immunization programs that target adolescents and adults of all age groups are necessary.[94] To date, only Australia, Austria, Canada, France, and Germany have incorporated adolescent immunization in their program. In the United States, two vaccines for adolescents and adults (Tdap) were licensed in 2005 and are now recommended for children and adolescents 10 to 18 years of age. They consist of reduced-dose diphtheria toxoid, tetanus toxoid, and three (PT, FHA, PRN) or five (PT, FHA, PRN and FIM 1 and 2) pertussis antigens. The vaccine containing five components is licensed for use for ages 11 to 64 years, while the three-component vaccine is licensed for use in 10- to 18-year-olds. Their reactogenicity is similar to that of dT vaccines, and their immunogenicity against diphtheria and tetanus is equivalent to that of dT.[95] They generate a robust immune response against their component pertussis antigens that lasts for at least 5 years.[96] The preferred age for Tdap immunization is 11 to 12 years, replacing the usual dose of dT. The routine use of Tdap in adolescents is expected to result in net health benefits and will likely be cost effective.[97] Tdap is the preferred vaccine for adolescents aged 11 to 18 years as part of routine wound management if they have not had a dose of tetanus toxoid within the previous 5 years. It is also recommended as a single booster dose of Tdap for adults aged 19 to 64 years who never received a dose of Tdap. The interval between the last dose of dT-containing vaccine and Tdap can be as short as 2 years without dose modification or increase in its side effects. People anticipating having close contact with an infant under 12 months of age should receive Tdap, preferably at least 2 weeks before beginning such contact. The recommended interval from the last tetanus toxoid–containing vaccine is 2 years, but shorter intervals are acceptable. Pregnant women should receive a dose of Tdap in the immediate postpartum period. Women contemplating pregnancy should be encouraged to receive a dose of Tdap. Health care workers should receive a single dose of Tdap as early as 2 years after their last tetanus toxoid–containing immunization. Priority should be given to those in contact with children under 12 months of age.[98]

PITFALLS AND CONTROVERSIES

The duration of immunity afforded by Tdap is not defined at this time. Antibody levels after a booster dose are maintained for at least 5 years. It is anticipated that booster doses of vaccine would not need to be given any more often than once every 10 years based on projected kinetics of antibody decay for antibodies to pertactin.

Immunization of susceptible pregnant women will need to be considered in order to provide the newborn with a good level of antibody through placental transfer. Immunization of close contacts of infants under 6 months of age would be a major step in controlling household exposure. Universal immunization of adults remains an elusive goal especially considering the large number of nonimmunized or underimmunized high-risk adults against such known pathogens as influenza and pneumococcus.[99]

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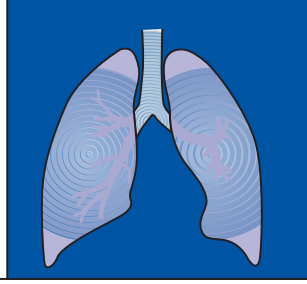

CHAPTER 39 Mycobacterial Infections

Delane Shingadia and David Burgner

TEACHING POINTS

- *Mycobacterium tuberculosis* (MTB) is the most prevalent chronic infection in the world, with two thirds of the global population infected.
- Most infection is asymptomatic (latent tuberculosis [TB] infection [LTBI]). In adults and older children, reactivation of LTBI causes active pulmonary TB disease in about 10% of individuals (so called postprimary disease).
- Children with TB are generally less infectious than adults and are almost always infected by an infectious adult.
- Children are at greatly increased risk of progression of LTBI to TB disease and of uncontrolled progressive primary infection. Identification and treatment of children with LTBI, particularly following household exposure, are therefore essential.
- There is increasing global resistance to anti-TB drugs; recent reports suggest that highly resistant TB may essentially be untreatable.

Mycobacterium Tuberculosis

EPIDEMIOLOGY

Mycobacterium tuberculosis (MTB) is the most prevalent chronic infection in the world. It has been estimated that there were 8.8 million new cases of tuberculosis (TB) globally in 2003 (140 per 100,000 population), of which 3.9 million (62 per 100,000) were smear-positive and 674,000 (11 per 100,000) were coinfected with human immunodeficiency virus (HIV). An estimated 1.7 million people (28 of 100,000) died from TB in 2003, including those coinfected with HIV (229,000).[1] Approximately one third of deaths occurred in children. Figure 39-1 shows the global TB notification rates in 2003 (rates of all TB cases per 100,000 population).[1]

The TB incidence rate has been falling or stable in five of six World Health Organization (WHO) regions but growing at 1.0% per year globally (Table 39-1). The Southeast Asian region is one of those with the largest total number of people with TB cases, with three countries—India, Indonesia, and Bangladesh—accounting for the majority of cases. However, the incidence has been rising more quickly in sub-Saharan African countries with higher HIV prevalence rates. While incidence rates in Western Europe have fallen since 1980, many Eastern European countries showed increasing rates during the 1990s, which peaked around 2001, and have since fallen.[1]

In 1989, the WHO estimated that there were 1.3 million annual cases of TB in children younger than 15 years.[2] However, there are many difficulties in estimating the burden of TB in children, and this is probably a gross underestimate. Issues include the difficulty in establishing a definitive diagnosis, the increased presence of extrapulmonary disease in young children, the lack of standard case definition, and the lower public health priority given to childhood TB compared with that of adult TB. In many resource-limited countries, surveillance data are often unreliable due to poor diagnostic facilities and reporting systems.[3] For purposes of WHO reporting, TB cases are defined as those that are sputum-smear positive for acid-fast bacilli. This means that more than 80% of children with TB will not be represented, as they will not be sputum-smear positive. The proportion of TB cases in individual countries that occur in children is highly variable. In low-prevalence countries this may be less than 5%, whereas in some high-prevalence countries it is estimated to be four times this figure.

Most of the accurate pediatric data come from low prevalence countries such as the United States and those in Western Europe. In the United States, the Centers for Disease Control and Prevention (CDC) case definition of TB includes a positive tuberculin skin test (TST), diagnostic investigations, signs and symptoms compatible with TB, and treatment with two or more antituberculous drugs. National rates in children aged 0 to 14 years have been falling from 3.1 per 100,000 in 1992 to 1.5 per 100,000 in 2001, with a constant 6% of total cases occurring in children. Case rates are the highest for ethnic minority groups. White children younger than 5 years have a rate of 0.5 per 100,000, compared with Hispanic, black non-Hispanic, and Asian/Pacific Island children, whose rates are 7.0, 6.2, and 6.5, respectively. In California, the overall rates of pediatric TB have been falling, and since 1992, this decline has been greatest in children born overseas.[4] Similarly, in low-prevalence countries in Europe, such as the United Kingdom, notification rates for TB have declined over the past 20 years.[5] National survey data from the United Kingdon show a decrease in TB rates in all age groups from 1978/1979, reaching their lowest levels in the mid-1980s before beginning to rise again. Rates in children and young people overall have remained relatively constant over the past 5 years.[6] In contrast to many other developed countries, TB notifications have increased substantially in London, which accounts for 40% of U.K. national

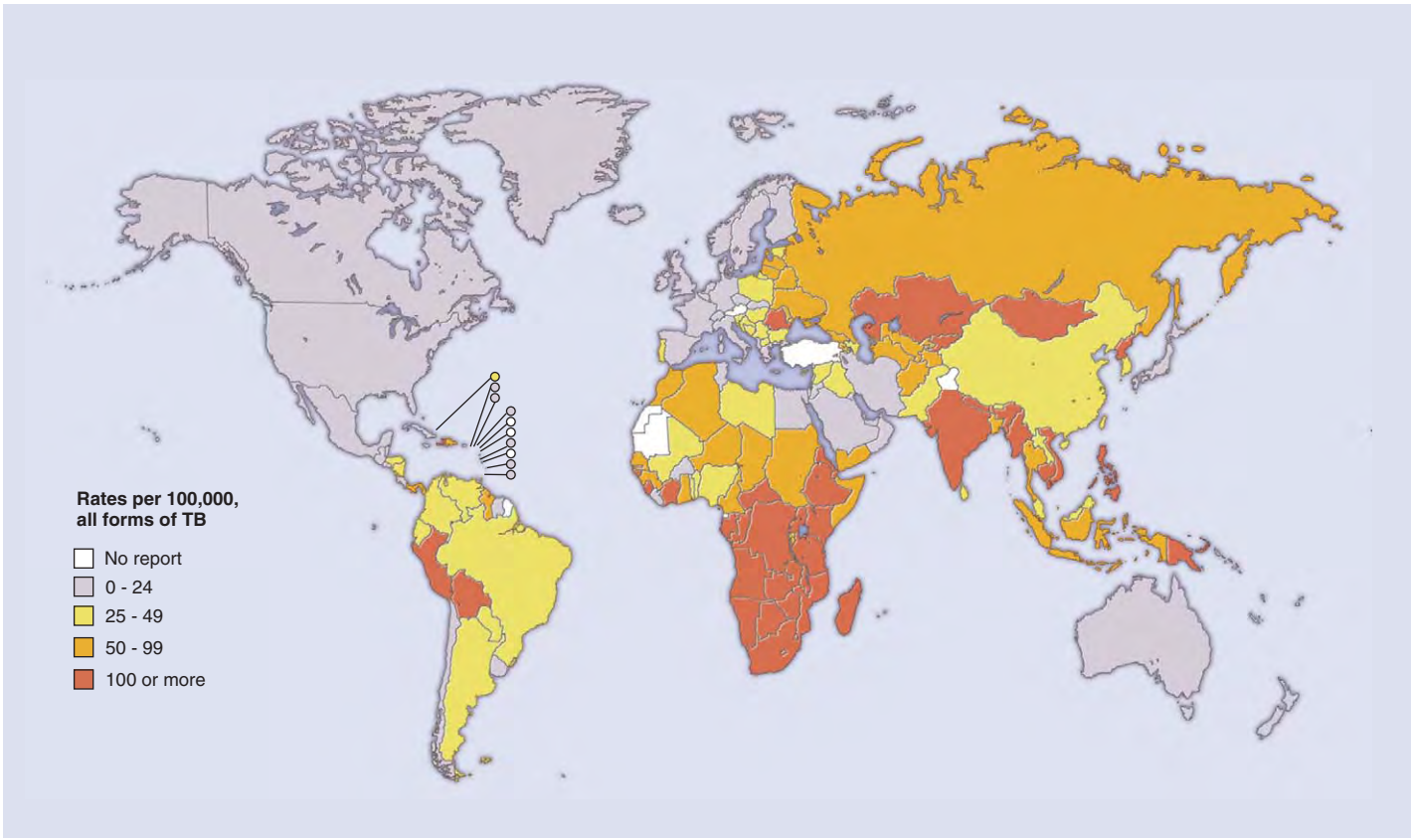

Figure 39-1 Tuberculosis notification rates, 2003. (Redrawn from WHO: Global Tuberculosis Control: Surveillance, Planning, Financing. WHO report 2005. Geneva, World Health Organization, 2005.)

Table 39-1
Estimated Number of Tuberculosis Cases and Incidence Rates Worldwide 1995-2005[1]

	1995		2000		2005	
Region	**Cases***	**Rate†**	**Cases***	**Rate†**	**Cases***	**Rate†**
Africa	1467	242	1857	290	2372	345
Americas	606	123	382	46	370	43
Eastern Mediterranean	745	168	587	121	634	122
Europe	202	47	468	54	439	50
Southeast Asia	3499	241	2986	194	2993	190
Western Pacific	2045	140	2031	120	1927	112
Global	8564	152	8311	137	8735	140

*In thousands.
†Per 100,000 population.

cases. Some areas have recorded rates of greater than 40 per 100,000 in children.[7] The proportion of black African children with TB in 1998 (44%) has increased substantially from 1993 (23%), whereas the proportion of pediatric cases from the Indian subcontinent (ISC) had fallen (21% in 1998 compared with 50% in 1993). Similar patterns have been reported in other low-prevalence countries in Europe, such as Sweden and Denmark.[8,9] In Australia, the majority of TB infection and disease also occurs in those born overseas. Humanitarian refugees, particularly from sub-Saharan Africa, account for many cases.

Accurate data from high-prevalence countries are less readily available. In South Africa, only 55% of children younger than 14 years with TB meningitis were notified.[10] The proportion of childhood TB to the total cases in South Africa is estimated to be 20%.[11] A study in an urban community in the Western Cape Province of South Africa (overall TB incidence estimated at 1149 per 100,000) found that 39% of the caseload occurred in children younger than 14 years.[12] In Botswana, 12% of all reported TB cases occurred among children younger than 15 years in 2000, although these accounted for only 2% of all smear-positive cases. In Malawi, the largest increases in cases in Blantyre from 1985 through 1995 occurred among children aged 1 to 5 years.[13] Because sub-Saharan Africa also has the highest burden of HIV infection, this will no doubt have a major impact on TB epidemiol-

ogy in this region. It has been estimated that based on contact with a smear-positive adult, 700,000 to 800,000 children would develop TB disease over 5 years.[14]

RISK FACTORS FOR TUBERCULOSIS IN CHILDREN

There have been several factors that have been associated with the resurgence of TB in children:

1. Increased travel and migration, particularly from countries with high rates of TB to resource-rich nations, has had a major impact on the epidemiology of TB in those nations. In North America, Australasia, and Europe, high-risk groups include immigrants as well as ethnic minorities, where higher rates of disease are observed in those born overseas compared with low rates in the nonimmigrant population.[15-21] Molecular epidemiologic studies undertaken in Norway and the United Kingdom both suggest that many of the new TB cases in immigrants are due to reactivation of infections acquired abroad.[20,22,23] Immigrant children born in regions with high prevalence who migrate to low prevalence countries are at much higher risk of developing TB for several reasons. First, they are more likely to be exposed to TB in their home country, often through an infectious adult within their household but also within refugee camps. One study of internationally adopted children in the United States found that 19% were TST positive.[24] Humanitarian refugees arriving in Western Australia, mainly from sub-Saharan Africa, have a TST positivity rate of approximately 25% (unpublished data).
2. Socioeconomic risk factors including poverty and crowding continue to be associated with a greater risk of children developing both latent infection and active TB.[25] In South Africa, a significant correlation was found between TB case notification rates in childhood and crowding, economic status, and parental education.[12] Similarly, the overall risk of TB was linked to deprivation, population density, and ethnicity in the United Kingdom.[26]
3. The HIV pandemic has had a profound effect on the incidence of TB, particularly in sub-Saharan Africa, where up to a quarter of the population are HIV infected. HIV is known to greatly increase the annual risk of progression from TB infection to active TB and is thought to be one of the principal causes of the resurgence of TB in this region. The average annual case rates for TB after 1985 have increased approximately twice as fast in countries with high versus low or intermediate HIV seropositivity rates.[27] In children, the association between HIV and infection is not as well characterized, with coinfection rates of 11% to 64%.[28] A multicenter U.S. study found a high annualized TB case rate (51 to 478 per 100,000) among HIV-exposed and HIV-infected children younger than 5 years compared with the 1992 overall U.S. case rate of 5.5 per 100,000 for children this age.[29] In Brazil, the numbers of children with TB with HIV coinfection increased from 23.5% to 31.4%.[30] Similarly high rates have been noted in South Africa, where in one study almost half of children under 12 years of age with culture-proved pulmonary TB were also HIV infected.[31] Despite the high rates of coinfection with HIV and TB in these children, it is still unclear whether HIV-infected children are more vulnerable to TB infection or more likely to progress to disease than HIV-negative children. An important risk factor for TB in HIV-infected children is that they are more likely to be a close contact of a smear-positive adult than HIV-uninfected children. Because TB is the most common opportunistic infection in HIV-infected adults in the developing world, children in this setting are more likely to be exposed to TB irrespective of their HIV status. In New York, Thomas and colleagues[32] found that HIV-infected children were at higher risk of TB than uninfected children born to HIV-infected mothers. Both groups had higher rates than other children in New York, suggesting that increased exposure to TB may also be a contributing factor irrespective of the child's HIV status. The difficulty of diagnosing TB in children, coupled with the difficulty of diagnosing HIV-associated pulmonary infections in children, may have important confounding effects on assessing the epidemiology of TB and TB/HIV coinfection in children. The outcome is also worse for children who are HIV infected with a higher mortality than those who are HIV negative when they develop TB. In Ethiopian children who were HIV positive, there was a 6-fold increased risk of death during an episode of TB compared with an HIV-negative child.[33] In a study of childhood TB in Cote d'Ivoire, Mukadi et al.[34] noted 50% mortality over the 6-month treatment period for HIV coinfected children who had $CD4^+$ percentage of less than 10%. In HIV-negative children, the mortality rate was 4%.
4. Drug-resistant TB is of great importance worldwide as it reflects TB control in the population. Cost of drug therapy, especially for multidrug-resistant (MDR) TB, is more expensive and treatment in many cases is more difficult to implement. However, there are limited data available on drug-resistant TB in children. In most children, definite confirmation of drug-resistant TB will not be possible, due to lower rates of microbiological identification from pediatric samples. Often, the diagnosis of drug-resistant TB will be made on the basis of confirmation of drug resistance in the adult index case. In high-prevalence communities, however, children may have multiple exposures within the same household, so even if close contacts have drug-sensitive disease, the possibility of resistant disease in the child still exists. Resistance patterns in children have generally been found to be similar to those of adults from the same areas and similar backgrounds. Children most often have primary resistance that has been transmitted to them by an adult with new or retreatment-resistant TB.[35] A large South African study, conducted between 1994 and 1998 in TB culture-positive children, found 5.6% had isoniazid (INH) resistance and 1% had MDR (defined as resistance to both INH and rifampicin).[36] These results were essentially the same as surveillance data from adults with TB during the same time period, with 3.9% INH resistance and 1.1% MDR. In the United Kingdom, the rate of INH resistance in pediatric cases is 6.5%, and that for MDR TB is 0.5%, again similar to the rates in adults of 6.4% and 1.2%, respectively.[6] Treatment outcome has also been poorly studied in children, with treatment completion of only 45% in children in Malawi.[37]

IMMUNE RESPONSE AND SUSCEPTIBILITY TO TUBERCULOSIS

The immunologic response to MTB is complex and reviewed only briefly here. The risk of developing TB infection or disease following exposure is influenced by the genetics of both the host and the pathogen.[38-40] Certain individuals appear to have enhanced innate resistance; at least 50% of heavily TB-exposed individuals do not develop infection, but the immunogenetic basis of the differential susceptibility is unclear. Most adults with TB disease have reactivation of previously contained latent TB infection (LTBI) due to increasing age, acquired immunodeficiency, alcoholism, or unknown factors. Reactivation of primary infection may also be seen in children, but they are also at risk of uncontrolled primary infection and hematogenous dissemination to extrapulmonary sites.

Investigation of individuals with disseminated infection due to low virulence nontuberculous mycobacteria have indicated that the interleukin (IL)-12–interferon (IFN)-γ pathway is central to host defense.[41] Bronchoalveolar lavage specimens from household contacts of TB demonstrate an increased frequency of IFN-γ producing cells that may contribute to local protection.[42] However, the immunologic basis of the development of LTBI is not well understood. It is thought that in the immunologically naïve host who lacks innate resistance, intracellular multiplication of MTB continues, leading to cell necrosis and release of bacilli into the alveolar space. T cells lacking immunologic memory migrate to this site of inflammation and may mediate monocyte- and macrophage–mediated killing of MTB, possibly through the local generation of nitric oxide and reactive nitrogen intermediates.[43] Bacilli released by lysed pulmonary cells spread to local draining lymph nodes and may spread to more distant sites hematogenously. Acquired resistance, generated by the initial interaction between the bacillus and the host, mediates the protection in the 90% of individuals who control their TB infection and do not develop TB disease.

The balance of Th1 and Th2 cytokines appears critical in controlling TB infection. In adult patients with progressive TB, there is a relative overexpression of Th2 cytokines IL-10 and transforming growth factor (TGF)-β, which suppress IFN-γ production.[44] $CD4^+$ T cells are clearly important, as depletion in animal models and in HIV infection is associated with greatly increased risk of TB disease. In those who develop protective immune responses to their initial TB infection, the primary focus usually heals with fibrosis and possibly caseation in older children. Regional lymph nodes also heal over several months, but lymphadenopathy may persist for years despite adequate therapy. Healed lesions may contain small numbers of viable MTB, which may cause disease if immunity wanes. Once protective immunity has developed, exogenous reinfection appears rare, although this may be important in overcrowded conditions and in immunocompromised populations.

There have been a number of studies that have attempted to define the immunogenetic basis of resistance to TB (for review, see References 38, 45-47). TB is clearly a genetically complex disease and susceptibility is inherited in a non-Mendelian manner. Thus, the relative contribution of each genetic locus is likely to be small, making identification of individual loci difficult.[48] There are important considerations regarding phenotypic definitions, as the immunologic pathways (and thus associations with the genes that control them) are likely to vary with the various manifestations of TB—LTBI, localized pulmonary infection, disseminated disease—and with different populations—children, immunocompetent adults, HIV-infected adults. Despite these caveats, a number of important findings are emerging. Antigen presentation, not surprisingly, is key to the generation of protective immunity. The main receptor for MTB on dendritic cells, which present antigens to T cells, is DC-SIGN. Variation in the promoter region of the gene encoding DC-SIGN (CD 209) is associated with protection from TB.[49] Amino acid sequence variation in the HLA binding groove is associated not only with differential risk of TB but also in markedly different responses to TB-specific antigens in vitro.[44] Genetic studies have also highlighted the importance of macrophages. The macrophage activator *SLC11A1* (formerly known as *NRAMP-1*) was initially shown to offer protection against various intracellular pathogens in animal models.[50] *SLC11A1* appears to prime macrophages and upregulate protective responses, including cytokine and nitric oxide production. Variation of the *SLC11A1* gene has been associated with differential TB susceptibility in adults and recently children, although the effects are not identical.[51,52] It is possible that *SLC11A1* variants slow progression from infection to disease in children. Low levels of vitamin D, an important immunomodulatory molecule and macrophage activator, increase susceptibility, and variation of the vitamin D receptor gene has been associated with increased susceptibility to TB disease in Indian migrants to the United Kingdom, although this finding has not been confirmed in other populations.[53,54] It appears that TB exhibits a degree of genetic heterogeneity—with different genetic variants operating in different ethnic groups—which makes interpretation of the data more difficult.[55] Newer methodologies, including genome-wide association studies and adequately powered genetic epidemiologic studies are likely to continue to yield insights into the complex immune response to MTB.

CLINICAL FEATURES

It is important to distinguish TB *infection* (also referred to as LTBI, discussed subsequently) from TB *disease*. In both, there is evidence of TB infection (TST or blood-based immunologic assay), but in latent infection, the clinical, radiologic, or microbiological evidence of disease is lacking. The majority of children (>50%) with TB disease will be asymptomatic. Of those who develop symptoms, most will have pulmonary manifestations, while 25% to 35% of children will have extrapulmonary symptoms.[56] Systemic complaints such as fever, night sweats, anorexia, and decreased activity occur less often. The most common symptoms at presentation in children with TB disease are cough in the preceding 3 months, persistent fatigue, and weight loss.[57]

INTRATHORACIC DISEASE

Pulmonary Disease

Following initial exposure and infection, the primary complex is characterized by a lung parenchymal infiltrate (commonly

subpleural and consisting of a minute cluster of macrophages around tubercle bacilli reaching 1 mm at 2 to 3 weeks in which multinucleate giant cells may develop) and regional lymph node enlargement. Most children are asymptomatic at this stage; the infiltrate may necrose, caseate, and undergo gradual dissolution, and the lymphadenopathy will resolve spontaneously in the majority of cases. In some children, particularly infants, the lymph nodes continue to enlarge, causing pressure effects on surrounding structures such as the trachea and bronchi, which may result in partial or complete bronchial obstruction. This obstruction may result in wheeze either as a presenting symptom or in some instances after commencement of antituberculous therapy. The term *epituberculosis* has been used to describe bronchial compression by enlarging lymph nodes causing atelectasis and subsequent parenchymal destruction.[58] Endobronchial disease may also occur when encroaching, enlarged lymph nodes erode into the bronchi with extrusion of caseous material into the bronchial lumen.[59] The clinical presentation may be insidious or acute. The right middle lobe syndrome may result due to chronic lobar atelectasis secondary to postinflammatory bronchial stenosis.[60] In general, the most common pulmonary symptoms of primary infection, if any, include nonproductive cough and mild dyspnea. There may be few clinical signs on examination; however, some infants and young children may have localized wheezing or decreased breath sounds accompanied by increased respiratory rate or respiratory distress. Older children and adolescents are more likely to develop adult-type reactivation disease[61,62] and will present with the classic symptoms of fever, malaise, weight loss, night sweats, productive cough, chest pain, and hemoptysis. Again, there may be very few or no clinical signs on physical examination.

Tuberculous Pneumonia

Primary and often fulminant tuberculous pneumonia in both immunocompromised and immunocompetent individuals, including older children, is reported rarely.[63] It may be segmental or lobar or involve extensive areas of the lung bilaterally. It is often severe and has been associated with acute respiratory distress syndrome.[64]

Pleural Disease

Pleural involvement may occur in reaction to the release of a few mycobacteria into the pleural space from a subpleural focus. This may result in clinically significant pleural effusions, which are often unilateral. Pleural fluid is typically yellow with elevated protein and white blood cells. Microscopy and culture yields from pleural fluid are often low; however, pleural biopsy will demonstrate caseating granulomas in the majority of cases. Clinical symptoms include fever, chest pain, and reduced air entry on the side of the effusion.

Cardiac Disease

Pericarditis is the commonest cardiac manifestation of TB, occurring in 1% to 4% of children.[65] Pericardial fluid is serofibrinous or slightly hemorrhagic. Clinical symptoms may be nonspecific, including low-grade fever, malaise, and weight loss; chest pain is unusual in children. Auscultation of the cardiovascular system may reveal a pericardial friction rub or reduced heart sounds.

EXTRAPULMONARY DISEASE

Lymphohematogeneous spread following primary complex formation occurs more commonly in children and results in disseminated TB, including miliary TB, and extrapulmonary TB. Extrapulmonary TB includes peripheral lymphadenopathy (65%), TB meningitis (10% to 15%), bone and joint disease (4%), and miliary TB (5%).[66]

Peripheral Lymphadenopathy

Local spread from primary infection in the lungs results in peripheral tuberculous lymphadenopathy, particularly in the supraclavicular and paratracheal regions. Lymphohematogenous spread may result in more distant lymph node involvement. Peripheral TB lymphadenopathy commonly presents as slowly enlarging, firm, nontender lymph nodes with no overlying skin discoloration. There are often no systemic symptoms such as fever or weight loss. With time, the enlarged lymph nodes become fluctuant and may discharge with sinus formation. The lymph nodes most often involved are in the anterior or posterior cervical and supraclavicular regions.

Miliary Tuberculosis

Miliary TB is the most common form of disseminated disease and usually occurs early after the infection, within the first 2 to 6 months, and may represent uncontrolled primary infection in children. The median age at presentation is 10.5 months, with about half of cases occurring in those younger than 1 year. The clinical manifestations of miliary TB are protean, with involvement of the lungs, spleen, and bone marrow. The presenting symptoms are often nonspecific: cough (72%), fever (61%), loss of appetite and weight (40%), and diarrhea and vomiting (33%). The main presenting signs are hepatomegaly (82%), splenomegaly (54%), lymphadenopathy (46%), and pyrexia (39%).[67] Like adults with military TB, children are usually smear negative. With progressive pulmonary disease, respiratory distress, hypoxia, and pneumothorax/pneumomediastinum may occur. Signs or symptoms of meningitis or peritonitis are found in 20% to 40% of patients with advanced disease. Choroid tubercles occur in 13% to 87% of patients and are highly specific for TB (Fig. 39-2).

Central Nervous System Tuberculosis

Involvement of the central nervous system, particularly meningitis, is among the more common manifestations of extrapulmonary disease.[68-72] Tuberculous meningitis is the most serious complication in children and is almost invariably fatal without treatment. The brain stem is the most common focus with cranial nerve involvement (III, VI, and VII).[73] The clinical progression of tuberculous meningitis may be rapid or gradual. Rapid progression tends to occur more often in infants who may experience symptoms for only several days before the onset of acute hydrocephalus, seizures, or cerebral edema.

Table 39-2 summarizes the clinical stages of TB meningitis (modified from British Medical Research Council study[74]).

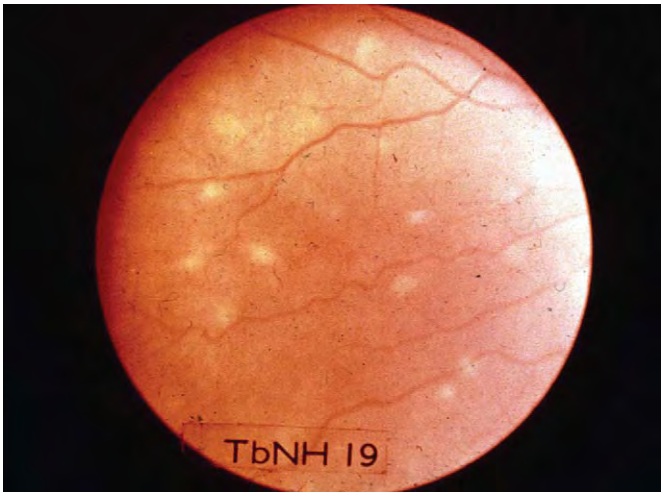

Figure 39-2 Choroid tubercles on retinal examination in patient with miliary tuberculosis.

Signs and symptoms may evolve and progress over time. Stage I (early) is characterized by nonspecific symptoms such as fever, headache, irritability, and malaise and usually lasts several weeks. There are few to no clinical signs, and at this stage, there is no reduction in consciousness. Infants may experience delay or loss of developmental milestones. Stage II (intermediate) is characterized by drowsiness and lethargy. Clinical signs are those of meningitis (including nuchal rigidity and positive Kernig or Brudzinski signs), cranial nerve palsies, vomiting, and seizures. This clinical picture usually correlates with the development of hydrocephalus and increased intracranial pressure. Stage III (advanced) is usually characterized by stupor or coma, often accompanied by gross paresis (hemiplegia or paraplegia), hypertension, and decerebrate posturing. Paresis most commonly reflects ischemic infarction from vasculitis, although it may be exacerbated by hydrocephalus. The prognosis of tuberculous meningitis correlates most closely with the clinical stage of illness at the time antituberculosis chemotherapy begins.[75] The majority of patients in the first stage have an excellent outcome, whereas most patients in the third stage who survive have permanent disabilities including blindness, deafness, paraplegia, and cognitive impairment.[76]

In children with TB meningitis, 40% to 80% will have abnormal chest radiographs, including hilar adenopathy (33%), infiltrates (33%), miliary pattern (20%), and pleural effusions (1%).[77] Cranial CT scans of the patients presenting with TB meningitis showed hydrocephalus in 80% to 90% and basilar enhancement in over 90% of cases. MTB may be cultured or identified by acid-fast stain from CSF or brain tissue from 63% of children. New tuberculoma may develop during treatment.[72] The Mantoux test is negative in 30% to 50% of all children on presentation with TB meningitis.[72,77]

Other Extrapulmonary Tuberculosis

Skeletal TB is a late complication of lymphohematogenous spread and usually presents many years following primary infection. The most common sites of involvement are the weight-bearing bones and joints such as the vertebral column (40% to 50%), hip, knee, and elbow. Vertebral TB may be very insidious, often presenting with referred pain, abnormal posturing, or paravertebral abscess formation.

Other extrapulmonary sites of TB are generally very rare in children, particularly genitourinary disease, which occurs many years after primary infection and hence is unlikely to occur in the pediatric age group.

Table 39-2
Stages of Tuberculous Meningitis[69]

Stage	Clinical Signs and Symptoms
I (early)	Nonspecific symptoms Few or no clinical signs of meningitis
II (intermediate)	Signs of meningitis Drowsiness or lethargy Cranial nerve palsies
III (advanced)	Stupor or coma Systemic toxicity Gross paresis or paralysis

DIAGNOSIS

Microscopy and Culture

Microscopic examination of clinical samples for acid-fast bacilli using the Ziehl-Neelsen (ZN) stain has been a standard diagnostic tool and is used globally for rapid TB diagnosis. Microscopy can detect 60% to 70% of culture-positive samples with a lower limit of detection of 5×10^3 organisms/mL. Newer fluorochrome stains, such as auramine and rhodamine, appear to have better detection compared with the ZN stain.[78] These tests have been widely adopted as they are easy to perform, cheap, and give rapid results. However, because younger children rarely produce sputum, early-morning gastric aspirate samples are often collected by aspiration of gastric contents via a nasogastric tube. The yield from microscopy of gastric aspirate samples in children with proved pulmonary TB is less than 20%, compared with 75% in adults.[79] The rates of detection on microscopy from other extrapulmonary samples, such as cerebrospinal fluid, are even lower.

Mycobacterial culture of gastric aspirates has provided a more useful method of diagnosis in children with suspected pulmonary TB. Three consecutive morning gastric aspirates yield MTB in 30% to 50% of cases and may be as high as 70% in infants.[80] The culture yield from other body fluids or tissues from children with extrapulmonary TB is usually less than 50% due to lower numbers of mycobacteria in these sites of disease.[81]

The role of bronchoscopy in evaluating children with pulmonary TB is controversial. Cultures from bronchoalveolar lavage fluid in children with suspected pulmonary TB has a low yield and does not significantly aid bacteriologic confirmation.[82] Indeed, the culture yield of a single bronchoscopic sample has been shown to be lower than that for three properly obtained gastric aspirates.[83] It has been suggested that bronchoscopy may, however, play a useful role in the diagnosis of endobronchial TB or bronchial obstruction, especially if transbronchial biopsy is performed.[84] Bronchoscopy may also be useful in excluding other causative agents such as opportunistic infections, particularly in immunocompromised children and those with HIV infection.

More recently, sputum induction with nebulized 5% saline has been used safely in young infants in resource-limited settings and found to be equivalent to the yield from three consecutive early-morning gastric aspirates.[85] The microbiological yield from sputum induction did not differ between HIV-infected and HIV-uninfected children with pulmonary TB, and all sputum induction procedures were well tolerated with only minor side effects, including increased coughing, epistaxis, vomiting, or wheezing.[86] However, there are concerns regarding spread of TB to other patients and staff, and it is recommended that sputum induction be performed with appropriate infection control procedures (e.g., negative pressured cubicles), and by appropriately trained staff. This technique may be difficult to use effectively in preschool-age children.

Regardless of the microbiological results, any sample should be cultured and susceptibility to antituberculous drugs determined. Bone marrow may be cultured in those with clinical disseminated disease.

Tuberculin Skin Test

A positive TST reaction is a hallmark of primary infection with MTB. In most children, tuberculin reactivity becomes apparent in 3 to 6 weeks with the associated onset of the immune response and, rarely, fever, erythema nodosum, or phlyctenular conjunctivitis, but occasionally can take up to 3 months after initial infection. Tuberculin reactivity due to MTB infection usually remains positive for the lifetime of the individual, even after treatment.[87]

The Mantoux test is the standard TST currently in use and uses 5 to 10 tuberculin units of purified protein derivative. The Mantoux test is the standard method used in many countries for detecting infection by MTB. This test involves the intradermal injection of purified protein derivative solution into the most superficial layer of the skin of the forearm, which raises an immediate wheal. The reaction is measured as millimeters of induration (not erythema) after 48 to 72 hours. Sometimes with strongly positive Mantoux tests, there may be marked induration, blister formation, and ulceration at the site of intradermal injection (Fig. 39-3). Percutaneous multipuncture devices, such as the Heaf test and Tine test, are no longer in common use. Interpretation of TST results differs around the world and is summarized in Table 39-3.

TST has both poor sensitivity (false-negative results) and specificity (false-positive results). The TST has the lowest sensitivity in younger children. Up to 10% of otherwise normal children with culture-proved TB do not react to tuberculin initially.[81] Most of these children will become reactive during treatment, suggesting that TB disease may itself contribute to immunosuppression. False-negative TST may also occur in children with severe TB disease and those with debilitating or immunosuppressive illnesses, malnutrition, or other severe infections. The rate of false-negative TST in children with TB

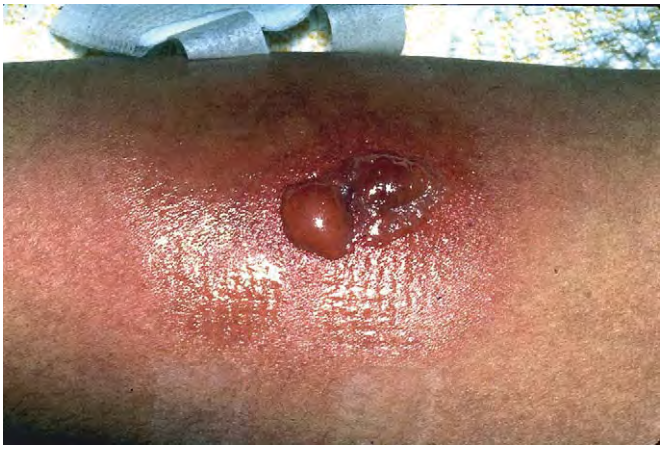

Figure 39-3 Strongly positive Mantoux test with marked induration and blistering.

Table 39-3
Summary of Interpretation of Positive TST Results for Mantoux Test in Children[145-148]

BTS Guidelines (UK)	WHO	American Academy of Pediatrics (USA)
Positive ≥6 mm (no bCG) ≥15 mm (bCG)	Positive >10 mm (no bCG) >15 mm (bCG)	Positive *>5 mm and one or more of the following:* Children in close contact with known or suspected contagious case of tuberculosis disease, i.e., households with active or previously active cases, if treatment cannot be verified as adequate before exposure, treatment was initiated after the child's contact or reactivation of latent tuberculosis infection is suspected *OR* Children suspected to have tuberculosis disease, i.e., chest radiograph consistent with active or previously active tuberculosis; or clinical evidence of tuberculosis disease *OR* Children receiving immunosuppressive therapy or with immunosuppressive conditions including HIV infection *>10 mm and one or more of the following:* Children at increased risk of disseminated disease, i.e., younger than 4 years of age or other medical condition, including Hodgkin's disease, lymphoma, diabetes mellitus, chronic renal failure, or malnutrition *OR* Children with increased exposure to tuberculosis disease, i.e., born or whose parents were born in high-prevalence regions of the world; or are frequently exposed to adults who are HIV-infected, homeless, users of illicit drugs, residents of nursing homes, incarcerated or institutionalized, and migrant farm workers *>15 mm* Children 4 years of age or older without any risk factors

who are infected with HIV is unknown, but it is certainly higher than 10% and is dependent on the degree of immunosuppression, particularly the $CD4^+$ count.

The converse problem may also occur, namely false-positive TST results. bCG (bacille Calmette-Guerin) vaccination may transiently cause a reactive TST, but most children who received bCG as infants have a nonreactive TST at 5 years of age.[88] A recent meta-analysis suggests that the effect of bCG on TST measurements was less after 15 years, and induration greater than 15 mm was more likely to be due to TB infection than bCG.[89] Among older children or adolescents who receive bCG, most develop a reactive TST initially; however, by 10 to 15 years postvaccination, the majority will have lost tuberculin reactivity.[90] Recent studies have shown that bCG vaccination had little impact on the interpretation of TST in children being tested as part of a contact investigation.[91] There have been concerns that false-positive TST may arise through antigenic cross-reactivity from asymptomatic infection by environmental nontuberculous mycobacteria.[92] Skin reactivity can also be boosted, probably through antigenic stimulation, by serial testing with TST in many children and adults who received bCG.[93]

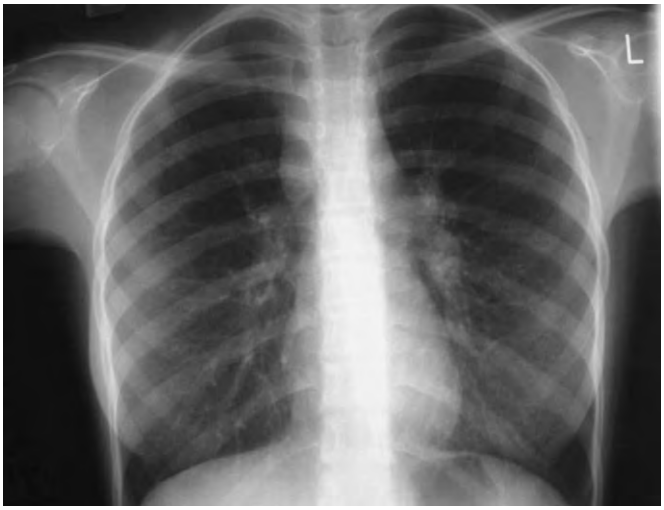

Figure 39-4 Chest radiograph showing hilar lymphadenopathy.

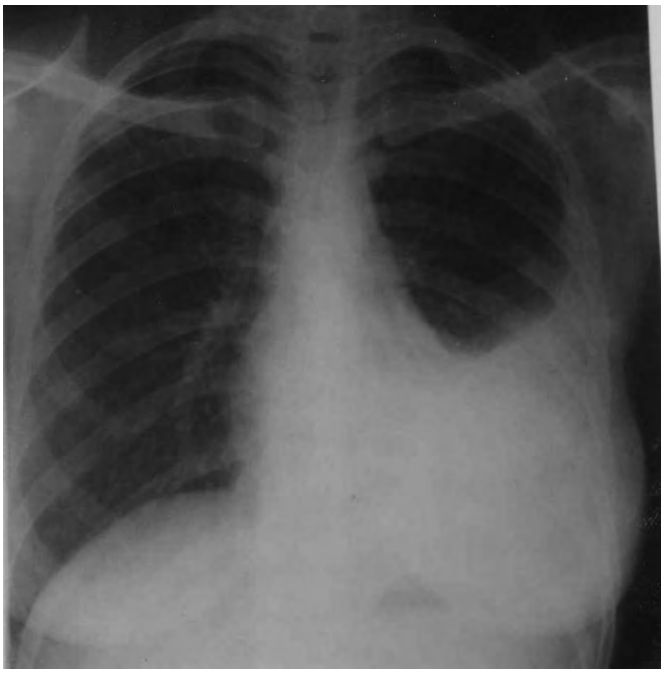

Figure 39-5 Chest radiograph showing left-sided pleural effusion.

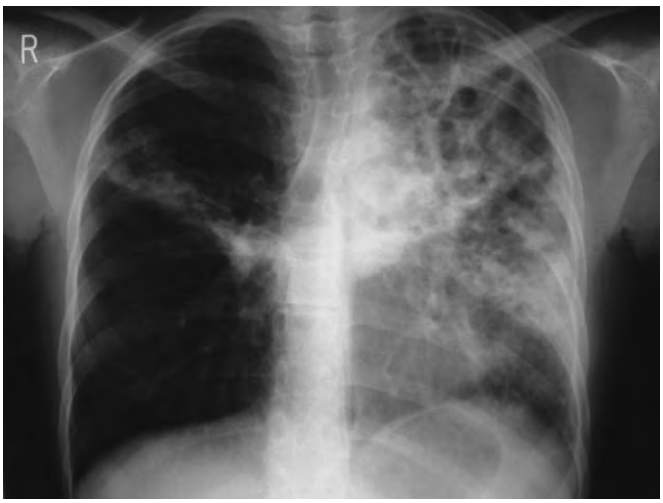

Figure 39-6 Chest radiograph showing postprimary adult-type left upper lobe cavitation.

Radiology

Radiologic evidence of pulmonary TB on chest radiography usually includes lymphadenopathy (hilar or mediastinal) (Fig. 39-4) and lung parenchymal changes. The latter include segmental hyperinflation, atelectasis, alveolar consolidation, pleural effusion/empyema (Fig. 39-5), and, rarely, a focal mass. Cavitation is rare in young children but is more common in adolescents (Fig. 39-6), who may develop adult-type postprimary disease and are more likely to be infectious.[94] Miliary TB is characterized by fine bilateral reticular shadowing, sometimes called a "snowstorm" appearance (Fig. 39-7). There is some evidence that lateral chest radiography improves the diagnostic yield.[95]

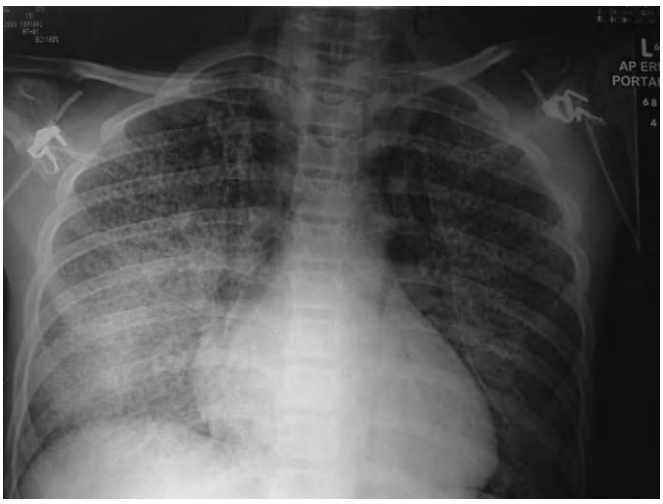

Figure 39-7 Chest radiograph showing miliary tuberculosis with pneumomediastinum.

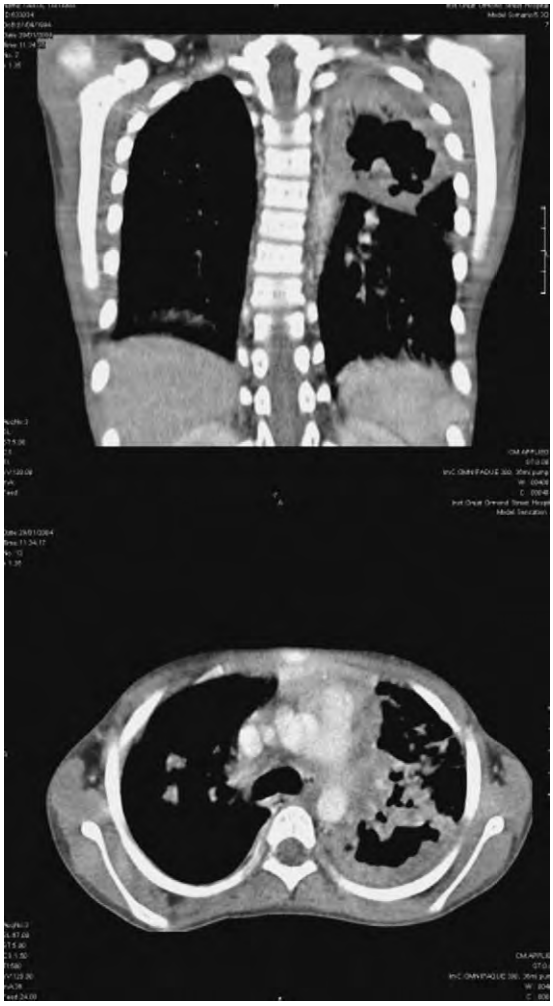

Figure 39-8 CT scans of chest showing left upper lobe cavitation.

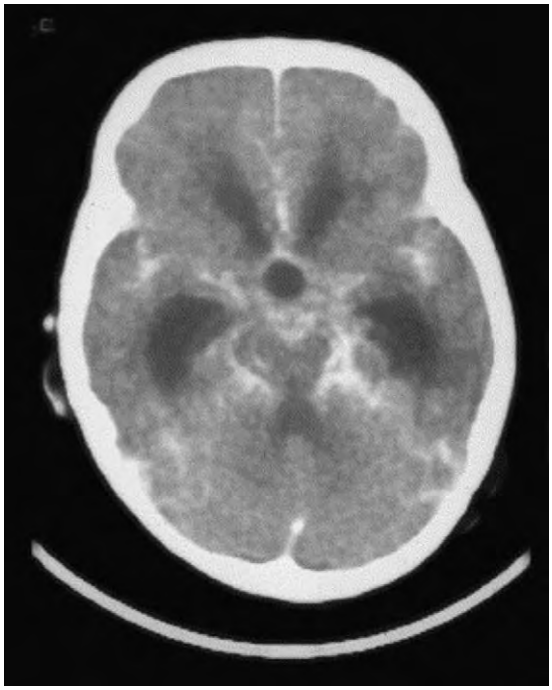

Figure 39-9 Head CT scan showing hydrocephalus and basal enhancement consistent with TB meningitis.

Computed tomography (CT) scanning has been useful in demonstrating early pulmonary disease such as cavitation (Fig. 39-8). CT imaging is also better than chest radiography in demonstrating bronchial involvement such as bronchial compression and bronchiectasis. CT may also be useful in detecting intrathoracic hilar lymphadenopathy, even in those with normal chest radiographs.[96-98] Furthermore, there is interobserver variability in the detection of mediastinal and hilar lymph nodes on CT in children with suspected pulmonary TB, and diagnostic accuracy might be improved by refining radiologic criteria for lymphadenopathy.[99]

CT has also been used for evaluation of pericardial effusions and is strongly suggestive of tuberculous disease when associated with mediastinal lymphadenoapthy and a positive TST.[100] Central nervous system disease, such as TB meningitis or tuberculoma, may also be identified on CT, especially as contrast demonstrates meningeal enhancement (Fig. 39-9).

Magnetic resonance imaging (MRI) has been found to be useful for musculoskeletal TB, particularly involving bones and joints.[101] Figure 39-10 shows a Pott's fracture of the spine that was identified on MRI.

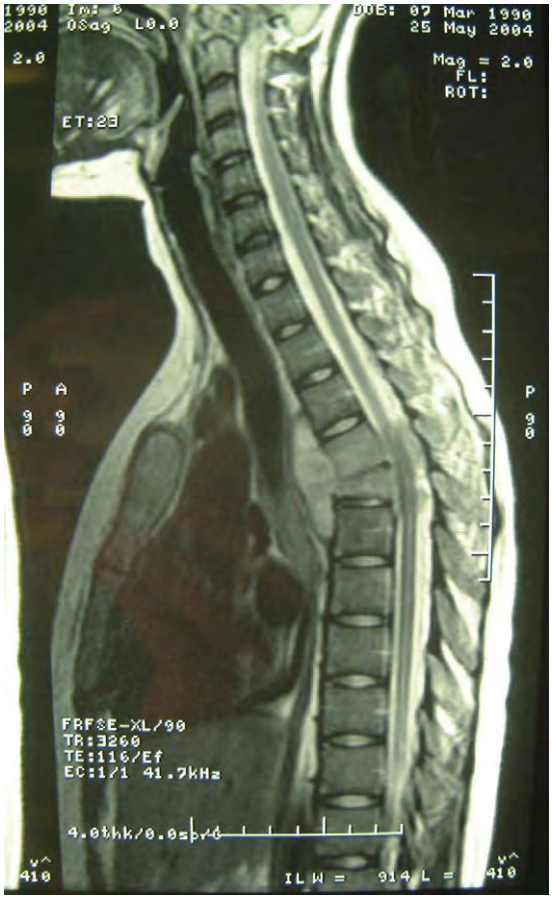

Figure 39-10 MRI of spine showing Pott's fracture of upper thoracic vertebra.

Diagnostic Approaches in Childhood Tuberculosis

The diagnosis of TB in children is based mainly on a combination of history of contact with an adult infectious case, clinical signs and symptoms, and investigations mentioned earlier, particularly chest radiograph and tuberculin skin testing. However, symptoms may often be nonspecific, with over half of children being asymptomatic with early disease.[94] A positive history of contact with a case of TB, especially if the source case was a parent or other member of the household who was also bacteriologically positive, has been strongly associated with disease in a child.[102] These epidemiologic, clinical, and diagnostic parameters have been used to devise simple, inexpensive, and reliable tests to enable accurate diagnosis of TB in children, especially in low-income countries. Several diagnostic approaches exist, and most are grouped broadly into four families based on point scoring systems, diagnostic classifications, diagnostic algorithms, or combinations of these.[103] An example of a diagnostic approach is that recommended by the WHO, which relies on stratified categories of suspected, probable, and confirmed TB[104] (Table 39-4). Most of these diagnostic approaches have not been standardized, making comparison difficult, and few have been properly validated.[103] Some diagnostic approaches have been modified for populations where HIV is prevalent; however, only one diagnostic approach has been specifically designed to diagnose TB in such a population.[13] In a high HIV prevalent population, clinical scoring systems have been found to have low specificity (25%), resulting in overdiagnosis of TB.[105] Further studies are needed to develop standardized diagnostic approaches that are relevant to developing countries with limited resources with a high burden of TB, malnutrition, and HIV/AIDS.

MOLECULAR DIAGNOSTICS

Due to the slow growth of most pathogenic mycobacteria, investigations have been developed for microbial detection directly from clinical specimens. Most have involved amplification of small amounts of bacterial nucleic acid using techniques such as polymerase chain reaction (PCR). PCR has been used successfully in identifying many infectious agents, allowing early diagnosis and institution of therapy. Although the specificity of a well-developed PCR can be high, the sensitivity is significantly less than that of the use of culture. The sensitivity of a good-quality PCR would be expected to be 90% to 100% and 60% to 70% on smear-positive and smear-negative culture-positive respiratory samples, respectively.[106-108] However, there are several problems with applying this technique to routine clinical care, including variations in methodology, high cost, and high risk of contamination resulting in false positives.

Several studies in children have found the PCR test on clinical samples to have a sensitivity of 40% to 60% compared with clinical diagnosis.[109-112] This compares favorably to standard cultures, which have a sensitivity of 30% to 40%. The specificity of PCR ranges from 80% to 96% but is dependent on the type of assay used. Furthermore, up to 39% of children with no radiographic or clinical evidence of tuberculous disease may also have positive PCR results.[113] With the limitations that exist, the results of PCR alone are insufficient to diagnose TB in children. PCR detection in other body fluids or tissues, such as cerebrospinal fluid, appears to have been even less successful.

In view of the problems highlighted above, PCR methods have a limited role in the diagnosis of TB in children; however, they may be useful where the diagnosis is not easily established using standard clinical, microbiological, and epidemiologic methods. PCR may also have a future role in the diagnosis of TB in immunocompromised children, or those with extrapulmonary TB.

Molecular methods have also been used for species confirmation, detection of rifampicin resistance and for molecular typing as part of epidemiologic investigation. Species confirmation will allow differentiation between MTB complex organisms (MTB, *M. bovis*, and *M. africanum*) and environmental mycobacteria. These tests are most effective when applied to samples in which mycobacteria have been detected microscopically. They may also be important in confirming TB before a large contact-tracing exercise is conducted. Molecular probes looking for mutations of the *rpoB* gene may be useful, particularly as a marker of MDR TB. Molecular typing of MTB strains, using techniques such as restriction fragment length polymorphism (RFLP), may be a useful epidemiologic tool to identify potential links between patients and impact on diagnosis and transmission of TB in a community.[114]

Table 39-4
WHO Provisional Guidelines for the Diagnosis of Pulmonary Tuberculosis in Children[99]

Suspected Tuberculosis
An ill child with a history of contact with a confirmed case of pulmonary tuberculosis
Any child:
Not regaining normal health after measles or whooping cough
With weight loss, cough, and wheeze not responding to antibiotic therapy for respiratory disease
With painless swelling in a group of superficial nodes
Probable Tuberculosis
A suspected case and any of the following:
Positive (>10 mm) induration on tuberculin testing
Suggestive appearance on chest radiograph
Suggestive histologic appearance on biopsy material
Favorable response to specific antituberculosis therapy
Confirmed Tuberculosis
Detection by microscopy or culture of tubercle bacilli from secretions or tissues
Identification of tubercle bacilli as *Mycobacterium tuberculosis* by culture characteristics

SEROLOGIC DETECTION

Serology has so far found little place in the routine diagnosis of children with TB, despite several assays that have been developed. ELISA has been used to detect antibodies to a host of MTB antigens including protein-purified derivative, killed MTB, and antigen A60.[115-117] However, none of these methods has adequate sensitivity, specificity, or reproducibility for use in the diagnosis of children with TB.

IMMUNODIAGNOSIS

The TST has poor specificity due to cross-reactivity with BCG immunization and environmental mycobacteria. Fur-

thermore, false negatives may occur in individuals with altered immunity such as HIV infection, immunodeficiency or immunosuppression, advanced TB, and malnutrition. New diagnostic tests have been developed based on in vitro T-cell–based IFN-γ assays. These tests rely on IFN-γ production by sensitized T cells to specific TB antigens. While initial tests used PPD as the stimulating antigen, newer assays use specific antigens, such as the early secretory antigenic target-6 (ESAT-6) antigen and culture filtrate protein 10 (CFP10). These antigens are present in MTB complex but absent from all strains of *M. bovis* bCG and almost all environmental mycobacteria. Two commercial IFN-γ assays, the Quanti FERON-TB Gold assay (Cellestis Limited, Carnegie, Victoria, Australia), and the T SPOT-TB assay (Oxford Immunotec, Oxford, UK), are currently available. Both tests measure IFN-γ release from T cells in response to using methods such as ELISA and enzyme-linked immunospot (ELISPOT) assay.[118] The QuantiFERON-TB Gold cultures whole blood with the TB-specific assays and measures IFN-γ in the culture supernatant, whereas the ELISPOT cultures peripheral blood mononuclear cells and directly counts the number of IFN-γ-secreting cells. The QuantiFERON-TB Gold test has been approved by the U.S. Food and Drug Administration (FDA) for diagnosis of TB infection and disease. The T SPOT-TB test is currently approved for use in Europe and is awaiting FDA approval.

Current evidence suggests that IFN-γ assays have the potential to become useful diagnostic tools in clinical and public health settings. Studies in different populations suggest that these tests have greater specificity (>90%) compared with TST, although sensitivity may be equivalent or less, especially for latent infection. Furthermore, there are limited data from specific populations, particularly children and immunosuppressed individuals. Nevertheless, new guidelines have incorporated IFN-γ testing as an alternative and/or adjunct to TST. However, the cost-effectiveness and utility of these tests, especially in certain population groups, remains unclear.

LATENT TUBERCULOSIS INFECTION

Although two thirds of the world's population is infected with TB, only about 1 in 10 overall will develop active TB disease. The remainder are latently infected, with no clinical or radiographic evidence of active TB disease, but with a positive immunologic investigation (TST or blood-based assay), indicating exposure to and immunologic memory of MTB. Such diagnostic tests are increasingly insensitive with decreasing age, but it is younger children and infants who are most at risk of developing TB disease, and life-threatening dissemination of infection outside the respiratory tree is common; up to 45% of children present with advanced pulmonary, miliary, or meningeal disease.[119] Thus empiric prophylactic treatment for LTBI may be commenced in younger children if there is a significant history of exposure to an infectious adult or evidence of exposure within the household, irrespective of the immunologic investigations. In general, the decision to initiate prophylactic therapy for LTBI is based on an assessment of the risk of transmission and the risk of LTBI progressing to TB disease. These include the age of the exposed individuals, their immunocompetence (particularly HIV infection), the nature and degree of exposure to TB, as well as clinical, radiographic, and laboratory findings.

Children younger than 10 years with TB disease who typically have paucibacillary disease are rarely infectious, as cavitating disease and sputum positivity are extremely unusual in children. With a few exceptions, it is almost invariably adults with pulmonary or laryngeal TB who infect children.[120] Smear-positive adults are generally more infectious than are those who are sputum positive on culture alone.[121] Thus, adults with cavities on chest radiographs are more infectious than those without, although severely immunocompromised adults may be highly infectious with initially normal or atypical chest radiographs. Although adults coinfected with TB and HIV infection are no more contagious than those without HIV infection, the often-delayed diagnosis increases the risk of transmission.[122] Once TB treatment is initiated, a contagious adult becomes noninfectious within a few weeks, although the exact time frame varies.[120]

The identification and treatment of a child with LTBI provide a cornerstone of TB control, and the identification of LTBI in a child is considered a sentential event, indicating recent and on-going transmission, often within a household.[123] LTBI in a child should prompt an investigation for the infecting adult index case, although identification of the source is successful in less than 50% of source-case investigations.[124,125] In those from a refugee-like background, whose LTBI is often identified on routine screening on arrival in a developed country, the epidemiology is more complex. Families have often spent prolonged periods in large overcrowded refugee camps, with ample opportunity for transmission from outside the household, and an adult infective source is less commonly identified.

The diagnosis of LTBI is made by exclusion of TB disease in a child with a positive TST or blood-based assay or, in a younger child, on a history of exposure to an infectious adult. The diagnosis of LTBI in children is often difficult. As discussed, the symptoms of TB disease in children are notoriously variable and often subtle; up to 50% of children with TB disease have no symptoms at presentation.[57] Weight loss and malaise are the most sensitive symptoms, whereas chronic cough is specific but not sensitive in high-incidence populations.[57] A history of drenching night sweats is rarely elicited. It is reasonable to actively investigate any child with a positive contact history or TST/blood-based assay and a clinical or radiographic suggestion of TB disease. Empiric treatment is often warranted in children with evidence suggestive of TB diseases, rather than LTBI. In children younger than 2 years, in whom diagnostic investigations are insensitive, most guidelines advocate commencing empiric therapy for LTBI on the basis of a history of exposure alone.[122,126] Some guidelines advocate retesting (with Mantoux or blood-based assay) these younger children after 8 to 10 weeks of preventive therapy and discontinuing LTBI treatment if the results are negative.[122] However, given the insensitivity of the investigations and lack of data to support this approach in young children, it may be more prudent to continue a full course of treatment for LTBI in those younger than 2 years, regardless of the results of investigations.[127]

The rationale for treating LTBI is the significant risk of progression to TB disease in untreated infection, especially in

children. The risk is greatest in younger children (<5 years of age), but the exact age-related risk is difficult to ascertain from the available data, which are historical and include studies of both adults and children. The highest risk is in infants and young children, where a risk of disease progression of 40% to 50% is widely quoted.[128,129] The risk decreases gradually through childhood to adult levels of about 10%. The risk of disease progression is greatest in the 12 to 18 months following exposure.

Treatment of LTBI is highly effective in reducing the risk of TB disease, especially in children, where efficacy is well over 90%. A study of over 4000 children with tuberculin reactivity showed a 60-fold increased risk of developing TB disease if prophylactic therapy was not given, equivalent to a number needed to treat (NNT) of 50 LTBI cases to prevent one case of TB disease.[127,130] A meta-analysis of over 73,000 adults and children exposed to MTB in various settings indicated that prophylactic therapy gave a relative risk of TB disease of 0.4, compared with no prophylaxis; a NNT of approximately 90.[131]

Various regimens have been suggested for LTBI treatment, but most have not been subjected to randomized controlled trials in children. Six months of isoniazid therapy is the cornerstone of prophylactic therapy and the current recommendation for LTBI in many countries, including the United States, United Kingdom, and Australia.[132] The main issue in children, in whom side effects are less common than in adults, is compliance, which is inadequate in up to a quarter of patients.[133] Poor compliance diminishes the efficacy of prophylactic therapy. Isoniazid suspension, which may be necessary in younger children who do not tolerate crushed tablets or whose weight precludes available tablet doses, has a short shelf-life and is not available commercially.

Alternative regimens for LTBI are widely used in children, but without a sound evidence base. Isoniazid and rifampicin for 3 months is well tolerated and generally more acceptable to children and families.[134] This combination has a potential advantage if drug resistance is suspected. A meta-analysis in adults showed that this combination was equally efficacious as 6 months isoniazid monotherapy.[135] Rifampicin monotherapy for 4 months is also used infrequently in children.[136] In adults with silicosis, who have a high risk of disease progression from LTBI, 3 months of rifampicin was as efficacious as 6 months of isoniazid,[137] but there are no studies in children. Data, again only from adults, indicate that the combination of rifampicin and pyrazinamide potentially causes fatal hepatotoxicity and is best avoided.[138,139]

As with treatment for TB disease, LTBI therapy should be supervised and undertaken from a centralized TB service, where community workers can monitor compliance and assist families. It is good practice to dispense medication a month at a time and to review children regularly. Treatment with isoniazid alone or in combination with rifampicin is generally well tolerated and side effects are rare in children compared with adults. The main concern is hepatotoxicity, which is more likely in the presence of viral hepatitis or preexisting liver dysfunction. Pretreatment liver function testing is reasonable, but repeated testing or pyridoxine supplementation is unnecessary in asymptomatic children.[140] Vitamin D status should also be assessed prior to therapy for LTBI and supplemented as necessary. Both rifampicin and isoniazid can depress vitamin D levels, which are often already low or deficient in migrant populations.[141]

TREATMENT OF TB DISEASE

Treatment of children can be divided broadly into treatment of TB infection and treatment of TB disease. As mentioned, the distinction between these different categories may be unclear in some patients, particularly young children.

Several controlled and observational trials of 6-month therapy in children with pulmonary TB caused by organisms known or presumed to be susceptible to the first-line drugs have been published.[142-149] Although 6 months of therapy with INH and RIF has been shown to be effective for treatment of hilar adenopathy and pulmonary TB, a three-drug regimen (isoniazid, rifampicin, and pyrazinamide) has been shown to have success rates of greater than 95% and low adverse reaction rates. In general, extrapulmonary TB in children can be treated with the same regimen as pulmonary disease; however, there are no data from children and extrapolations have been made from studies in adults. Meningitis and disseminated TB, however, may not be adequately treated with 6 months' duration, and longer treatment durations of 9 to 12 months are recommended. The optimal treatment of TB in children and adolescents with HIV infection is unknown. Treatment durations of at least 9 months have been suggested.[150] Treatment schedules, policies, and drug doses as advocated by a number of national and international bodies often differ. Tables 39-5 and 39-6 compare drug regimens and dosages recommended in the United Kingdom, United States, and the WHO.[150-153] Traditionally, antituberculous regimens have included bactericidal and bacteriostatic drugs that have required treatment for long periods, between 18

Table 39-5
Recommended Dosages of First-Line Standard Antituberculous Drugs for Children[145-148]

	British Thoracic Society		American Thoracic Society		World Health Organization	
Drug	**Daily**	**Intermittent**	**Daily**	**Intermittent**	**Daily**	**Intermittent**
Isoniazid	5-10 mg/kg	15 mg/kg 3 times weekly	10-15 mg/kg	20-30 mg/kg twice weekly	5 mg/kg	10 mg/kg 3 times weekly
Rifampicin	10 mg/kg	15 mg/kg 3 times weekly	10-20 mg/kg	10-20 mg/kg twice weekly	10 mg/kg	10 mg/kg 3 times weekly
Pyrazinamide	35 mg/kg	50 mg/kg 3 times weekly	35 mg/kg	50 mg/kg twice weekly	25 mg/kg	35 mg/kg 3 times weekly
Ethambutol	15 mg/kg	30 mg/kg 3 times weekly	15 mg/kg	50 mg/kg twice weekly	15 mg/kg	30 mg/kg 3 times weekly

Table 39-6
Recommended Treatment Schedules for Tuberculosis Disease in Children[145-148]

	British Thoracic Society	American Thoracic Society	World Health Organization
Hilar adenopathy	2 months of RHZE then 4 months of RH	2 months of RHZ(E*) then 4 months of RH	2 months of RHZ then 4 months of RH
Pulmonary tuberculosis	2 months of RHZE then 4 months of RH	2 months of RHZ(E*) then 4 months of RH	2 months of RHZE then 4 months of RH
Extrapulmonary tuberculosis	2 months of RHZE then 4 months of RH	2 months of RHZ(E*) then 4 months of RH	2 months of RHZE then 4 months of RH
TB meningitis	2 months of RHZE then 10 months of RH	2 months of RHZE then 9-12 months of RH	2 months of RHZS then 4 months of RH
HIV	2 months of RHZE then 4-7 months of RH	2 months of RHZ then 7 months of RH	2 months of RHZE then 4 months of HR or 6 months of HE

R, rifampicin; E, ethambutol; H, isoniazid; S, streptomycin; Z, pyrazinamide.
*If resistance is suspected.

and 24 months. More recently, multidrug regimens have been used with more rapid microbiologic cure rates that allow shorter durations of therapy (short-course chemotherapy). Isoniazid, rifampicin, and pyrazinamide are mainstays of antituberculous therapy. Other agents often used in children include streptomycin and ethambutol.

Adverse reactions to antituberculosis therapy occur in children on anti-TB therapy, but generally the drugs are well tolerated. Gastrointestinal reactions such as nausea, vomiting, and abdominal pain are common, particularly in the first few weeks of therapy. In most cases, these reactions can be managed symptomatically. Isoniazid and rifampicin may both be hepatotoxic, causing elevation of serum aminotransferase levels (considered significant if three or more times the upper limit of normal). These hepatotoxic abnormalities are rarely severe in children, and modest increases in aminotransferases generally resolve spontaneously. All drugs used in treating TB can cause skin rash, which is usually minor and may be managed symptomatically. Isoniazid has also been associated with symptomatic pyridoxine deficiency, particularly in severely malnourished children. Supplemental pyridoxine is indicated in these malnourished children as well as in breastfeeding infants (dose is 5 mg in infants from birth to 1 month, 5 to 10 mg in infants and children less than 12 years, and 10 mg in children 12 to 18 years). Both isoniazid and rifampicin may cause suppression of vitamin D metabolism, which may result in symptoms of hypocalcemia.[141] Pyrazinamide is generally well tolerated in children and rarely causes hepatic dysfunction. Ethambutol has been associated with retrobulbar neuritis, which presents with blurred vision, central scotoma, and color blindness. Trebucq reviewed the literature regarding recommendations for ethambutol use in children and concluded that ethambutol was safe in children older than 5 years at a dosage of 15 mg/kg/day and also in younger children without undue fear of side effects.[154] It is often appropriate to obtain a baseline ophthalmologic assessment in younger children before starting ethambutol therapy. This should be repeated after 1 to 2 months.

Compliance by the patient and monitoring by the physician are major determinants of the success of drug treatment. Compliance in children is further compounded by the fact that children may have mechanical difficulties in taking medications, many of which are not specifically packaged or produced in pediatric formulations. Difficulties with taste, consistency of formulations, and gastrointestinal toxicity may be important factors in children that may dramatically affect treatment compliance.

DOTS (which stands for "directly observed therapy, short course" or "direct observation of therapy") has become a cornerstone for TB control across the globe. However, DOTS is only one of five key elements; these include government commitment to sustained TB control activities, case detection by sputum smear microscopy, standardized treatment regimens of 6 to 8 months for all confirmed smear-positive cases with DOTS for at least 2 months, a regular uninterrupted supply of essential antituberculosis drugs, and a standardized recording and reporting system. DOTS has been adopted by 148 of 210 countries worldwide and almost 55% of the world's population lives in countries providing DOTS. The WHO recommends that the DOTS strategy be applicable to all patients with TB, including children in whom high success rates (over 95%) can be achieved.[104] Many countries have adopted a universal DOTS policy, whereas others such as the United Kingdom use a selective policy for those who may be unreliable in taking their therapy.[151]

Respiratory Tuberculosis Including Hilar Adenopathy

In most cases, there is usually a history of contact with a smear-positive patient, commonly a family member. Treatment should consist of rifampicin and isoniazid for 6 months, supplemented by pyrazinamide for the first 2 months. Ethambutol should also be included in the first 2 months in children who are at high risk of isoniazid resistance. This includes those who are known or suspected to be HIV positive and those who are from other ethnic groups or are recent arrivals such as immigrants and refugees. For children aged 5 years or more, ethambutol is recommended for routine treatment without taking any more precautions than for adults. A routine ophthalmology review is recommended in young infants.

Central Nervous System Tuberculosis (Meningitis and Tuberculoma)

Quadruple therapy with rifampicin and isoniazid, with an initial 2 months of pyrazinamide and ethambutol or strepto-

mycin, is recommended for central nervous system TB. Both ethambutol and streptomycin cross the blood-brain barrier rather poorly, and only when the meninges are inflamed. Nevertheless, streptomycin is recommended by the WHO and the American Thoracic Society for TB meningitis. An alternative drug that achieves good cerebrospinal concentrations in children with TB meningitis is ethionamide, particularly when a dosage of 20 mg/kg/day is used.[155] A total duration of 12 months is generally recommended, although the WHO recommends a minimum of 6 months of therapy. Adjunctive steroid therapy is often given at the start of treatment. Advice from an infectious diseases specialist should be sought.

Other Extrapulmonary Tuberculosis

There are no clinical efficacy trials for the treatment of extrapulmonary TB in children. Present recommendations are based on trials in adults, which show favorable responses to 6 months of three or four drug combinations for non–life-threatening extrapulmonary disease. Treatment of TB adenitis, bowel disease, pericarditis, bone and joint disease, and other end-organ disease should be with the standard 6-month regimen. However, some authorities recommend longer courses of between 9 and 12 months for bone and joint disease.[150]

Multidrug-Resistant Tuberculosis

Single, multiple, and multidrug resistance is increasing worldwide. Isoniazid resistance has been found in 6.8% to 7.2% of isolates in children less than 15 years old in England and Wales from 1995 through 1999. MDR (defined as resistance to both isoniazid and rifampicin) over the same period was 0.5% to 0.7%. Higher levels of resistance occur in ethnic minority groups, especially those from the Indian subcontinent and sub-Saharan Africa. As children have lower rates of TB isolation, MDR TB is often initially identified only in the adult index case or in other contacts.

Treatment of patients with drug-resistant TB should be carried out only by specialists with appropriate experience in the management of such cases. The most common isolated drug resistance is to isoniazid. It is particularly important to add ethambutol as a fourth agent where isoniazid resistance is suspected or in those patients at higher risk of resistance. Treatment should be continued for 9 to 12 months, initially with rifampicin, pyrazinamide, and ethambutol for 2 months, followed by rifampicin and ethambutol for the complete duration of therapy. Isolated resistance to other first-line drugs is unusual and appropriate therapy must begin based on recommended guidelines.[151] Rifampicin resistance most commonly occurs in conjunction with isoniazid resistance (called MDR TB). Treatment should be carried out by a specialist with substantial experience in managing complex resistant cases and only in hospitals with appropriate isolation facilities. Such treatment should also be monitored closely not only for drug toxicity but, more important, to ensure compliance. Treatment will in most cases involve five or more drugs and for durations of at least 2 years. Several alternative antituberculosis drugs may need to be used, although the efficacy of these drugs has not been evaluated in children. The drugs that have been used previously include aminoglycosides (streptomycin, amikacin, capreomycin, kanamycin), ethionamide/prothionamide, cycloserine, quinolones (ciprofloxacin, ofloxacin), rifabutin, macrolides (azithromycin, clarithromycin), and *para*-amino salicylic acid.

Recently, *extensively drug-resistant tuberculosis* (XDR TB) has been reported in a number of countries.[156-158] XDR TB isolates are resistant to at least isoniazid and rifampin (MDR TB), and also exhibit additional resistance to at least three of the six classes of second-line drugs used to treat MDR TB. XDR TB is of particular concern among HIV-infected or immunocompromised individuals. Individuals are more likely to develop TB disease once they become infected with MDR and have a much higher mortality than those with other forms of TB.[157] The greatest concern is that XDR TB leaves some patients virtually untreatable with currently available drugs. To date, XDR TB has not been reported in children, but pediatric infection is probably inevitable in high-incidence populations, which often have high rates of HIV coinfection.

Corticosteroids

Corticosteroids have been found to be beneficial in situations where the host response to MTB contributes to significant tissue damage. Corticosteroids have been shown to significantly decrease mortality and long-term neurologic sequelae in patients with TB meningitis.[159,160] Children with bronchial obstruction due to enlarged lymph nodes may also benefit from corticosteroid therapy.[161] Corticosteroids may also be of benefit in extensive pulmonary TB, pericardial effusion, and pleural effusion. A dosage of 1 to 2 mg/kg (maximum of 60 mg) for 4 to 6 weeks is recommended, followed by a period of weaning doses.

PREVENTION AND CONTROL

The control of TB requires collaboration between health care professionals and public health departments in an effort to identify individuals who are contagious, provide effective and timely treatment to them, and also identify and investigate contacts of these individuals. Epidemiologic investigation of contacts of infectious individuals is aimed at identifying those with evidence of infection so that they may receive chemoprophylaxis to prevent future development of disease (see section on latent infection). WHO has focused on a DOTS strategy to ensure that TB control is effective particularly in high prevalence areas. The five key components of DOTS include the following:

- *Sustained political commitment* to increase human and financial resources and make TB control a nationwide activity and an integral part of the national health system
- *Access to quality-assured TB sputum microscopy* for case detection among persons presenting with symptoms of TB, screening of individuals with prolonged cough by sputum microscopy and special attention to case detection among HIV-infected people and other high-risk groups, such as people in institutions

- *Standardized short-course chemotherapy to all cases of TB under proper case-management conditions* including direct observation of treatment; proper case management conditions imply technically sound and socially supportive services
- *Uninterrupted supply of quality-assured drugs* with reliable drug procurement and distribution systems
- *Recording and reporting system enabling outcome assessment* of each patient and assessment of the overall program performance

bCG Vaccine

The WHO recommends neonatal bCG vaccination in countries with a "high prevalence" of TB, even in those with a high prevalence of HIV infection. bCG vaccine is also recommended for children at particular risk of TB exposure in low-endemic countries and for those exposed to MDR MTB.[162] bCG is used in over 150 countries and is mainly given in the neonatal period. However, there are some countries with low prevalence, such as the United States and Australia, that do not routinely vaccinate with bCG, based on the uncertain efficacy against pulmonary TB in adolescents and adults, as well as the need to maintain the utility of tuberculin testing as a diagnostic test in the population.

The protective efficacy of bCG remains controversial, varying from 0% to 80% in different populations and geographic regions.[163] Meta-analysis of prospective trials has shown a combined relative risk (RR) for TB of 0.49 (95% confidence interval, 0.34 to 0.70); that is, a protective effect of 51%.[164] Another meta-analysis has shown that the combined protection against meningeal and miliary TB was 86%.[165]

For the first time, after 80 years of widespread use of bCG, evaluations of new vaccine candidates in humans are available. Alternative approaches in vaccine development include subunit vaccines based on MTB antigens, recombinant bCG vaccines, and attenuated MTB vaccines. Another approach has been a prime-boost strategy, which may be relevant in populations already heavily vaccinated with bCG.[166] While vaccines are in different stages of development and use in humans, bCG remains the only vaccine currently available for the prevention of TB.

Nontuberculous Mycobacteria

Nontuberculous mycobacteria (NTM) include mycobacterial species associated with human infection, excluding those belonging to the MTB complex (MTB, *M. bovis*, and *M. africanum*) and also excluding *M. leprae*. NTM are also referred to as atypical or environmental mycobacteria, and only a fraction of the many species cause human disease. Apart from cervical lymphadenitis, infection in immunocompetent children is relatively unusual, and most NTM are weakly pathogenic. Disseminated NTM infections in children with previously unrecognized immunodeficiencies have highlighted crucial immunologic mechanisms in the host defense to mycobacteria in general.

EPIDEMIOLOGY, RISK FACTORS, AND PATHOGENESIS

The classification of NTM has historically been made based on their microbiological characteristics, such as pigment production and rate of growth,[167,168] but this classification does not correlate well with clinical significance and disease. The most common species causing disease in children are two very closely related species, *M. avium* and *M. intracellulare*, which have been grouped taxonomically as *M. avium* complex (MAC). MAC infection is also common in adults with HIV/AIDS and is commonly isolated from the sputum of those with cystic fibrosis. Other common pathogenic species are *M. kansasii*, *M. fortuitum*, and *M. marinum*. Unlike most NTM, *M. fortuitum*, together with *M. chelonae* and *M. abscessus*, grow quickly (days rather than weeks) in vitro and are collectively known as "rapid growers."

NTM are ubiquitous in the environment, particularly in water, soil, and some animals. MAC is found in brackish warm water and poultry. The rapid-growing mycobacteria are relatively resistant to sterilization procedures and have been commonly reported to cause nosocomial infections as a result of contamination of fluids or devices in hospitals.[169] *M. marinum* is found in fish tanks and swimming pools and causes cutaneous infections by direct inoculation through broken skin (called "fish tank" or "swimming pool" granuloma).[170] *M. ulcerans*, which is found in fish, water insects, and snails, causes necrotic and often progressive skin lesions (Buruli ulcer), particularly in tropical countries, where it is extremely prevalent.[171] Significant outbreaks have also been reported from temperate countries.[172] Most infection with NTM is acquired through the oropharyngeal mucosa (the presumed portal of entry for cervical lymphadenitis) or, more rarely, through the respiratory and gastrointestinal tracts. Iatrogenic inoculation, for example, via central venous catheters or tympanostomy tubes, also occurs.

Given their wide distribution, exposure to NTM is ubiquitous, but clinical disease is relatively rare. Infection is acquired predominantly from environmental sources, and person-to-person transmission does not usually occur. In immunocompetent hosts, infection is usually limited to the portal of entry and regional lymph nodes. Dissemination of infection to distal sites is usually seen in those with immunodeficiency, particularly T cell–deficiency states such as advanced HIV/AIDS; MAC infection is an AIDS-defining illness. Detailed genetic analysis of a Maltese pedigree with previously unexplained and frequently fatal NTM infection identified a rare functional mutation of the IFN-γ receptor,[173] highlighting the importance of protection by this immunologic pathway. Deficiencies of key determinants of IFN-γ secretion, such as IL-12, also predispose to overwhelming infections with weakly pathogenic NTM and other intracellular organisms.[174] The pathogenesis of NTM infection is poorly understood. NTM may act as saprophytes as well as true pathogens, and distinguishing low-level infection from colonization may be problematic.

CLINICAL MANIFESTATIONS

The common manifestations of NTM are shown in Table 39-7.[175,176] Cervical lymphadenitis, predominantly caused by

Table 39-7
Clinical Manifestations of Nontuberculous Mycobacteria Infections

Predominant NTM species	Site of infection	Comments
MAC *M. kansasii* *M. fortuitum*	Cervical lymph nodes	Usually less than 6 years Subacute infection Usually unilateral
M. ulcerans *M. marinum* *M. chelonae* *M. fortuitum*	Cutaneous infection	Buruli ulcer Fish tank or swmming pool granuloma
MAC *M. kansasii* *M. abscessus*	Pulmonary infection	Usually immunocompetent host May be seen in CF May resemble MTB
MAC *M. kansasii* *M. abscessus* *M. chelonae* *M. marinum*	Skeletal infection	Usually direct inoculation Often associated with disseminated disease
MAC (other species rarely)	Disseminated infection	May be recovered from blood, bone marrow, reticuloendothelial system Implies immunodeficiency state

MAC, is the most common presentation seen in children, although globally Buruli ulcer is the third most common mycobacterial disease after MTB and leprosy.[5]

PULMONARY DISEASE

NTM infection of human lung tissue either follows primary invasion or secondary infection of previously damaged or abnormal lung parenchyma. Among the conditions reported in association with pulmonary NTM disease are cystic fibrosis, recurrent aspiration, lipoid pneumonia, and ciliary dyskinesia.[177,178] NTM isolation in children with cystic fibrosis is well recognized but often exemplifies the difficulties in distinguishing infection from colonization. The presence of a heavy growth of a single NTM species on repeated specimens with clinical and radiographic deterioration and no other clear etiology suggests true NTM infection.[179]

In general, NTM pulmonary infection may present as air-space filling processes or "pneumonia," as obstructing endobronchial lesions,[180] or as a compressive peribronchial lymphadenopathy.[181] Intrathoracic lymphadenitis without airway involvement has also been described. NTM secondarily invades regions of bronchiectasis caused by other disorders, and NTM may also be the primary cause of bronchiectasis. The radiographic signs of pulmonary NTM infection are usually nonspecific but may mimic MTB.

Unlike in adults, pulmonary NTM infection in infants and children is more likely to be associated with marked lymphadenitis and less likely to cause focal, destructive parenchymal disease. This pattern of disease is closely analogous to infection with MTB. Pleural disease in children caused by the NTM, as with adults, is uncommon. The tissue response typically has granulomatous features. Noncaseating granulomas, necrotizing granulomas, or, less commonly, caseation necrosis may be present. The rapid growing mycobacteria may elicit a dimorphic response with both granulomatous and pyogenic features.

DIAGNOSIS

Diagnosis is often problematic because of the wide distribution of the NTM in the environment, the saprophytic (rather than pathogenic) abilities of NTM and their relatively frequent contamination of laboratory cultures. Thus, establishing a specific pulmonary diagnosis should include (1) characteristic signs and/or symptoms; (2) representative radiographic abnormalities; (3) isolation, preferably repeatedly, of the mycobacteria from secretions or tissues; (4) granulomatous features on histopathology, if tissue is available; (5) absence of evidence for other potential pathogens; and (6) inferential evidence including plausible histories of exposure (where applicable), skin test reactivity (if available), and occasionally responses to therapeutic trials. Clearly isolation of NTM from a sterile site strongly suggests disseminated infection. Unlike other bacteria, isolates of NTM from a draining sinus are often clinically significant. Culture of NTM (rapid growers notwithstanding) can take several weeks. Newer liquid culture media have reduced culture times to days. Molecular techniques, such as PCR, can differentiate NTM from MTB,[182] but, as with MTB, diagnostic PCR sensitivity falls if the mycobacteria are not present in large numbers.

Skin testing for NTM infection is difficult to interpret because of the lack of sensitivity and specificity of available antigens. Although PPD derived from MAC is available, it is not routinely used in most centers and its use has not been standardized. The Mantoux test will generally discriminate between TB and NTM infection despite antigenic cross-reactivity.[176,183] The newer blood-based immunologic diagnostic methods that are gaining popularity for the diagnosis of TB use only predominantly TB-specific antigens and therefore largely distinguish between MTB and NTM responses.

DIFFERENTIAL DIAGNOSES

For many young children, even with careful evaluation, it may be difficult to exclude MTB infection, and empiric anti-TB treatment (possibly with additional treatment for NTM infections) may be warranted. This is particularly true in the cases of infants or young children in whom TB may rapidly progress to life-threatening or disabling forms of TB, including miliary, meningeal, or spinal disease. Disseminated NTM infection implies an underlying immunodeficiency.

TREATMENT

Prevention of NTM disease is limited to prophylactic antibiotics against MAC in HIV-infected individuals older than 6 years with significant immunodeficiency.[176] Typically, clarithromycin or (if MTB is definitely excluded) rifabutin is used. With highly active antiretroviral therapy, such anti-MAC prophylaxis is indicated infrequently in children with HIV.

Simple cervical lymphadenitis, especially that caused by MAC, is treated with complete surgical excision; adjunctive antibiotic therapy is only used where excision is incomplete. Other NTM infections are treated with combinations of antimicrobials for protracted periods. Many NTM are resistant to standard anti-TB medications. The choice of anti-NTM therapy is guided by the causative species, the site of infection, the in vitro susceptibilities, any underlying conditions, and the need to presumptively treat MTB infection until this can be excluded. In general in vitro susceptibility testing of NTM correlates poorly with clinical response.[184]

Combination therapy to prevent acquired drug resistance is an essential component of the treatment of TB and a principle that is also applied to NTM. Single drugs, no matter how efficacious, are subject to selection of drug-resistant variants, leading to clinical resistance to the individual agent. As in TB, therapy is generally extended well beyond the time of initial bacteriologic and clinical improvement. This is necessary to prevent recurrence by eliminating persistent, slow-growing, or semidormant bacilli that may reactivate if chemotherapy is prematurely terminated. Recommended drugs and drug regimens for the common NTM diseases include newer macrolides (clarithromycin or azithromycin), cefoxitin, rifabutin or rifampicin, trimethoprim-sulfamethoxazole, amikacin, and ciprofloxacin. Various drug combinations are recommended for different clinical scenarios (Table 39-8), often for prolonged periods.[176] Specialist advice should be sought prior to commencing therapy. It should be emphasized that these drug regimens represent generally uncontrolled experience rather than appropriate randomized trials. Surgical treatment for NTM disease may be useful, including resection of localized and refractory pulmonary disease associated with irreversible damage to the airways or lung parenchyma.

Immunologic interventions may be appropriate in selected instances. Where NTM disease occurs as a result of immunosuppressive therapy given for other disorders, it is desirable to stop or minimize the predisposing immunosuppressive treatments. Despite aggressive drug therapy, cures are seldom achieved if there is significant immunosuppression. Underlying immunodeficiency states, such as HIV, should be treated if possible. Recent case reports suggest a possible role for exogenous IFN-γ in selected patients with disseminated NTM disease, many of whom had non–HIV-related abnormalities of T-cell and/or macrophage function.[185]

Table 39-8
Suggested Antibiotic Regimens for Nontuberculous Mycobacteria Infection

	Suggested Drug Regimen	Additional or Alternative Agents	Comments
M. avium complex	Clarithromycin or azithromycin, plus ethambutol plus rifampicin	Ciprofloxacin Amikacin Rifabutin	Excision is usually curative for cervical lymphadenitis. Usual duration: up to 24 months for disseminated disease. Rifabutin lowers bioavailability of macrolides
M. kansasii	Rifampicin, ethambutol, and isoniazid		Usual duration: 12 to 18 months. Amikacin may be used initially for 2 to 4 months for more extensive disease. Debridement is necessary for osteomyelitis
M. abscessus	Clarithromycin plus amikacin plus cefoxitin		Otitis media may require only initial triple therapy and then prolonged clarithromycin. Surgical debridement may be necessary. Pulmonary disease (e.g., in CF) may require surgical resection. Most strains are resistant; treatment is rarely curative.
M. chelonae	Clarithromycin plus amikacin	Cefoxitin, ciprofloxacin	Usual duration: 6 to 12 weeks for palliation.
M. fortuitum	Initial therapy cefoxitin and amikacin, followed by a macrolide, doxycycline,* or ciprofloxacin	Trimethoprim-sulfamethoxazole may be used as follow-on therapy for catheter infections	Choice of oral therapy depends on susceptibilities. Usual duration: 4 to 6 months, attempting cure.
M. marinum	None if minor Trimethroprim-sulfamethoxazole, clarithromycin, doxycycline, or rifampicin		Surgical debridement may be necessary if extensive.

*Doxycycline should only be given to those older than 8 years.

PITFALLS AND CONTROVERSIES

- TB in children is often overlooked, especially in settings where it is relatively rare. The signs and symptoms are often subtle and are generally nonspecific (e.g., chronic cough) or insensitive (e.g., night sweats). Weight loss or lack of adequate weight gain is probably the most predictive symptom.
- Although children with TB disease are rarely infectious, their family or household members may well be the source of their infection. Timely assessment of household contacts and appropriate infection control measures are therefore needed following diagnosis of TB in children.
- Microbiological diagnosis of LTBI is not possible because in this situation MTB is never isolated from the sputum. Furthermore, in up to half of the cases of TB disease in children, a microbiological confirmation of TB (either by microscopy or culture) is not made.
- Children with TB disease should be investigated for HIV coinfection.
- The TST has been used in the diagnosis of TB for close to a century. However, this test is both nonspecific (it cross-reacts with both bCG and environmental nontuberculous mycobacteria) and insensitive, especially in younger children and immunocompromised individuals. Newer immunologic diagnostic methods, which measure IFN-γ responses following incubation with MTB-specific antigens, have shown great promise in improving the accuracy of TB diagnosis. Their comparative utility in children is largely unknown. It is likely that further developments in these methods, incorporating additional MTB-specific antigens, will eventuate. However, these methods need to be affordable, easy to use, and cost-effective, particularly in populations with high TB incidence and with limited resources.
- The optimal treatment of LTBI in children is unknown. Although most recommendations suggest 6 months of INH monotherapy, treatment completion may be poor, especially in children. There is a large, and largely anecdotal, experience of using INH and RIF combination for three months as an alternative, but there have been no trials of comparing compliance, acceptability, or outcome for this regimen.
- Treatment of XDR TB highlights the lack of development of novel anti-TB therapies that are urgently needed in the face of increasing and essentially untreatable MTB in several parts of the world.
- The current and only vaccine against TB (bCG) has variable efficacy (0% to 80%) and on average reduces the risk of TB disease by just over 50%. Newer vaccines are currently being developed using a variety of strategies and will hopefully be more effective in preventing TB.

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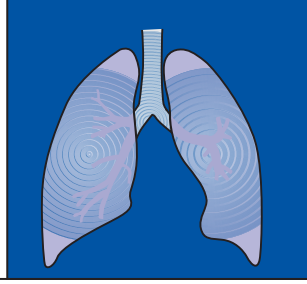

CHAPTER 40 *Mycoplasma* Infections

Ziad M. Shehab

TEACHING POINTS

- While community-acquired pneumonia is commonly due to *Mycoplasma pneumoniae*, the most common manifestation of this infection is tracheobronchitis.
- Severe pneumonia secondary to *M. pneumoniae* is uncommon except in individuals with sickle cell disease or immunodeficiencies.
- The mainstay of diagnosis for *M. pneumoniae* infections is serological testing. Specific IgM antibodies appear in 80% of patients 9 or more days after onset of symptoms. PCR is a more sensitive detection method but is not yet widely available.
- Agents effective in therapy of *M. pneumoniae* infections are the macrolides, tetracyclines, and the newer quinolones.
- *Ureaplasma urealyticum* is associated with bronchopulmonary dysplasia in premature newborns but its causality has not been demonstrated. Empiric therapy of infants colonized with *U. urealyticum* for the prevention of chronic lung disease is not supported.

Mycoplasma pneumoniae has long been recognized as the agent of primary atypical pneumonia, especially in children. It is one of 17 *Mycoplasma* species infecting humans. In addition to *M. pneumoniae*, the genital mycoplasmas, which include *Mycoplasma hominis*, *M. fermetans*, *M. genitalum*, *Ureaplasma urealyticum*, and *Ureaplasma parvum*, have been recognized as agents of human disease.[1]

Mycoplasmas are the smallest self-replicating organisms that are able to live outside the host cell. Because they have no cell wall, these agents are pleomorphic, do not stain well with the usual bacteriologic stains such as Gram stain, are susceptible to drying, and are not killed by cell wall–active agents such as penicillins and cephalosporins. Like bacteria, they multiply by binary fission. The genome, which was completely sequenced in 1996, is very small and accounts for the saprophytic nature of this organism and its fastidious growth requirements.[2]

MYCOPLASMA PNEUMONIAE INFECTIONS

Epidemiology

Our understanding of the epidemiology of mycoplasma infections is the result of population-based studies done over the past four decades as well as improved diagnostic tools that have become available more recently. Infections occur endemically in urban settings, although epidemics occur periodically at irregular intervals of about 4 years. Although these outbreaks can occur at any time of the year, they are more commonly seen in the autumn, and they last several months.[3-17] These infections occur throughout life and are commonly manifested as respiratory infections, particularly in school-age children and adolescents.[3,9,10]

Infection and disease with *M. pneumoniae* are common. In the daycare center study by Fernald and associates,[18] the yearly risk of infection was estimated to be 12%, and most infections were asymptomatic (74%) or mildly symptomatic, manifesting with coryza and cough. In subjectively healthy individuals, the isolation rate of *M. pneumoniae* ranged from 4.6% to 13.5%.[13]

Seroepidemiologic studies show antibody prevalence rates rising from 28% in 7- to 12-month-old infants to 55% in 13- to 24-month-old infants, 67% in 25- to 60-month-old infants, and 97% in people over the age of 17 years.[20]

The rate of infection is highest in 5- to 9-year-old children. The rate is double that in children under 5 years of age or in adolescents and is about 4 times higher than that in adults; most infections in children under 5 years of age occur in 2- to 4-year-olds, with very few infections occurring in patients under 6 months of age, presumably because of transplacentally derived immunity.[21] Clinical disease secondary to *M. pneumoniae* infections is manifest mostly in those 5 to 9 years of age, followed by those 10 to 14 years of age. Recent studies show that *M. pneumoniae* is responsible for up to 23% of community-acquired pneumonias in children under 4 years of age and that infections may be just as common in very young children as in older age groups.[9,16]

In volunteer studies, the incubation period is 1 to 2 weeks and may be up to 3 weeks in community or family outbreaks, presumably because of the potentially higher inocula encountered in volunteer studies.[22-24] Intrafamilial spread occurs slowly but extensively, yielding an infection attack rate of 65% of families, including 84% of children and 41% of adults. Of the secondary cases, 71% had lower respiratory tract involvement, 14% had otitis media, 10% had pharyngitis, and 15% were asymptomatic. The progression of the disease in communities is slow, although rapid epidemics can occur. Recurrent infections are usual.[19,20,25]

Pathogenesis of Pulmonary Infection

Mycoplasmas are primarily mucosal pathogens living a parasitic existence on the epithelial cells of their host. *M. pneumoniae* is an exclusive pathogen of humans.[2] Infections with *M. pneumoniae* are acquired via the respiratory route from small-particle aerosols or more likely from large droplets. The organism attaches to a receptor on respiratory epithelia via a terminal structure containing an electron-dense core representing a cluster of adhesins. The P adhesin that is concentrated in the attachment tip is the major adhesin involved in attachment of *M. pneumoniae* to its host cell.[26,27] Recent experimental evidence has shown that it can replicate in vitro for 6 months.[28] Once adherence occurs, the organism remains extracellular. Cellular damage occurs primarily in the epithelium of the bronchi and bronchioles.[29,30] Injury to the cell is accompanied by ciliostasis.[31] It renders the host cell more susceptible to the action of catalases making the cell more susceptible to oxidative stress.[32] It is not known to produce exotoxins.

Specific serum antibody develops after infection, as does secretory antibody in respiratory secretions. After opsonization, macrophages release cytokines such as tumor necrosis factor α (TNF-α), interleukin (IL)-1, -5, and -6, and a mononuclear cell inflammatory response is seen.[1] Specific cell-mediated immune responses increase with age and are likely the result of repeated infections. It has been postulated that primary infection may sensitize the young infant so that more severe disease develops on reinfection. Only 11% of children younger than 4 years of age with documented prior infection had specific cell-mediated immunity compared to 58% of children older than 4 years and 87% of adults.[18]

Clinical Manifestations

RESPIRATORY DISEASE

M. pneumoniae infections involve the upper and/or lower respiratory tracts. The manifestation of tracheobronchitis is more commonly seen than that of pneumonia.

Pneumonia. Mycoplasmal pneumonia is a common form of community-acquired pneumonia that occurs after only 3% to 10% of infections and accounts for up to 40% of episodes of pneumonia in the general population.[1,4,33] The illness typically presents with a gradual onset of malaise, headache, and fever to 100° to 103° F (38° to 39° C) occurring over several days to 1 week.[34] Cough presents 3 to 5 days after the onset of symptoms and is initially nonproductive but may become productive of mucoid or mucopurulent sputum that can sometimes be blood tinged.[35] Associated symptoms may include chills, hoarseness, sore throat, chest pain, headache, nausea, vomiting, and diarrhea. Dyspnea can develop in more severe cases. The cough can sometimes be paroxysmal, mimicking that of pertussis. Coryza is an unusual finding except in young children, and its presence as a prodrome suggests a different diagnosis.[36] Pneumonia is rare in children under 5 years of age. School-age children are more likely to develop a bronchopneumonia involving one or more lobes.

Findings on physical examination are relatively minimal and include crackles in 78% of patients, wheezes on auscultation in 32%, and bronchial breathing in 27%.[36] However, early in the course of the illness, the chest examination may be entirely normal. Audible wheezing is described in up to 40% of children, including patients who do not have asthma.[37] Nonexudative pharyngitis, cervical lymphadenopathy, conjunctivitis, otitis media, and rash have also been noted.[38] The severity of the clinical symptoms often exceeds that of the physical signs detected.[4] Recovery is the rule in *M. pneumoniae* pneumonia. Although the clinical course is quite variable, the fever typically lasts for about 1 week and the illness usually resolves within 3 to 4 weeks. The duration of symptoms may be shortened by early antimicrobial use.[1,4,35] It is important to note that the presentation of *M. pneumoniae* pneumonia may be similar to that of other atypical agents, especially *Chlamydophila pneumoniae*, respiratory viruses, and *Streptococcus pneumoniae*. Coinfections with other respiratory pathogens are not uncommon.[9,11,13,14,16]

Pulmonary function abnormalities in the form of decreased lung diffusion capacity and abnormal lung function may persist up to 3 years.[37,39,40] In a noncontrolled study of children without asthma, the mean forced vital capacity, 1-second forced expiratory volume, and forced expiratory flow were significantly reduced.[37] Radiologic abnormalities observed by CT scans persist for months to years in 37% of children.[41] Abnormal lung diffusion is observed in 50% of children.[39]

Severe pneumonia is uncommon and may occur in healthy children and adults of all ages,[8,11,36,42-47] but especially in those with sickle cell disease,[48-50] immunodeficiency,[51] drug-induced immunosuppression,[52] and preexisting cardiopulmonary dysfunction.[53] Massive lobar consolidation, pleural effusions,[42,45,49] pneumatoceles, lung abscesses,[54,55] adult respiratory distress syndrome,[56,57] and the evolution of obliterative bronchiolitis and diffuse interstitial fibrosis have all been observed but are rare.[58]

The radiologic findings are highly variable and are usually unilateral (87%) and involve the lower lobes, the midlung fields (less frequent), and the upper lobes (least frequent).[59] In the early stages, the pattern is reticular and interstitial; patchy and segmental areas of consolidation are noted later. Lobar involvement is occasionally seen. Hilar adenopathy occurs in 34% of patients, and effusions are seen in 20% when lateral decubitus films are used.[60] A hallmark of *M. pneumoniae* infections is the often poor correlation among the degree of clinical symptoms, pulmonary physical findings, and findings on chest radiographs.[3,45,52] Using high-resolution CT scanning of the lungs, Kim and colleagues[41] demonstrated abnormal findings 1 to 2 years after their infection in 37% of children with a history of *M. pneumoniae* compared to 12% in the group with Mycoplasma upper respiratory tract infection. The changes consisted of mosaic perfusion, bronchiectasis, bronchial wall thickening, decreased vascularity, and air trapping.

The differential diagnosis of community-acquired pneumonia includes that of viral pneumonia (caused by influenza virus, parainfluenza virus, respiratory syncytial virus, and adenovirus) as well as infection caused by *Chlamydophila pneumoniae* and *Legionella pneumophila.* One of the characteristics that helps identify mycoplasmal pneumonia is the generally mild course of the illness with a progressive onset. The fever tends to be low grade, and constitutional symptoms are prominent. Ear, throat, and skin involvement are common, but coryza is not. Adenoviral and mycoplasmal pneumonias share clinical and radiologic features and may not be separable clinically.[17] Hoarseness is more likely to occur with

C. *trachomatis* infections than with mycoplasmal pneumonias.[61]

Respiratory Disease Other Than Pneumonia. *M. pneumoniae* infections have been associated with a variety of clinical syndromes. Pharyngitis was present in 32% of children with lower respiratory infection in one series but was not a major manifestation of the infection.[36] Glezen and associates[62] found that only 3% of children and adolescents with pharyngitis had *M. pneumoniae* infections, with a peak incidence in the 12- to 14-year age group. Serologic evidence of infection was demonstrated in 11% of adults with pharyngitis.[63]

Otitis media was noted in 27% of children in the series by Stevens and colleagues[36]; however, no attempt was made to establish the etiology of the otitis. The body of evidence would suggest a minimal role for Mycoplasma organisms in the etiology of otitis or bullous myringitis.[64] Radiographic evidence for sinusitis is commonly detected, but attempts at isolating the organism from middle ears and sinuses have largely been unsuccessful. Approximately 2% of cases of laryngotracheobronchitis,[3,65,66] 10% to 20% of cases of acute bronchitis,[3,15,17] 4% to 5% of cases of bronchiolitis, and 2% to 5% of cases of nonspecific upper respiratory infection[3,67] are due to *M. pneumoniae*. Mycoplasmas may also be associated with wheezing illnesses in children with asthma.[68] They are detected more commonly by culture and/or PCR from the airways of children and adults with asthma than from matched controls.[68,69] Some studies suggest that treatment of Mycoplasma infections in asthmatics results in improved lung function, and it is unclear whether this improvement is the result of the macrolide's antibacterial or anti-inflammatory effects.[70,71]

NONRESPIRATORY DISEASE

A variety of extrapulmonary complications have been described. Such complications commonly occur 1 to 21 days after the onset of respiratory illness, although concomitant respiratory symptoms are absent in some patients. Most of the diagnoses have been based on the results of serologic testing, mostly 4-fold rises in complement fixation titers, rather than on culture confirmation.

Neurologic Manifestations. The incidence of neurologic disease has been estimated at 0.1%; in selected populations such as hospitalized patients, it may be as high as 7%.[72] Onset occurs 3 to 23 days after respiratory illness, which itself was demonstrated in 79% of patients.[73] A variety of syndromes has been described, the most frequent of which is meningoencephalitis. Others include transverse myelitis, cranial neuropathy, myeloradiculopathy, a poliomyelitis-like syndrome, cerebellar ataxia, a brainstem syndrome, psychosis, cerebral infarction, focal encephalitis, and Guillain-Barré syndrome. The prognosis has been variable, and the mortality rate is estimated at about 10%. Recovery is slow and is often associated with permanent sequelae.[74,75]

Dermatologic Manifestations. Erythematous maculopapular or vesicular exanthems are the most common cutaneous manifestations of *M. pneumoniae* infection, although vesiculopustular, bullous, urticarial, and petechial lesions can occur. The most serious manifestations are erythema multiforme and Stevens-Johnson syndrome.[76,77] Ninety percent of patients between 4 and 20 years of age had clinical or radiographic evidence of pneumonia.[76] The duration of the rash typically exceeds 1 week.

Cardiac Manifestations. Cardiac involvement may occur in up to 4.5% of patients. Pericarditis and myocarditis are most frequent; congestive heart failure, heart block, and infarction have also been described.[38,78]

Gastrointestinal Manifestations. Nonspecific gastrointestinal complaints often accompany *M. pneumoniae* infections. Occasionally, hepatic dysfunction and, rarely, jaundice develop with increases in transaminase levels.[79,80]

Hematologic Manifestations. Hemolytic anemia is a common manifestation of mycoplasmal infection. The results of the direct Coombs test are usually positive. Other reported manifestations include bone marrow suppression, thrombocytopenia, and disseminated intravascular coagulation.[38]

Musculoskeletal Manifestations. Myalgias and arthralgias occur in 15% to 45% of patients. These manifestations have generally been transient and have resolved during the acute phase of the illness. Occasionally, frank arthritis may be severe and may last up to 18 months.[81]

Genitourinary Manifestations. Both glomerulonephritis and interstitial tubulonephritis have been described.[38]

Diagnosis

CULTURE

M. pneumoniae can be cultured from the throat or nasopharynx of infected individuals. The culture systems are not widely available and require 2 to 3 weeks before identification can be accomplished. Culture-based diagnosis is insensitive, expensive, and laborious and has been replaced by serologic- or molecular-based diagnostic approaches.[82]

ANTIGEN DETECTION AND DNA PROBES

Antigen detection techniques are generally insensitive and are not recommended for diagnostic purposes. DNA probes also suffer from a lack of sensitivity and are not available in the United States.[82]

SEROLOGY

Serologic assays are the mainstay of diagnosis of mycoplasmal infections because cultures and molecular diagnostic methods are not widely available.

Cold Agglutinin Identification. Cold agglutinins usually appear by the end of the first week or the beginning of the second week of illness and disappear by 2 to 3 months. Cold agglutinin responses are nonspecific and consist mostly of immunoglobulin M (IgM). They occur in association with half the cases of *M. pneumoniae* infection. A 4-fold rise in antibody or a titer greater than 1:64 suggests a recent *M. pneumoniae* infection. Cold agglutinins may become positive with a variety of viral infections and collagen vascular diseases and are not recommended for diagnosis.[82]

Specific Serologic Tests. The most widely available serologic assay is the complement fixation (CF) test, which has been used as the standard. Sera from patients in the acute and convalescent stages are run in pairs, and a 4-fold rise or fall in antibody titer is diagnostic of infection. A titer greater than 1:32 in a single serum sample is also considered diagnostic. The test measures primarily IgM antibodies and, to a lesser extent, IgG. Therefore, a negative test does not

exclude reinfection. The glycolipid antigen used in the assay cross-reacts with other plant and human antigens and has been reported in some investigations to cross-react in patients with Legionnaires' disease. In a recent 12-year study, the sensitivity and specificity of this test were 90% and 94%, respectively, in patients with pneumonia.[83]

Although the CF test used to be the gold standard, it has largely been replaced by immunofluorescent[84,85] and enzyme-linked immunosorbent assays,[86] which are more sensitive and specific. The diagnosis of primary infection is best made by detection of IgM antibody to *M. pneumoniae;* IgG levels remain elevated for several weeks and are not useful diagnostically. Whereas children and adolescents show primarily an IgM response, patients older than 40 years often do not. Thus, the absence of an IgM response does not necessarily indicate the absence of infection, especially in adults. Specific IgM antibodies are detectable in 80% of persons with *M. pneumoniae* pneumonias if sera are sampled 9 days or more after the onset of symptoms; only 40% of sera have detectable IgM antibodies 7 to 8 days after the onset of symptoms, and rarely does a sample have IgM when tested earlier.[87] The antibody peaks at 10 to 30 days and falls to undetectable levels in 12 to 26 weeks. A major limitation of serologic methods is that antibody responses may not be apparent in immunocompromised children or in infants under 12 months of age.[88] One should also note that there is a lot of variability in the sensitivity and specificity of commercially available serological assays when their performance is measured against a PCR gold standard.[89]

POLYMERASE CHAIN REACTION

Throat swabs have a higher yield than nasopharyngeal swabs for the detection of *M. pneumoniae* by the PCR and are the preferred specimens.[90] The PCR is highly sensitive and can be applied to a variety of body fluids, including cerebrospinal fluid. Nucleic acid amplification methods are the preferred methods in diagnosing *M. pneumoniae* infections. A large number of in-house PCR assays have been published, but there has not been large-scale validation and standardization of these assays.[82,91,92]

NONSPECIFIC LABORATORY DATA

The white blood cell count is usually normal, but there may be an absolute neutrophilia. The white blood cell count and erythrocyte sedimentation rate may be elevated in one third of patients with lower respiratory tract infections.

Therapy

M. pneumoniae is susceptible to the macrolides, tetracyclines, and the newer quinolones. Because it has no cell wall, it is resistant to beta-lactam antibiotics including penicillins, cephalosporins, and other cell wall–active agents. Sulfonamides, trimethoprim, and rifampin are also ineffective. Macrolides are the drugs of choice in children as tetracyclines are not indicated for children under 8 years of age, and the quinolones are not generally indicated in children under 18 years of age. The preferred macrolide is azithromycin because of its high level of activity against *M. pneumoniae* and its prolonged half-life (Table 40-1). The treatment is most effective when initiated within 4 days of the onset of symptoms,[93] but the evidence regarding efficacy of antibiotics in lower respiratory tract infections in children is not conclusive.[94] A positive culture in the absence of symptoms is not an indication for antimicrobial therapy. Similarly, upper respiratory tract illnesses or acute bronchitis caused by *M. pneumoniae* are not indications for therapy. The treatment does not appreciably affect the culture positivity. There are no good data on the benefit of steroids in the treatment of severe pulmonary or extrapulmonary infections, although some advocate their use in severe central nervous system infections.[95] Newer macrolides such as azithromycin have shown efficacy when used for a 3- to 5-day course.[1,96,97] Prophylaxis can be considered in the setting of outbreaks in institutional settings.[98]

Table 40-1
Recommended Antimicrobial Treatment for Mycoplasmal and Ureaplasmal Infection, by Age Group

Age Group	Primary Agents			Alternate Agent
	Azithromycin	Erythromycin	Clarithromycin	Tetracyclines
<1 mo	**Recommended** 10 mg/kg/day as a single dose for 5 days	Associated with pyloric stenosis. Use if azithromycin unavailable 40-50 mg/kg/day in 4 divided doses for 14 days	Not recommended	Not recommended except for severe CNS infections because of staining of dental enamel
1-5 mo	10 mg/kg/day as a single dose for 5 days	40-50 mg/kg/day in 4 divided doses for 14 days	15 mg/kg/day in 2 divided doses for 7 days	Not recommended
Infants (≥6 mo) and children	10 mg/kg/day in a single dose on day 1 then 5 mg/kg/day (max 250-500 mg) on days 2-5	40-50 mg/kg/day (max 2 g/day) in 4 divided doses for 14 days	15 mg/kg/day in 2 divided doses (max 1 g/day) for 7 days	Contraindicated for children <8 yr of age or during pregnancy Doxycycline: 4 mg/kg/day divided in 2 doses for 10-14 days (maximum 100 mg per dose) Tetracycline: 40-50 mg/kg/day (max 2 g/day) in 4 divided doses for 10-14 days.

UREAPLASMA AND GENITAL *MYCOPLASMA* INFECTIONS

Epidemiology

The main reservoir of human *Ureaplasma urealyticum* is the genital tract of sexually active men and women. It is a very common isolate in the lower genital tract. *Ureaplasma* spp. can be found in 40% to 80% of lower genital tract specimens of adult women, whereas *M. hominis* may be detected in 21% to 53%.[99] Infection of the chorioamnion is less common and is associated with chorioamnionitis, premature birth, and perinatal morbidity and mortality. *M. hominis* rarely invades the chorioamnion and amniotic fluid.

Pathogenesis of Pulmonary Infection

U. urealyticum and *M. hominis* can be transmitted to the fetus or neonate by way of an ascending intrauterine infection, by the hematogenous route through placental infection, or by passage of the newborn through an infected birth canal. Vertical transmission rates for *U. urealyticum* have been reported to be 18% to 88%, with isolation rates inversely proportional to gestational age. While *Ureaplasma* spp. can be detected in the lower respiratory tract of premature neonates for prolonged periods of time, colonization of full-term infants is transient and declines beyond 3 months of age.[100] The organisms attach to mucosal surfaces and release inflammatory cytokines that can cause damage to the respiratory epithelium. They are able to incite an inflammatory response in the bloodstream and respiratory tract. Indeed, colonized neonates who had *Ureaplasma* in their tracheal secretions in the first 24 hours of life are more likely to have neutrophils in their tracheal aspirates on day 2 compared to noncolonized newborns. Increased inflammatory cells are also a feature of bronchopulmonary dysplasia. *Ureaplasma* spp. colonization of the airways of neonates is associated with increases in proinflammatory tracheal cytokines (TNF-α, IL-1β, and IL-8) and sometimes blockage of IL-6 and/or IL-10.[100] These cytokine changes are thought to occur in association with a coinflammatory stimulus such as bacterial infection or hyperoxia.[101] In the neonatal mouse model, Crouse[102] has demonstrated that hyperoxia leads to persistence of *U. urealyticum* in the lungs and potentiates the inflammatory response leading to lung damage. A recent pooled analysis of observational studies demonstrates the association between *Ureaplasma* colonization and bronchopulmonary dysplasia but not its causation.[103]

Clinical Manifestations

Ureaplasma spp. may cause congenital and neonatal pneumonia. Maternal vaginal colonization is associated with wheezing up to the fifth year of life but not with asthma.[104] They can also cause lower respiratory tract infections in immunocompromised children. They have been associated with the development of bronchopulmonary dysplasia in preterm neonates. Bacteremia has been described and can occur in association with pneumonia and/or meningitis. Central nervous system infections are sometimes associated with the development of hydrocephalus with or without cerebrospinal fluid pleocytosis.[100] It is unlikely that genital mycoplasmas are a significant cause of systemic infection in healthy infants outside the neonatal period.[105] Genital mycoplasmas have been isolated from brain abscesses, osteomyelitis, pericardial fluid, and soft tissue abscesses.[100] Antibody is critical in host defenses against systemic ureaplasmal infections. Indeed, arthritis, subcutaneous abscesses, persistent urethritis, and cystitis occur in hypogammaglobulinemic patients.[106]

Diagnosis

Culture remains the standard for detection of genital mycoplasmas. The organisms typically grow in 2 to 5 days on specialized media. Specimens should be inoculated in special transport media at the bedside.[82,107] The PCR assay is not commercially available and remains a research tool. Serologic assays have not been standardized and are not recommended for diagnosis. Cultures of blood, cerebrospinal fluid, and respiratory secretions should be considered for sick neonates with pneumonitis or central nervous system disease, especially those with hydrocephalus with or without cerebrospinal fluid pleocytosis.

Therapy

Ureaplasmas are generally susceptible to macrolides and the tetracyclines. They are resistant to the lincosamides. In contrast, *M. hominis* is inherently resistant to the macrolides and is susceptible to the lincosamides. Both tend to be susceptible to the quinolones, but their use in children is limited by potential damage to the cartilage.

The macrolides are the preferred agents for treatment of these infections. Erythromycin is used less commonly now because of concerns about the risk of pyloric stenosis. Azithromycin and clarithromycin allow for easier dosing and better tolerability. The use of tetracyclines may be indicated for central nervous system infections. Generally, a course of 10 to 14 days is recommended for serious systemic infections (see Table 40-1). Treatment with macrolides will sometimes eradicate ureaplasmas from the lower respiratory tract, but no significant effect on respiratory outcome has been demonstrated.[108]

PITFALLS AND CONTROVERSIES

Our understanding of the contribution of *M. pneumoniae* infections to chronic lung disease remains incomplete. The need for the development of rapid sensitive assays for diagnosis that are reasonably priced is acute. Presently, serology is the only means by which *M. pneumoniae* infections are diagnosed routinely and suffers from lack of sensitivity and specificity. A reliable, widely applicable method of detection of the organism or its nucleic acids is needed for diagnosis and management as well as understanding the impact of this infection on chronic lung disease and for evaluation of antimicrobial therapies.

The association between *U. urealyticum* infections and bronchopulmonary dysplasia is well supported, but evidence of causality is lacking. To know whether antimicrobial therapy of colonized infants will result in eradication of the organism and decrease the risk of chronic lung disease will require a large-scale trial.

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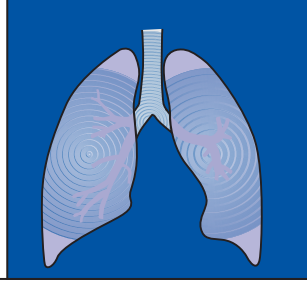

CHAPTER 41 Chlamydial Infections

Margaret R. Hammerschlag and Swati Kumar

TEACHING POINTS

- Chlamydiae comprise a diverse group of obligate intracellular organisms capable of causing respiratory disease in humans. Chlamydial infections are frequently subclinical and of long duration. Epidemiology and presentation vary from species to species.
- *Chlamydia pneumoniae* causes a variety of respiratory disease including pneumonia and bronchitis in adults and children and is transmitted person to person. Clinically, pneumonia due to C. *pneumoniae* cannot be readily distinguished from community-acquired pneumonia caused by other organisms, especially *Mycoplasma pneumoniae*.
- *Chlamydia trachomatis* is primarily a sexually transmitted infection, which can cause a distinctive pneumonia in infants born to women with active genital infection.
- *Chlamydia psittaci* is the causative agent of psittacosis, which is usually acquired from exposure to sick birds.

Chlamydiae are obligate intracellular pathogens that have established a unique niche within the host cell. Chlamydiae cause a variety of diseases in animal species at virtually all phylogenic levels. Recent taxonomic analysis using the 16S and 23S rRNA genes has suggested a new classification of species belonging to the order *Chlamydiales*.[1] The genus *Chlamydia* would be split into two genera, *Chlamydia* and *Chlamydophila* (Table 41-1). The genus *Chlamydia* would contain C. *trachomatis* and two new species, *Chlamydia muridarum* (formerly the agent of mouse pneumonitis, MoPn) and C. *suis*. The second genus was named *Chlamydophila* and would contain C. *pecorum*, C. *pneumoniae*, C. *psittaci*, and three new species split out from C. *psittaci:* C. *abortus*, C. *caviae* (formerly C. *psittaci* guinea pig conjunctivitis strain), and C. *felis*. The new classification scheme remains controversial the division into two genera has not been universally accepted. However, most experts on the field accept the splitting up of C. *psittaci* into separate species, given its biological and genetic heterogeneity. The species capable of causing respiratory disease in humans are C. *pneumoniae*, C. *trachomatis*, and C. *psittaci*.

The new classification scheme of Chlamydiales also identified two additional families of chlamydia-like organisms, Parachlamydiaceae and Simkaniaceae. Parachlamydiaceae was further subdivided into two genera, *Parachlamydia* with *Parachlamydia acanthamoebae* (Hall's coccus) as a type species and the genus *Neochlamydia* with *Neochlamydia hartmanellae* as the type species. These organisms appear to be endosymbionts of free-living ameba. Recent studies have suggested that they may be a cause of respiratory disease in humans, especially nosocomial pneumonias.[2]

Chlamydiae have a gram-negative envelope without detectable peptidoglycan, although recent genomic analysis has revealed that both C. *pneumoniae* and C. *trachomatis* encode proteins forming a nearly complete pathway for synthesis of peptidoglycan, including penicillin-binding proteins.[3] Chlamydiae also share a group-specific lipopolysaccharide antigen and use host adenosine triphosphate for the synthesis of chlamydial proteins. Although chlamydiae are auxotrophic for three of four nucleoside triphosphates, they do encode functional glucose-catabolizing enzymes that can be used for generation of ATP. As with peptidoglycan synthesis, for some reason these genes are turned off. All Chlamydiae also encode an abundant protein called the major outer membrane protein (MOMP, or OmpA) that is surface exposed in C. *trachomatis* and C. *psittaci* but apparently not in C. *pneumoniae*. The MOMP is the major determinant of the serologic classification of C. *trachomatis* and C. *psittaci* isolates.

Chlamydiae are characterized by a unique developmental cycle with morphologically distinct infectious and reproductive forms: elementary body (EB) and reticulate body (RB).[3] Following infection, the infectious EBs, which are 200 to 400 μm in diameter, attach to the host cell by a process of electrostatic binding, and are taken into the cell by endocytosis that does not depend on the microtubule system. Within the host cell, the EB remains within a membrane-lined phagosome. The phagosome does not fuse with the host cell lysosome. The inclusion membrane is devoid of host cell markers, but lipid markers traffic to the inclusion, which suggests a functional interaction with the Golgi apparatus. The EBs then differentiate into RBs that undergo binary fission. After approximately 36 hours, the RBs differentiate into EBs. At about 48 hours, release may occur by cytolysis or by a process of exocytosis or extrusion of the whole inclusion, leaving the host cell intact. Chlamydiae may also enter a persistent state after treatment with certain cytokines such as interferon-γ, treatment with antibiotics, or restriction of certain nutrients.[4] While Chlamydiae are in the persistent state, metabolic activity is reduced. The ability to cause prolonged, often subclinical, infection is one of the major characteristics of Chlamydiae.

Table 41-1
Classification of *Chlamydiales*

Genus	Species	Host(s)	Major Diseases
Chlamydia	*C. trachomatis*	Man	Trachoma, urethritis, cervicitis, PID, neonatal conjunctivitis and pneumonia, LGV
	C. suis	Pigs	Gastrointestinal disease
	C. muridarum	Mice	Pneumonia
Chlamydophila	*C. pneumoniae*	Man Koalas Bandicoots Amphibians Reptiles	Pneumonia, bronchitis
	C. psittaci	Birds Man	Gastrointestinal disease Pneumonia
	C. abortus	Cattle Sheep	Abortion
	C. pecorum	Cattle Sheep Koalas	Pneumonia, gastrointestinal disease Genital infections, conjunctivitis
	C. felis	Cats	Keratoconjunctivitis
	C. caviae	Guinea pigs	Conjunctivitis, genital infections

INFECTIONS DUE TO *CHLAMYDIA PNEUMONIAE*

C. *pneumoniae* is a common cause of lower respiratory tract diseases, including pneumonia in children and bronchitis and pneumonia in adults.[5,6] The first isolates of C. *pneumoniae* were obtained during studies of trachoma in the 1960s.[5] Subsequent serologic studies demonstrated that the organism caused an outbreak of mild pneumonia among school children in Finland in 1978.[7] In 1986, the organism was isolated from the respiratory tract of college students with acute respiratory disease (bronchitis and pneumonia) seen in Seattle.[5]

Epidemiology

C. *pneumoniae* is primarily a respiratory pathogen in humans. The organism has also been isolated from nonhuman species, including horses, Australian marsupials (koalas and bandicoots), reptiles, and amphibians, where it can cause symptomatic and asymptomatic respiratory infection. The potential role these infections may play in transmission to humans is unknown. C. *pneumoniae* appears to affect individuals of all ages.[5,6,8] The proportion of community-acquired pneumonias associated with C. *pneumoniae* infection has ranged from 2% to 19%, varying with geographic location, the age group examined, and the diagnostic methods used (Table 41-2). Several studies of C. *pneumoniae* in lower respiratory tract infection in pediatric populations have found evidence of infection from none to more than 18%; however, most of these studies have relied entirely on serology for diagnosis.[9-12] Results of a large U.S. multicenter study of community-acquired pneumonia in children 3 to 12 years of age found evidence of C. *pneumoniae* infection, based on culture, in 14% and of *Mycoplasma pneumoniae* in 22%.[9] The prevalence of C. *pneumoniae* infection in children 6 years of age or younger was 15%; in those older than 6 years of age, it was 18%. Almost 20% of the children with C. *pneumoniae* infection were coinfected with *M. pneumoniae*. C. *pneumoniae* may also be responsible for 10% to 20% of episodes of acute chest syndrome in children with sickle cell disease, 10% of episodes of bronchitis, and 5% to 10% of episodes of pharyngitis in children.[13,14] Transmission probably occurs from person to person through respiratory droplets. Spread of the infection can occur among members in the same household or individuals in enclosed populations such as military recruits and in nursing homes.[15]

Clinical Manifestations

Infections caused by C. *pneumoniae* cannot be readily differentiated from those caused by other respiratory pathogens, especially *M. pneumoniae*.[9,10,16] The pneumonia usually presents as a classic atypical (or nonbacterial) pneumonia characterized by mild to moderate constitutional symptoms

Table 41-2
Selected Studies of *Chlamydia pneumoniae* Acute Lower Respiratory Tract Infection in Children

					No. Positive Results/No. Tested (%)		
Study (Ref)	Year	Country	Age	No.	Culture	PCR	MIF
Block et al.[9]	1995	US	3-12 yr	260	34/260 (13.1)	ND	48/260 (18.5)
Harris et al.[10]	1998	US	6 mo-16 yr	456	31/420 (7.3)	ND	37/420 (8.8)
Heiskanen-Kosma et al.[11]	1998	Finland	<15 yr	201	ND	ND	29/201 (14.4)
Wubbel et al.[12]	1999	US	6 mo-16 yr	168	2/168 (1.2)	5/168 (2.9)	10/186 (6)

ND, not done; MIF, microimmunofluorescence; PCR, polymerase chain reaction.

including fever, malaise, headache, cough, and frequently pharyngitis. However, severe pneumonia with pleural effusions and empyema has been described.[17] C. *pneumoniae* may serve as an infectious trigger for asthma.[18,19] C. *pneumoniae* has been isolated from middle ear aspirates of children with acute otitis media but is usually associated with bacterial otitis media.[20] Asymptomatic respiratory infection has been documented in 2% to 5% of adults and children and may persist for a year or more.[18,21]

Diagnosis

As previously stated, it is not possible to differentiate C. *pneumoniae* from other causes of atypical pneumonia on the basis of clinical and laboratory findings.[6,16] Auscultation reveals the presence of crackles and often wheezing. The chest radiograph often appears worse than the patient's clinical status would indicate and may show mild, diffuse involvement or lobar infiltrates with small pleural effusions. The complete blood count may be elevated with a left shift but is usually unremarkable.

Specific diagnosis of C. *pneumoniae* infection is based on identification of the organism by isolation in tissue culture or by polymerase chain reaction (PCR).[22] C. *pneumoniae* grows best in cycloheximide-treated HEp-2 and HL cells.[23] The optimum site for culture is the posterior nasopharynx; the specimen is collected with wire-shafted Dacron-tipped swabs. The organism can be isolated from sputum, throat cultures, bronchoalveolar lavage fluid, and pleural fluid, but few laboratories perform culture.

PCR appears to be the most promising technology in the development of a rapid, specific, nonculture method for detection of C. *pneumoniae*. Numerous in-house PCR assays for detection of C. *pneumoniae* in clinical specimens have been reported and some are currently offered by laboratories.[22,24] However, none of these assays are commercially available or have Food and Drug Administration (FDA) approval. None are standardized or have been extensively validated compared with culture for detection of C. *pneumoniae* in respiratory specimens. Recent data have demonstrated major problems with both interlaboratory and intralaboratory reproducibility, even when the same assay is used with the same specimens.[25] Real-time PCR may be the method of choice.

Serologic diagnosis can be accomplished using the microimmunofluorescence (MIF) or the complement fixation (CF) tests.[22] The CF test is genus-specific and is also used for diagnosis of lymphogranuloma venereum and psittacosis. Its sensitivity in hospitalized patients with C. *pneumoniae* infection and children is variable. The Centers for Disease Control and Prevention (CDC) has proposed modifications in the serologic criteria for diagnosis.[22] Although the MIF test was considered to be the only currently acceptable serologic test, the criteria were made significantly more stringent. Acute infection, using the MIF test, was defined by a fourfold increase in IgG titer or an IgM titer of 16 or greater; use of a single elevated IgG titer was discouraged. An IgG titer of 16 or greater was thought to indicate past exposure, but neither elevated IgA titers nor any other serologic marker was thought to be a valid indicator of persistent or chronic infection. As accurate diagnosis would require paired sera, this would be a retrospective diagnosis. The CDC did not recommend the use of any enzyme immune assay (EIA) test for detection of antibody to C. *pneumoniae*.[22] However, a number of studies have documented a very poor correlation between serology, using MIF or EIA and detection of the organism by culture and/or PCR, especially in children.[9,10,18] Several studies of C. *pneumoniae* infection in children with pneumonia and asthma show that more than 50% with culture-documented infection have no detectable MIF antibody, even after more than 6 weeks of follow-up.[9,10,18,26]

Treatment

The optimum dose and duration of antimicrobial therapy for C. *pneumoniae* infections remain uncertain.[27] Most treatment studies have relied on serology only for diagnosis, thus the microbiologic efficacy cannot be assessed.[27] Prolonged therapy (≥2 weeks) may be desirable because recrudescent symptoms, and persistent positive cultures have been described following 2 weeks of erythromycin and 30 days of tetracycline or doxycycline.[5] Tetracyclines, macrolides (erythromycin, azithromycin and clarithromycin), and quinolones have excellent in vitro activity. Like C. *psittaci*, C. *pneumoniae* is resistant to sulfonamides.[28] The results of several treatment studies have shown that erythromycin (40 mg/kg/24 hr divided twice daily orally for 10 days), clarithromycin (15 mg/kg/24 hr divided twice daily orally for 10 days), and azithromycin (10 mg/kg/24 orally on day 1, 5 mg/kg/24 hr orally on days 2 to 5) are effective for eradication of C. *pneumoniae* from the nasopharynx of children with pneumonia in approximately 80% of cases.[29-32] Persistence has not been associated with the development of antibiotic resistance.

Prognosis

Clinical response to antibiotic therapy varies. Most patients improve clinically even if the organism persists. Coughing often persists for several weeks even after therapy.

INFECTIONS DUE TO *C. TRACHOMATIS*

C. *trachomatis* is subdivided into two biovars: lymphogranuloma venereum (LGV) and trachoma (the agent of human oculogenital diseases other than LGV). Although the strains of both biovars have almost complete DNA homology, they differ in growth characteristics and virulence in tissue culture and animals. In developed countries, C. *trachomatis* is the most prevalent sexually transmitted disease, causing urethritis in men, cervicitis and salpingitis in women, and conjunctivitis and pneumonia in infants.[33-36] C. *trachomatis* is a very rare cause of any respiratory infection in older children and adults.

Epidemiology

There are an estimated 3 million new cases of chlamydial sexually transmitted infections each year in the United States.[35] C. *trachomatis* is a major cause of epididymitis and is the cause of 23% to 55% of all cases of nongonococcal urethritis, although the proportion of chlamydial nongonococcal urethritis has been gradually declining. As many as

50% of men with gonorrhea may be coinfected with C. *trachomatis*.[34] The prevalence of chlamydial cervicitis among sexually active women is 2% to 35%. Rates of infection among adolescent girls, 15 to 19 years of age, exceed 20% in many urban populations but can be as high as 15% in suburban populations as well.[35] C. *trachomatis* genital infection has been reported in 5% to 30% of pregnant women with a risk of vertical transmission at parturition to newborn infants of about 50%.[37] The infant may become infected at one or more sites including the conjunctivae, nasopharynx, rectum, and vagina. Transmission is rare following cesarean section with intact membranes. The introduction of systematic prenatal screening for C. *trachomatis* infection and treatment of pregnant women has resulted in a dramatic decrease in the incidence of neonatal chlamydial infection in the United States.[38] However, in countries where prenatal screening is not done, such as the Netherlands, C. *trachomatis* remains an important cause of neonatal infection, accounting for over 60% of neonatal conjunctivitis.[39]

Pneumonia

Pneumonia due to C. *trachomatis* develops in 10% to 20% of infants born to women with active, untreated chlamydial infection. Only about 25% of infants with nasopharyngeal chlamydial infection develop pneumonia.[37] C. *trachomatis* pneumonia of infancy has a very characteristic presentation.[40-42] Onset is usually between 1 and 3 months of age and is often insidious with persistent cough, tachypnea, and absence of fever. Auscultation reveals crackles; wheezing is uncommon. The absence of fever and wheezing helps to distinguish C. *trachomatis* pneumonia from respiratory syncytial virus (RSV) pneumonia. A distinctive laboratory finding is the presence of peripheral eosinophilia (>400 cells/mm^3). The most consistent finding on chest radiograph is hyperinflation accompanied by minimal interstitial or alveolar infiltrates.

Diagnosis

Definitive diagnosis of C. *trachomatis* infection in infants and children is by isolation of the organism by cultures of specimens obtained from the conjunctiva or nasopharynx.[43] Several nonculture methods, specifically direct fluorescent antibody staining (DFA) and EIAs, are approved for diagnosis of chlamydial conjunctivitis in infants.[43] These tests have sensitivities of greater than 90% and specificities of greater than 95% for conjunctival specimens compared with culture. Their accuracy for nasopharyngeal specimens is not as good. The current method of choice for detection of C. *trachomatis* from genital specimens from adults and adolescents are nucleic acid amplification tests (NAATs).[43] However, data on use of NAATs in infants and children or from respiratory specimens are limited. There are currently three FDA-approved, commercially available NAATs for detection of C. *trachomatis:* PCR (Amplicor Chlamydia test; Roche Molecular Diagnostics, Nutley, NJ); strand displacement amplification (SDA) (ProbeTec; BD Diagnostic Systems, Sparks, Md); and transcription mediated amplification (TMA) (Amp CT; Gen-Probe, San Diego, Calif).[43] PCR and SDA are DNA amplification tests that use primers that target gene sequences on the cryptogenic C. *trachomatis* plasmid, which is present at approximately 10 copies/cell. TMA is an rRNA amplification assay. All three assays are also available as coamplification tests for simultaneously detecting C. *trachomatis* and *Neisseria gonorrhoeae*. The currently available commercial NAATs have FDA approval for cervical swabs from adolescent and adult women, urethral swabs from adolescent and adult men, and urine from adolescent and adult men and women. The latest version of TMA was recently approved for use with vaginal swabs in adolescents and adults. Currently, none of these assays has FDA approval for use with respiratory specimens. Preliminary data suggest that PCR is equivalent to culture for detection of C. *trachomatis* in the conjunctiva and nasopharynx of infants with conjunctivitis.[44]

Treatment

The recommended treatment regimen for C. *trachomatis* conjunctivitis or pneumonia in infants is erythromycin (base or ethylsuccinate, 50 mg/kg/24 hr divided four times daily orally for 14 days).[34] The rationale for using oral therapy for conjunctivitis is that 50% or more of these infants have concomitant nasopharyngeal infection or disease at other sites, and studies have demonstrated that topical therapy with sulfonamide drops and erythromycin ointment is not effective. The failure rate with oral erythromycin remains 10% to 20%, and some infants require a second course of treatment. The results of one small study suggest that a short course of azithromycin (20 mg/kg/24 hr once daily orally for 3 days) was as effective as 14 days of erythromycin.[38] Mothers (and their sexual contacts) of infants with C. *trachomatis* infections should be empirically treated for genital infection. An association between treatment with oral erythromycin and infantile hypertrophic pyloric stenosis has been reported in infants younger than 6 weeks of age who were given the drug for prophylaxis after nursery exposure to pertussis.[45,46]

Prevention

Neonatal ocular prophylaxis with topical erythromycin or tetracycline ointment, or silver nitrate, does not appear to prevent chlamydial ophthalmia or nasopharyngeal colonization with C. *trachomatis* or chlamydial pneumonia. Silver nitrate is no longer available in the United States. The most effective method of controlling perinatal chlamydial infection appears to be screening and treatment of pregnant women.[34] For treatment of C. *trachomatis* infection in pregnant women, the CDC currently recommends azithromycin (1 g orally as a single dose) or amoxicillin (500 mg orally three times daily for 7 days) as first-line regimen. Erythromycin base (500 mg orally four times daily for 7 days or 250 mg orally four times daily for 14 days) and erythromycin ethylsuccinate (800 mg four times daily for 7 days, or 400 mg orally four times daily for 14 days) are listed as alternative regimens.[34] Reasons for failure of maternal treatment to prevent infantile chlamydial infection include poor compliance and reinfection from an untreated sexual partner.

PSITTACOSIS (*CHLAMYDOPHILA PSITTACI*)

Chlamydophila psittaci, the agent of psittacosis (also known as parrot fever and ornithosis), is primarily an animal

pathogen and causes human disease infrequently.[47] In birds, C. *psittaci* infection is known as avian chlamydiosis.[47]

Etiology

The known host range of C. *psittaci* includes 130 avian species. C. *psittaci* affects psittacine birds (parrots, parakeets, macaws, etc.) and nonpsittacine birds as well (ducks, turkeys).[47,48] Strains of C. *psittaci* have been analyzed by patterns of pathogenicity, inclusion morphology in tissue culture, DNA restriction endonuclease analysis, and monoclonal antibodies, which indicate that there are seven avian serovars.[48] Two of the avian serovars, psittacine and turkey, are of major importance in the avian population of the United States. Each is associated with important host preferences and disease characteristics.

Epidemiology

From 1988 to 2003, there were 935 cases of psittacosis in the United States reported to the CDC.[47] Eighty-five percent of cases were associated with exposure to birds; 70% of these reported cases were the result of exposure to caged pet birds, which were usually psittacine birds including cockatiels, parakeets, parrots, and macaws. Among caged nonpsittacine birds, chlamydiosis occurs most frequently in pigeons, doves, and mynah birds. Persons at highest risk of acquiring psittacosis include bird fanciers and owners of pet birds (43% of cases) and pet shop employees (10% of cases).

Inhalation of aerosols from feces, fecal dust, and nasal secretions of animals infected with C. *psittaci* is the primary route of infection.[47] Source birds are either asymptomatic or have anorexia, ruffled feathers, lethargy, and watery green droppings. Psittacosis is uncommon in children, in part because children may be less likely to have close contact with infected birds. Cleaning the cage is an important high-risk activity. Several major outbreaks of psittacosis have occurred in turkey processing plants; workers exposed to turkey viscera are at the highest risk of infection.

Clinical Manifestations

Infection with C. *psittaci* in humans ranges from clinically inapparent to severe infection involving multiple organ systems as well as pneumonia.[49-51] The mean incubation period is 15 days after exposure, with a range of 5 to 21 days. Onset of disease is usually abrupt with fever, cough, headache, and malaise. The fever is high and often is associated with rigors and sweats. The headache can be so severe that meningitis is considered. The cough is usually nonproductive. Crackles may be heard on auscultation. Chest radiographs are usually abnormal with variable infiltrates, and pleural effusions may be present. The white blood cell count is usually not elevated, but a mild leukocytosis may be present. Elevated levels of aspartate aminotransferase, alkaline phosphatase, and bilirubin are common.

Diagnosis

The diagnosis of psittacosis can be difficult because of the varying clinical presentations. A history of exposure to birds or association with an active case are important clues, but as many as 20% of patients with psittacosis have no known contact.[47] Person-to-person spread has been suggested but not proved. Other infections that cause pneumonia with high fever, unusually severe headache, and myalgia include C*oxiella burnetii* (Q fever), *Mycoplasma pneumoniae*, C. *pneumoniae*, tularemia, tuberculosis, fungal infections, legionnaires' disease, and, most commonly, bacterial and viral respiratory infections.

The mainstay of diagnosis remains serology using the complement-fixation (CF) test, which is genus-specific. According to recommendations from the CDC, a confirmed case of psittacosis requires a compatible clinical illness, usually with a reliable history of avian exposure. Laboratory confirmation may be by one of the three following methods: (1) culture of C. *psittaci* from respiratory secretions; (2) a 4-fold or greater increase in CF or MIF titer in sera collected at least 2 weeks apart; or (3) a single MIF IgM titer greater than or equal to 1:16.[47] A probable case should be epidemiologically linked to a confirmed case or have a single CF or MIF antibody titer of 1:32 or more in at least one serum sample obtained after onset of symptoms. As with use of the MIF for diagnosis of C. *pneumoniae* infections, cross-reactions with other C*hlamydia* species and bacteria can occur.[51] Early treatment of psittacosis with tetracycline may abrogate the antibody response.

The organism can also be isolated by culture from sputum or pleural fluid. Although C. *psittaci* will grow in the same culture systems used for isolation of C. *trachomatis* and C. *pneumoniae*, very few laboratories culture for C. *psittaci*, mainly because of the potential biohazard.

Treatment

Recommended treatment regimens for psittacosis are doxycycline (100 mg orally twice daily) or tetracycline (50 mg/kg/day to maximum of 500 mg orally four times daily) for at least 10 to 14 days after the fever abates.[47] The initial treatment of severely ill patients is doxycycline hyclate (4.4 mg/kg/24 hr divided every 12 hours intravenously; maximum: 100 mg/dose). Erythromycin (500 mg four times daily orally in an adult) is an alternative drug if tetracyclines are contraindicated (e.g., children younger than 9 years of age and pregnant women), but may be less effective. Remission is usually evident within 48 to 72 hours. Initial infection does not appear to be followed by long-term immunity. Reinfection and clinical disease can develop within 2 months of treatment; there are two well-documented cases of reinfection reported.

Prognosis

The mortality of untreated psittacosis is 15% to 20% but is less than 1% with appropriate treatment. Severe illness leading to respiratory failure and fetal death has been reported among pregnant women.

Prevention

Several control measures are recommended to prevent transmission of C. *psittaci* from birds. Bird fanciers should be cognizant of the potential risk. C. *psittaci* is susceptible to most disinfectants and detergents as well as heat, but is resistant to acid and alkali.[47] Accurate records of all bird-

related transactions aid in identifying sources of infected birds and potentially exposed persons. Newly acquired birds, including birds that have been to shows, exhibitions, fairs, or other events, should be isolated for 30 to 45 days, or tested or treated prophylactically before adding them to a group of birds. Care should be taken to prevent transfer of fecal material, feathers, food, or other materials between birdcages. Birds with signs of avian chlamydiosis (e.g., ocular or nasal discharge, watery green droppings, or low body weight) should be isolated and should neither be sold nor purchased. Their handlers should wear protective clothing and a disposable surgical cap and use a respirator with an N95 or higher-efficiency rating (not a surgical mask) when handling them or cleaning their cages. Infected birds should be isolated until fully treated, which is generally 45 days.

INFECTIONS DUE TO OTHER *CHLAMYDIALES* SPECIES

The most studied member of this group of organisms has been *Simkania negevensis*, which was first identified as a contaminant in tissue culture in Israel.[2,52] The *S. negevensis* 16S and 23S ribosomal DNA each have 80% to 87% sequence identity with members of the *Chlamydiales*. The organism has been associated with a variety of respiratory illnesses including bronchiolitis in infants from Canada and Israel, community-acquired pneumonia and COPD in adults from Israel and respiratory tract infection in children and adults from Cornwall, UK. *S. negevensis* has a life cycle similar to *Chlamydiales* with a biphasic intracellular morphology with electron dense non-replicating EBs and replicating RBs of comparable sizes. There are distinct differences in that the growth cycle is longer, 12 to 15 days compared to 48 to 72 hours for *Chlamydiaceae*. Unlike *Chlamydia*, *S. negevensis* is totally resistant to penicillin. *S. negevensis* has been found to be present in drinking water and reclaimed waste water in the Negev, Israel. The organism has also been shown to be able to replicate in amebae and survive for long periods in amebal cysts, which would allow it to survive in water. Based on this, it has been proposed that *S. negevensis* may be transmitted to humans via drinking water. *Simkania* and related organisms are also called environmental chlamydiae.

P. acanthamoebae, previously called Hall's coccus, is an endosymbiont of *Acanthamoeba*. The organism was first described as bacteria-like structures in trophozoites of *Acanthamoeba* isolated from patients with fever and pneumonia associated with use of humidifiers.[2] The bacteria-like structures were subsequently identified as *P. acanthamoebae*. The organism has been isolated from nasal mucosa of healthy human volunteers and a BAL specimen from a patient with a diagnosis of viral pneumonia. However, it appears that *P. acanthamoebae* is a rare cause of pneumonia in humans. Greub and colleagues[53] were able to identify *P. acanthamoebae* DNA by PCR in only 1 of 1200 BAL specimens from patients with pneumonia of unknown etiology. This patient was a 31-year-old man who was HIV positive who presented with cough, fever, and bilateral infiltrates on chest radiograph. No other pathogens including *C. pneumoniae*, *Legionella pneumophila*, *Pneumocystis carinii*, and mycobacteria were detected. A subsequent study from the same group using serology suggested that *P. acanthamoebae* might be responsible for approximately 8% of pneumonias seen in a series of patients with head trauma and suspected aspiration pneumonia.[54] The in vitro susceptibilities of *P. acanthamoebae* appear to be similar to those of chlamydia except that they are constitutively resistant to quinolones.[55]

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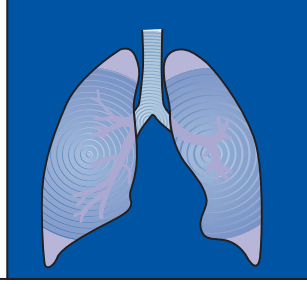

CHAPTER 42 Fungal Infections

Jay M. Lieberman and Felice C. Adler-Shohet

TEACHING POINTS

- In a patient with pneumonia, a history of travel to or residence in an endemic area should raise suspicion for the diagnosis of an endemic mycosis, such as coccidioidomycosis, histoplasmosis, or blastomycosis.
- The likelihood of clinical manifestations of histoplasmosis is determined by the intensity of the exposure and the host's immune status.
- Coccidioidomycosis and histoplasmosis usually cause self-limited infections—specific antifungal therapy is indicated only for disseminated, progressive, or severe disease.
- Invasive pulmonary aspergillosis is a potentially lethal infection in immunocompromised patients; the diagnosis requires a high degree of clinical suspicion and therapy must often be initiated before the diagnosis is confirmed.
- Effective therapy of invasive aspergillosis requires aggressive antifungal therapy and withdrawal or reduction of immunosuppressive therapy; surgical intervention is sometimes needed as well.

Fungi that cause pulmonary infections can be divided into endemic mycoses, which commonly occur in people, usually immunocompetent, who live in certain geographic areas, and opportunistic fungi that cause infection in high-risk, usually immunocompromised, hosts. The endemic mycoses discussed in this chapter include coccidioidomycosis, histoplasmosis, blastomycosis, and paracoccidioidomycosis, whereas the opportunistic mycoses include aspergillosis and cryptococcosis.

COCCIDIOIDOMYCOSIS

Coccidioides immitis, the primary etiologic agent of coccidioidomycosis, usually produces a self-limited pulmonary infection in otherwise healthy individuals. Extrapulmonary dissemination occurs rarely in normal hosts but is more common in infants and immunocompromised patients. Because of its variable clinical course and protean manifestations, coccidioidomycosis presents challenges in diagnosis and treatment.

The disease was first described in an Argentinian soldier with skin lesions in 1892. It was originally thought to be a protozoan organism until the fungal etiology was established in 1900. In 1936, primary and secondary forms of the disease were described—the primary form is commonly known as San Joaquin Valley or Valley Fever.

Until recently, C. *immitis* was considered the sole etiologic agent of coccidioidomycosis. However, a second species, C. *posadasii,* has been proposed based upon genotypic differences.[1] C. *immitis* is a dimorphic fungus that exists as a mycelium (mold) in nature and the laboratory and as a spherule containing endospores in host tissues at 37° C. When spherules rupture, they can release up to 10^5 endospores into the surrounding tissues (Figs. 42-1 and 42-2).

Epidemiology, Risk Factors, and Pathogenesis

Coccidioidomycosis is endemic to the southwestern United States and parts of Central and South America, including northwestern Mexico (Fig. 42-3). C. *immitis* naturally occurs in the soil of these areas, where the climate is arid to semiarid with low annual rainfalls. In the United States, where an estimated 150,000 people are infected annually, the disease is endemic in certain parts of Arizona, California, New Mexico, Texas, and Utah.[2] In Arizona, there has been a substantial increase in the number of cases, which is postulated to be due to environmental and climactic changes, namely hot, dry conditions.[3] Sporadic, nonendemic cases occur as a result of travel through endemic areas, inhalation of contaminated fomites, or laboratory exposure.

A history of dust exposure in endemic areas is of particular significance. Outbreaks of coccidioidomycosis have been associated with construction, archaeological digs, and other causes of soil disruption, including earthquakes.[4] During windstorms, construction work, or farming, the arthroconidia (spores) break from the parent mycelium in the soil and become airborne; even a single fungal spore can result in infection.

When arthroconidia are inhaled, primary pulmonary infection occurs. Spherules develop and grow in the lung, fill with endospores, and a polymorphonuclear reaction occurs around them. The infection remains confined to the respiratory tract in most healthy people, but extrapulmonary dissemination may occur in immunocompromised patients and, rarely, in healthy people. The incubation period is usually 10 to 16 days depending on the quantity of arthroconidia inhaled. In immunocompromised patients, reactivation of primary infection can occur months to years later.[5]

The annual risk of infection in endemic areas is about 3% based on repeated skin testing. Although primary coccidioidomycosis affects all age groups and races equally,

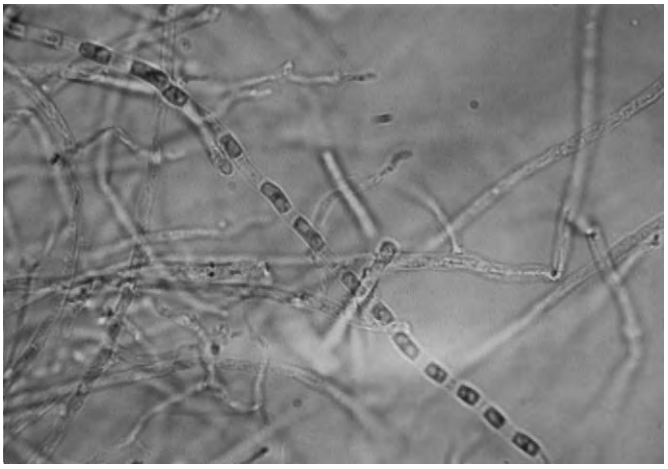

Figure 42-1 Mycelial form of *Coccidioides immitis* showing arthroconidia at 25° C (original magnification, ×400).

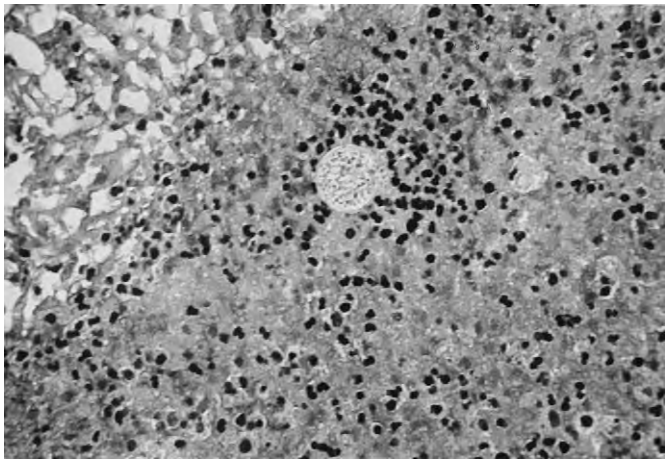

Figure 42-2 Tissue form of *Coccidioides immitis* showing a spherule filled with endospores (original magnification, ×100).

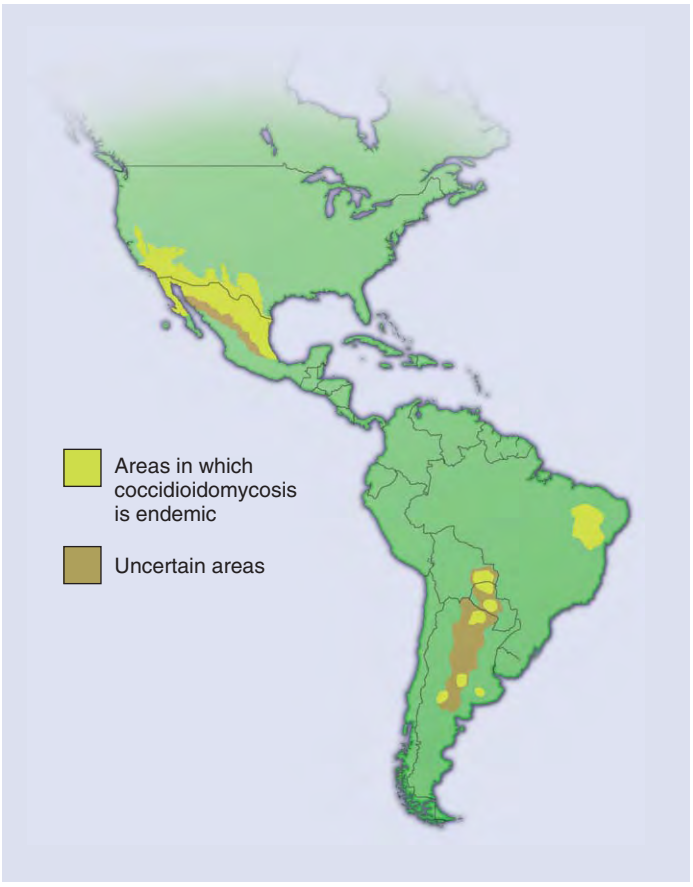

Figure 42-3 Map showing areas endemic for coccidioidomycosis.

the risk of dissemination is higher in certain groups, including infants and the elderly, Filipinos, Hispanics, African Americans, immunocompromised patients, and pregnant women.[2,6]

Person-to-person transmission does not occur and no special isolation precautions are recommended for a person with coccidioidomycosis. The spherule form of the fungus has very low infectivity, and the infective arthroconidia are generally not expelled in high numbers, even in patients with cavitary disease. Nonetheless, care should be taken when handling dressings or wounds that may contain infectious material.

Clinical Features

The majority of infections are asymptomatic, but approximately 40% of infected children develop an influenza-like illness with headache, fever, cough, and malaise. Children may also experience pleuritic chest pain and night sweats. Other clinical manifestations include arthralgias and myalgias, and a variety of rashes, including erythema multiforme or erythema nodosum.[6,7]

In patients with acute pulmonary infection, chest radiographs are abnormal in approximately half of patients. Lobar or segmental consolidation may be seen, often with ipsilateral hilar adenopathy (Fig. 42-4). Pleural effusions occur, and can be quite large. Cavities are rare in children—when they occur, they are usually solitary and have distinctive thin walls. In more than half of patients, they resolve spontaneously within 2 years. Rarely, however, they can result in hemoptysis or can rupture into the pleural space.[6]

More than 90% of primary infections resolve spontaneously. Although dissemination or severe pulmonary disease is seen mostly in immunocompromised patients, severe respiratory disease leading to respiratory failure can occur in immunocompetent children. Such severe disease, which can result in diffuse pulmonary involvement, may occur after a large magnitude exposure leading to multiple sites of infection or because of hematogenous dissemination.[6]

Chronic pulmonary lesions are rare, but approximately 5% of adults and older children develop adenopathy or residual lesions such as cysts, nodules, calcifications, cavities, fibrosis, and bronchiectasis. Solitary nodules are not uncommonly found in asymptomatic patients, which can pose a diagnostic dilemma in a patient not known to have had prior infection with coccidioidomycosis. In patients with fungemia, the chest radiograph often demonstrates a miliary or reticuloendothelial pattern and mediastinal adenopathy.

In about 0.5% of cases, disease spreads beyond the respiratory tract. Symptoms of extrapulmonary disease usually manifest a few months after the primary infection.[6] The

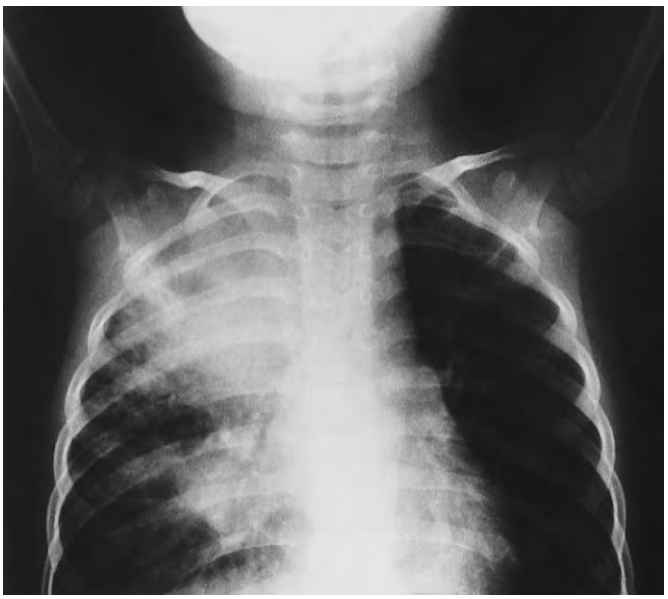

Figure 42-4 Chest radiograph of a 4-year-old girl with disseminated coccidioidomycosis.

most common site of dissemination is the skin, where verrucous, papular, and nodular lesions occur that can form sinuses and abscesses. The next most frequent site of spread is the skeletal system. The bones most commonly involved are the vertebrae, skull, ribs, and long bones. Arthritis is monoarticular in 90% of cases and occurs most frequently in the knees, ankles, and elbows. Meningitis is the most serious form of disseminated coccidioidomycosis; although transient remissions occur, it is fatal if not treated.

Diagnosis

A history of travel to or residence in an endemic area should raise suspicion for the diagnosis. However, cases of fomite transmission have been reported in nonendemic areas. A travel history in HIV-infected patients years before active disease might be relevant because, in these patients, there can be a reactivation of prior dormant infection. Laboratory data associated with, but nonspecific for, coccidioidomycosis include leukocytosis, an elevated erythrocyte sedimentation rate, and eosinophilia.

Demonstration of C. *immitis* in tissues indicates infection. Histopathologic features include acute suppuration around arthroconidia, and granulomatous inflammation and possibly caseating necrosis around developing spherules. Spherules may be identified freely or within macrophages.

The diagnosis can be confirmed by culture, but C. *immitis* poses a significant risk to laboratory personnel, and the laboratory should be notified when C. *immitis* is suspected. Although the fungus is fast growing and cultures may be positive as early as 2 days, cultures should be kept for 4 weeks before being discarded as negative.

Serologic testing can play an important role in diagnosing and managing patients with coccidioidomycosis.[8] Acute infection can be diagnosed by measuring IgM antibodies against tube-precipitin by latex agglutination, enzyme immunoassay, or immunodiffusion. The latex agglutination test is rapid and sensitive but not specific and, therefore, a positive test needs to be confirmed by another means. An IgM response can be detected in approximately 75% of patients with primary disease, appears between 1 and 3 weeks after the onset of clinical symptoms, and lasts 3 to 4 months.[7]

The IgG response can be measured by enzyme immunoassay, complement fixation (CF), or immunodiffusion tests that use a heat-labile antigen isolated from the spherule phase of C. *immitis*. Clinical laboratories use different diagnostic test kits and, therefore, positive results should be confirmed at a reference laboratory. These antibodies are usually detected 1 to 2 months after infection.[8] They provide both diagnostic and prognostic information, as CF titers >1:16 are associated with severe pulmonary disease or dissemination.[7] With therapy, these titers fall, and with resolution of the infection, CF antibodies usually disappear. Therefore, serial CF titers should be followed to assess the response to therapy. Low or negative titers in immunocompromised patients must be interpreted with caution.

Skin tests were used in the past, but are no longer available in the United States. Skin testing had value as an epidemiological tool, but was not helpful in the diagnosis of acute disease because a positive skin test did not differentiate between acute and past infection and because a negative skin test did not rule out disease.

Treatment

Primary coccidioidomycosis usually resolves spontaneously in healthy children and adults, and antifungal therapy is generally not indicated for uncomplicated primary infection.[7] There is no evidence that treatment of the primary infection reduces the morbidity of the infection or the likelihood of the development of more serious complications.[2,5] Patients who might benefit from treatment are those in whom symptoms persist for several weeks and those who have or are at high risk for dissemination, such as immunocompromised patients. Treatment is also indicated for patients with enlarging or spreading infiltrates or CF titers greater than 1:16.[2]

The azole antifungals, primarily itraconazole and fluconazole, have supplanted amphotericin B as therapy of choice for most patients with coccidioidomycosis. For uncomplicated acute pneumonia, therapy can be initiated with an oral azole and continued for 3 to 6 months[2] (Table 42-1). There is some evidence that patients treated with itraconazole may be less likely to relapse than patients treated with fluconazole.[9]

Whether or not antifungal therapy is given, the patients must be reassessed every month or so to be sure their symptoms, radiograph, and serologies are improving and that there is no evidence that they are developing disseminated disease.

For more severe disease, therapy should be initiated with amphotericin B, although the patient can be changed to an oral azole after he or she has clinically improved. Treatment should be continued for at least a year if the patient has diffuse or miliary disease.

For immunocompromised patients, it is reasonable to continue suppressive therapy with fluconazole or itraconazole for life. However, suppressive therapy with oral azoles has not been 100% effective in preventing relapses.

Table 42-1
Recommended Doses of Selected Antifungal Drugs in Children

Drug	Route	Dose
Amphotericin B deoxycholate	IV	0.5-1.5 mg/kg once daily
Amphotericin B lipid complex	IV	5 mg/kg once daily
Amphotericin B cholesteryl sulfate complex	IV	3-6 mg/kg once daily
Liposomal amphotericin B	IV	3-5 mg/kg once daily
Anidulafungin	IV	0.75-1.5 mg/kg once daily
Caspofungin	IV	70 mg/m^2 loading dose, then 50 mg/m^2 once daily
Fluconazole	IV/PO	6 mg/kg once daily (up to 12 mg/kg per day divided twice daily for serious infections)
Itraconazole	IV/PO	5-10 mg/kg per day divided into 2 doses
Ketoconazole	PO	3.3-6.6 mg/kg once daily
Micafungin	IV	4-12 mg/kg once daily (higher dose needed for patients <8 yr of age)
Voriconazole	IV/PO	8 mg/kg every 12 hr for 1 day, then 7 mg/kg every 12 hr

IV, intravenous; PO, oral.
Higher doses of some of the drugs are sometimes used in patients with invasive aspergillosis or mucormycosis. Experience with some of the drugs in children is limited.
Adapted from American Academy of Pediatrics: Antifungal drugs for systemic fungal infections. In Pickering LK, Baker CJ, Long SS, McMillan JA (eds): Red Book: 2006 Report of the Committee on Infectious Diseases, ed 27. Elk Grove Village, IL, American Academy of Pediatrics, 2006, pp 774-784.

Surgical intervention may be required for symptomatic patients with persistent cavities or a parapneumonic process.

HISTOPLASMOSIS

Histoplasmosis is the most common mycosis in the United States, although fewer than 5% of infected individuals become symptomatic. Children younger than 2 years of age and immunocompromised patients are among those most likely to develop disseminated disease.

Histoplasma capsulatum was first described in 1906 on autopsy of a patient with disseminated disease. For many years, histoplasmosis was described as a rare and uniformly fatal disease. In 1946, it was demonstrated that a large number of pulmonary calcifications resulted from *H. capsulatum* infection.

H. capsulatum is a dimorphic fungus that exists in mycelial form in the environment at 25° C and in yeast form in tissues at 37° C (Fig. 42-5). The organism is slow growing, requiring 2 to 4 weeks for colonies to appear. However, isolates have been identified in less than 7 days when a large number of infecting cells have been present.

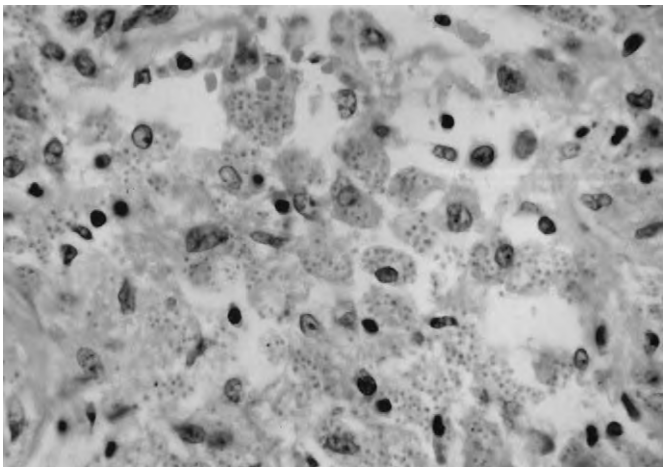

Figure 42-5 Tissue form of *Histoplasma capsulatum* at 37° C (original magnification, ×100).

Epidemiology, Risk Factors, and Pathogenesis

Histoplasmosis has a worldwide distribution but is more prevalent in parts of North and Central America.[10] Histoplasmosis is endemic to the midwestern United States, particularly the Ohio and Mississippi River valleys (Fig. 42-6). The natural habitat of *H. capsulatum* is soil, particularly soil that has been contaminated by bat or bird droppings, which creates an environment of high nitrogen content that enhances the organism's growth by accelerating sporulation. Infection occurs by inhalation of spores, causing a localized or patchy pneumonitis.

Outbreaks have been reported among pigeon or chicken breeders, explorers of caves with bats, and in populations living close to construction that causes the fungus to become airborne. A large outbreak occurred among high school students in Indiana after the soil in the school courtyard, which was known to be a bird roosting site, was tilled.[11]

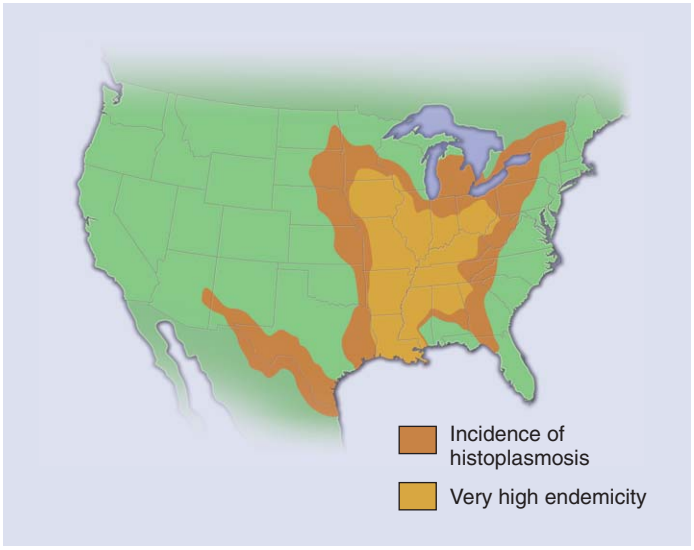

Figure 42-6 Map showing areas endemic for histoplasmosis.

The incubation period is variable but is usually no more than a few weeks after exposure. Person-to-person transmission does not occur.

After inhalation of *H. capsulatum* spores, they undergo transition to a yeast phase in the lower respiratory tract. Hematogenous dissemination, when it occurs, does so within the first two weeks after inhalation, before the development of specific immunity. The ability of the organism to cause clinical symptoms depends on the host's immune status and the magnitude of the inhaled inoculum.[10] Decreased cellular immunity of the host enhances the likelihood of dissemination. *H. capsulatum* yeast cells are phagocytosed by human macrophages, but killing does not occur. The yeast cells replicate inside macrophages and spread via the lymphatic or hematogenous route, where new foci of infection develop. These lesions eventually develop caseating necrosis or heal with fibrosis and calcification.

Reactivation of dormant infection can occur during periods of immunosuppression. Reinfection can occur in the setting of a high inoculum exposure, although it usually results in less severe symptoms than a primary infection with a high inoculum.

Clinical Features

The likelihood of clinical manifestations of histoplasmosis is determined by the intensity of the exposure and the host's immune status. Although approximately 90% of infections are asymptomatic, symptoms develop in more than 75% of normal individuals after heavy exposure.[10] Following infection, symptomatic patients often develop an acute flu-like illness with headache, fever, fatigue, dry cough, and myalgias. Other symptoms, more common after high inoculum exposures, may include chest pain, chills, arthralgias, night sweats, and shortness of breath.

Approximately 10% to 20% of patients with acute pulmonary disease develop pericarditis, a symmetric polyarticular arthritis, or erythema nodosum. Chest radiography in acute pulmonary histoplasmosis is characterized by enlarged hilar or mediastinal lymph nodes and patchy infiltrates. Pulmonary effusion occurs in about 10% of adults and fewer than 5% of children with acute disease.[12] These clinical manifestations usually resolve within a few weeks without antifungal therapy.

Progressive dissemination or cavitary disease develops after heavy exposure to *H. capsulatum* in about 1 of 2000 infected individuals. Risk factors for dissemination include old or very young age, chronic debilitating disease, and impaired cellular immunity. Notably, otherwise healthy infants younger than 2 years of age can develop progressive, disseminated histoplasmosis.[13]

Patients with disseminated histoplasmosis usually have prolonged fever, malaise, cough, and weight loss. Hepatosplenomegaly is found in 30% of adults and 89% of infants.[14] Patients may have shock, disseminated intravascular coagulation, respiratory failure, renal failure, endocarditis, and adrenal insufficiency. Thrombocytopenia and anemia are common laboratory findings. Chest radiographs are characterized by lobar or diffuse reticulogranular infiltrates, cavitation, hilar adenopathy, or any combination thereof. However, 40% to 50% of immunocompromised patients with disseminated histoplasmosis have normal chest radiographs.[14,15]

Chronic histoplasmosis resembles tuberculosis and usually occurs in patients with chronic obstructive lung disease or in immunocompromised patients. They may have a chronic cough, fevers, night sweats, hemoptysis, and weight loss. Calcified lesions, fibrosis, cavitation, and nodules may be seen on chest radiography.

Diagnosis

Isolation of *H. capsulatum* by culture is the definitive method of diagnosis, although growth requires 1 to 6 weeks on standard mycologic media. Cultures are positive from bronchoscopy or lung biopsy in approximately 85% of cases of disseminated or chronic pulmonary histoplasmosis and are often positive in patients with acute pulmonary disease following high inoculum exposure.[10] However, they are usually negative from patients with the more common acute pulmonary disease. Blood and bone marrow cultures are especially useful for the diagnosis of disseminated histoplasmosis, and should be done by the lysis centrifugation method for optimal yield.[10,13] Silver stain of the peripheral blood, particularly the buffy coat, may reveal the diagnosis in disseminated disease.

In tissues, areas of caseous necrosis with a surrounding fibrous capsule that prevents the spread of the organism are characteristic. The fungus may also be seen in tissues inside macrophages.

The standard serologic tests are an immunodiffusion assay and complement fixation test.[10] Serologic tests are positive in greater than 90% of patients with symptomatic disease, and approximately 80% of patients with disseminated disease, but 2 to 6 weeks are required for seroconversion. The CF and immunodiffusion tests peak 2 to 3 months after infection and decline over 2 to 5 years. The sensitivity of serologic testing is increased by performing both complement fixation and immunodiffusion. Although complement fixation is more sensitive, especially early in disease, the immunodiffusion test remains positive longer and is more specific. CF titers of 1:32 and 4-fold increases in titer provide the best evidence of acute infection. However, the height of the titer does not correlate with the severity of infection.

There are a number of potential pitfalls of serologic tests. Immunocompromised patients with disseminated disease may have low or negative titers, which can delay the diagnosis.[16] False-positive results can occur in patients with other infections, such as blastomycosis, coccidioidomycosis, paracoccidioidomycosis, and tuberculosis.[17] Moreover, patients with a history of histoplasmosis who have other illnesses may have borderline titers, as do about 1% to 3% of residents from endemic areas.

H. capsulatum polysaccharide antigen detection by radioimmunoassay or enzyme immunoassay from blood, urine, cerebrospinal fluid, or bronchoalveolar fluid provides a rapid means of diagnosing disseminated or extensive acute pulmonary disease. Antigen is often negative in immunocompetent patients with acute pulmonary disease. Antigen can be detected in the urine or blood of 50% to 80% of patients with disseminated histoplasmosis and in the bronchoalveolar lavage fluid of 70% of AIDS patients with pulmonary disease.[18]

False-positive results have been reported in patients with blastomycosis and paracoccidioidomycosis. Antigen levels decline in response to treatment and may be a useful tool for the follow-up of patients with histoplasmosis.[19]

Skin testing is not useful for diagnostic purposes because the skin test is positive in 80% to 90% of people without evidence of active disease in endemic areas. Furthermore, up to 50% of immunocompromised patients with disseminated disease have negative skin test results. The histoplasmosis skin test is not available in the United States.

Treatment

In the majority of immunocompetent children with uncomplicated primary pulmonary histoplasmosis, disease is self-limited and therapy is not required.[13,20] No controlled trials have been performed to evaluate the effect of antifungal therapy on the course of disease for patients with nonprogressive pulmonary disease. Pericarditis and rheumatologic manifestations including arthritis and erythema nodosum typically do not require antifungal therapy because they are probably immune mediated—nonsteroidal anti-inflammatory agents are often prescribed. If corticosteroids are used for patients with pericarditis, concurrent antifungal therapy is recommended.

Antifungal treatment is recommended for patients with progressive pulmonary disease, disseminated disease, symptoms persisting more than 2 to 4 weeks, or acute pulmonary disease complicated by adult respiratory distress syndrome or obstruction.[13,20]

Oral itraconazole is generally considered the drug of choice for most patients with histoplasmosis, although amphotericin B remains the mainstay of therapy for severe, progressive, and disseminated disease (see Table 42-1). The lipid-based amphotericin B agents may have a role—in a controlled clinical trial in adult AIDS patients with disseminated histoplasmosis, patients treated with liposomal amphotericin B had improved survival compared to those treated with conventional amphotericin B.[21]

Therapy with amphotericin B should be initiated in children with life-threatening, progressive, disseminated disease or those with chronic cavitary histoplasmosis. Once the patient's clinical condition has stabilized, therapy can be switched to itraconazole. Immunocompetent patients should receive at least 6 months of therapy, whereas immunocompromised patients require life-long suppressive therapy after the acute course is completed.

Fluconazole appears to be less effective than itraconazole for pulmonary histoplasmosis, but may be useful as follow-up therapy for meningitis or as suppressive therapy if the patient does not tolerate itraconazole.[13,20]

Corticosteroids may be helpful in conjunction with antifungal therapy in patients with pulmonary histoplasmosis complicated by obstruction or adult respiratory distress syndrome.

BLASTOMYCOSIS

Blastomycosis is an endemic mycosis of the central, midwestern, and southeastern United States (Fig. 42-7). It can cause a chronic granulomatous and suppurative disease that occurs primarily in young and middle-aged men who work or recreate outdoors. Blastomycosis was once thought to be restricted to North America, but the disease has also been described in Africa and India.

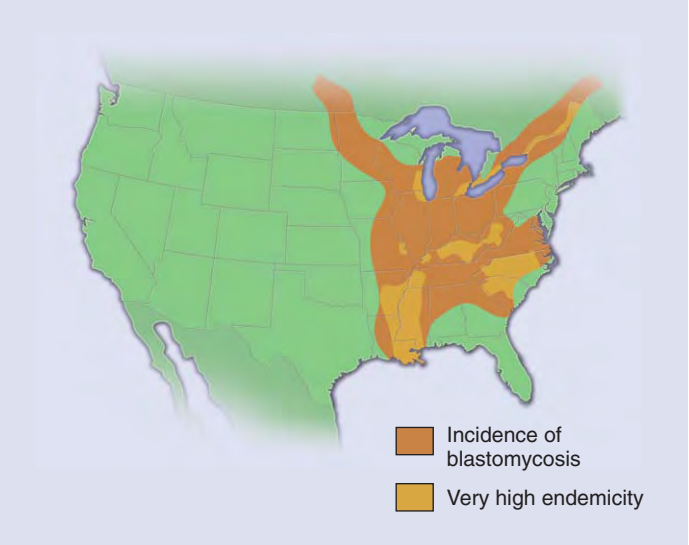

Figure 42-7 Map showing areas endemic for blastomycosis.

Blastomyces dermatitidis, the etiologic agent of blastomycosis, is a dimorphic fungus that exists in yeast form at 37° C and in infected tissues and in a mycelial form at room temperature and in soil. Microscopically, the mycelial form is characterized by pyriform conidia produced on long to short conidiophores that resemble lollipops. The yeast form is thick walled and usually produces a single bud with a broad base (Figs. 42-8 and 42-9).

Epidemiology, Risk Factors, and Pathogenesis

Isolation of *B. dermatitidis* from nature has proved difficult, and so the precise ecology of the fungus is not well known, although it has been isolated on rare occasions from soil and decaying wood. Pulmonary infection occurs after inhalation of conidia. Those conidia that escape ingestion by alveolar macrophages and killing by neutrophils and monocytes

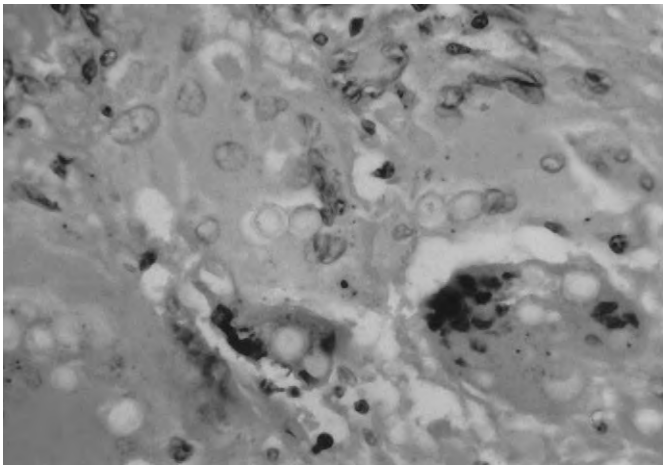

Figure 42-8 Thick-walled spherical yeast form of *Blastomyces dermatitidis* (*arrow*) (original magnification, ×400).

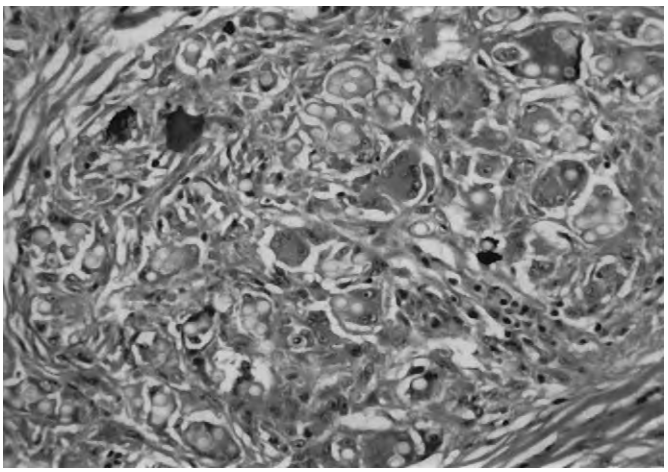

Figure 42-9 Cutaneous blastomycoses illustrating tissue form at 37° C (original magnification, ×100).

undergo conversion to the yeast form, which is more resistant to phagocytosis and killing. A granuloma forms as a result of an inflammatory response consisting principally of macrophages and neutrophils. The fungus may spread hematogenously to other organs.

Clinical Features

The two most common forms of disease are pulmonary and chronic cutaneous blastomycosis, although the clinical presentation is highly variable.[22] Patients with primary pulmonary blastomycosis typically have nonspecific symptoms including fever and malaise. The primary pulmonary form can resolve spontaneously, disseminate to other organs, or develop into a chronic pulmonary disease. The chest radiograph in acute pulmonary disease is characterized by alveolar infiltrates often involving the lower lobes or mass-like infiltrates. Diffuse miliary or reticulonodular patterns can occur in neonates[23] or in patients with the chronic form. Chronic pulmonary disease is characterized by cavitation or fibronodular lesions predominantly of the upper lobes, although cavitary disease is not seen as commonly with blastomycosis as it is with histoplasmosis. Acute lung disease may mimic bacterial pneumonia, whereas chronic disease may resemble tuberculosis or lung cancer.

Cutaneous blastomycosis is the most common form of extrapulmonary disease and can occur with or without lung involvement.[22] Skin lesions can be nodular, verrucous, or ulcerative and subcutaneous lesions may be found. Lesions occur most frequently on the face, hands, wrists, and lower extremities. Other sites of dissemination include bones, the genitourinary system, and the central nervous system (as meningitis or abscesses).

Diagnosis

Because blastomycosis is rarely encountered in children, the diagnosis is often not considered. The key to making a diagnosis is to include blastomycosis in the differential diagnosis in appropriate patients and to send specimens for histopathology and fungal culture. Growth of the organism in culture is relatively easy if an appropriate specimen is submitted for fungal culture. Growth usually occurs within 2 to 4 weeks of incubation and provides a definitive diagnosis. The organism has characteristic features that distinguish it from other yeast, including a thick refractile cell wall that suggests the diagnosis when seen by microscopy in a tissue specimen.

Serologic methods such as complement fixation and immunodiffusion are not helpful because of their low sensitivity and specificity. There is significant cross-reactivity with histoplasmosis. Up to 80% of patients with blastomycosis develop precipitins to antigen A of *B. dermatitidis* and enzyme immunoassay is more sensitive than immunodiffusion in detecting antibodies to antigen A, but is not routinely available.

Treatment

Blastomycosis in immunocompetent patients is often self-limited, but most experts advocate antifungal therapy for all cases of acute pulmonary disease.[22,24] Chronic disease generally does not resolve without treatment. There are no therapeutic studies in children, but based upon the experience in adults and anecdotal data in children, amphotericin B remains the drug of choice for the treatment of life-threatening and central nervous system infections (see Table 42-1).

Children with mild to moderate infections can be treated with itraconazole,[25] which can also be used as step-down therapy for non–central nervous system infections after a patient's condition has stabilized on amphotericin B. Fluconazole has also been shown to be effective and may be appropriate therapy for children with central nervous system infections after initial therapy with amphotericin B. The total duration of therapy is usually at least 6 months for pulmonary and nonpulmonary disease, although some experts recommend 12 months of therapy for osteomyelitis.[26]

Children treated with azoles should be monitored closely, as a review of pediatric blastomycosis cases at Arkansas Children's Hospital suggested that the response to azoles was limited.[27] Immunocompromised patients should generally be placed on suppressive therapy with fluconazole or itraconazole after the primary course of therapy for the duration of their immunosuppresson.[22,24]

PARACOCCIDIOIDOMYCOSIS

Paracoccidioidomycosis, sometimes called South American blastomycosis, is caused by the dimorphic fungus *Paracoccidioides brasiliensis*. The disease is endemic to parts of Latin America, primarily Brazil, Colombia, and Venezuela. Disease occurs mostly in adults and is rare in children.

Clinical Features

Paracoccidioidomycosis is classified into acute and chronic types.[28] The acute form occurs in children and young adults; most commonly, it involves the reticuloendothelial and skeletal systems—patients have lymphadenopathy, and involvement of the liver, spleen and bone marrow as well as bones, joints, skin, and mucous membranes. The fungus can remain dormant within lymph nodes for years. The chronic form is more common, occurs in adults, and can be limited to the lungs or disseminate to other organs. The chest radiograph in pulmonary paracoccidioidomycosis is characterized by nodules, cavities, and lobar or diffuse infiltrates.

Diagnosis

P. brasiliensis grows as a yeast at 37° C and as a mold at 25° C. Direct examination of a clinical specimen is the best method to establish the diagnosis. The yeast form frequently has a pilot-wheel appearance with multiple buds. The organism grows on culture fairly easily. Serologic tests are of both diagnostic and prognostic value. Complement fixation, enzyme immunoassay, and immunodiffusion are the most widely used serologic tests.

Treatment

Amphotericin B remains the therapy of choice for disseminated or progressive disease, but is not curative by itself and itraconazole or a sulfonamide is usually used in combination. Itraconazole is the drug of choice for less severe or localized infections and for patients whose condition has been stabilized after a course of amphotericin B therapy. Therapy should continue for at least 6 months to reduce the likelihood of relapse.[29]

ASPERGILLOSIS

There are three major clinical syndromes associated with pulmonary aspergillosis—aspergilloma, allergic bronchopulmonary aspergillosis, and invasive aspergillosis. Invasive pulmonary aspergillosis is a major cause of morbidity and mortality in patients with hematologic malignancies and in transplant recipients.

There are more than 180 species of *Aspergillus*, but the majority of invasive infections are caused by *A. fumigatus*.[30,31] *A. flavus*, *A. terreus*, *A. niger*, and *A. nidulans* are other significant pathogens in immunocompromised patients. The mold reproduces asexually, and its conidia are readily aerosolized, which can be inhaled by a susceptible host and result in pulmonary infection. Growth into filamentous forms, which have the propensity to invade blood vessels, leads to pulmonary inflammation and the potential for hematogenous dissemination.

Aspergillus organisms rarely cause disease in the normal host unless they are inhaled at high concentrations. Bronchopulmonary colonization occurs most frequently in patients with asthma, bronchiectasis, cystic fibrosis, and primary ciliary dyskinesia syndrome.

Epidemiology, Risk Factors, and Pathogenesis

Aspergillus species are ubiquitous in the environment and are especially common in soil and decaying vegetation. Infection occurs primarily through inhalation of spores, although the fungus can also be acquired via aerosolization from a contaminated water source. Person-to-person transmission does not occur.

Macrophages and neutrophils are the main host defenses against *Aspergillus* infection. Patients with impaired macrophage function, such as those treated with prolonged corticosteroids or transplant recipients, and patients with neutropenia or neutrophil dysfunction (e.g. chronic granulomatous disease) are at risk for invasive pulmonary aspergillosis. Prolonged neutropenia is the most important risk factor for patients with hematologic malignancies or after transplantation—in patients with chemotherapy-induced granulocytopenia, the risk of infection increases progressively after the sixth day of neutropenia.[32]

A retrospective cohort study estimated that more than 650 cases of invasive aspergillosis occurred among immunocompromised children in the United States in 2000. The highest incidence was seen in children who had undergone allogeneic bone marrow transplantation and those with acute myelogenous leukemia, each of which had an approximately 4% risk of invasive disease.[33]

Invasive aspergillosis is frequently a hospital-acquired infection, and outbreaks have occurred among immunocompromised patients during hospital construction. Reactivation of an endogenous organism has also been reported to cause disease.

Clinical Features

Allergic bronchopulmonary aspergillosis results from a hypersensitivity reaction to the fungus—this clinical entity is discussed in Chapter 46.

Aspergillomas, or "fungal balls," occur most frequently in patients with pre-existing cavities or congenital pulmonary cysts that become secondarily infected with *Aspergillus*. The chest radiograph is characterized by an ovoid opacity surrounded by a halo that usually involves the upper lobes or the superior segment of a lower lobe. The lesion is typically unilateral, although bilateral involvement occurs in 5% to 10% of cases. Fungal balls also sometimes occur in patients with mild to moderate immunosuppression who do not have preexisting cavities. In contrast to classic aspergillomas, these subacute or "semi-invasive" infections can progress and lead to hemorrhagic complications.[30]

Clinical signs of invasive pulmonary aspergillosis can be nonspecific. Patients usually have fever, but may or may not have respiratory tract symptoms, such as cough or pleuritic chest pain. A common clinical scenario is the child who has persistent fever after resolution of prolonged neutropenia. Hemoptysis sometimes occurs as a result of the propensity for *Aspergillus* to invade blood vessels. Patients may also present with signs and symptoms related to dissemination of the infection to other sites, such as the brain, liver, or kidneys. Patients with documented invasive pulmonary aspergillosis should be evaluated for other sites of infection.

Findings on chest radiography are variable, ranging from patchy infiltrates in any lobe of the lungs to classic nodular or cavitary lesions. The chest radiograph can even be normal while the patient is neutropenic because of the lack of inflammatory response. A CT scan of the chest may reveal lesions suggestive of aspergillosis not appreciated on chest radiograph. As the disease progresses, pulmonary infarction occurs, and wedge-shaped densities with the crescent sign are seen on the chest radiographs (Figs. 42-10 and 42-11).

Aspergillus can also cause infection in immunocompromised hosts at other sites along the respiratory tract,[30] including invasive sinusitis or tracheobronchitis. Invasive sinusitis is a life-threatening infection and the presenting findings can be subtle. Infection of the tracheobronchial tree can present with symptoms of fever, airway obstruction, cough, or hemoptysis.

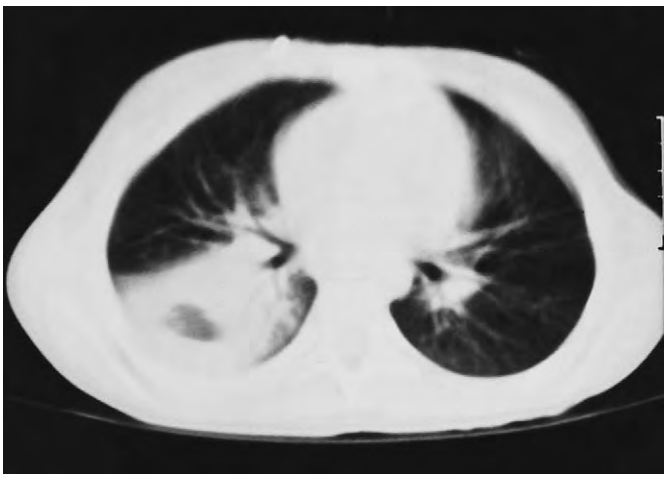

Figure 42-10 Computed tomography scan of the chest in a 6-year-old child with acute nonlymphocytic leukemia and aspergillosis in the right lower lobe.

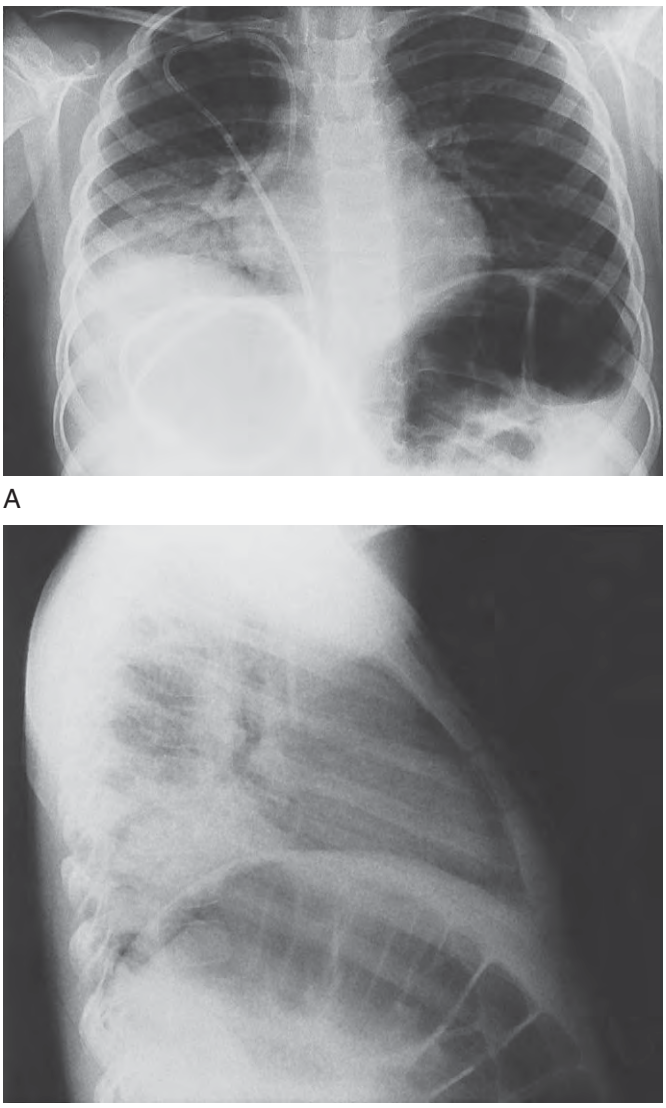

Figure 42-11 Posteroanterior **(A)** and lateral **(B)** chest radiographs of a 6-year-old child with acute nonlymphocytic leukemia and aspergillosis.

Diagnosis

The diagnosis of invasive aspergillosis can be challenging. The most effective diagnostic approach combines a high degree of clinical suspicion with radiologic studies and subsequent cultures and histopathology obtained from the lower respiratory tract.

Demonstration of tissue invasion on histologic examination is highly suggestive of invasive aspergillosis, but other fungi, including *Fusarium* spp. and *Pseudoallescheria* spp. can be indistinguishable on tissue samples, and mucormycosis can also be confused with aspergillosis.[30,34] Therefore, isolation of the organism by culture from biopsy specimens is essential to confirm the diagnosis and determine the species. However, the potential risks of invasive procedures in immunocompromised patients should be weighed against the benefits. Although *Aspergillus* can colonize the respiratory tract, its isolation from sputum or bronchoalveolar lavage fluid in an immunocompromised patient with pneumonia is highly suggestive of invasive disease.

A serologic assay to detect galactomannan, a molecule found in the *Aspergillus* cell wall, is commercially available for diagnosing invasive disease, but almost all studies have been done in adults. False-positive tests occur more commonly in children than adults,[31,35] and a negative test does not exclude the diagnosis. Polymerase chain reaction may prove to be a useful diagnostic tool for rapid, noninvasive diagnosis, although its role has not yet been determined.[36]

Treatment

Invasive aspergillosis is a potentially lethal infection in immunocompromised patients and, therefore, aggressive therapy must often be initiated before the diagnosis is confirmed. The overall in-hospital mortality of immunocompromised children with invasive aspergillosis in a large retrospective study was 18%,[33] which is much better than historical data.

Effective therapy requires both antifungal therapy and withdrawal or reduction of immunosuppressive therapy; surgical intervention is sometimes needed as well.[30] Unfortunately, there have not been any large-scale clinical trials evaluating the treatment of invasive aspergillosis in children. Therefore, treatment decisions must be extrapolated from data in adults (see Table 42-1).

For decades, high-dose amphotericin B (1 to 1.5 mg/kg/day) was the standard of care for patients with invasive pulmonary aspergillosis, although response rates were suboptimal. With the availability of lipid formulations of amphotericin B, many clinicians prefer their use because higher doses of amphotericin B can be administered (5 to 10 mg/kg/day) with less toxicity.[37] There are no controlled clinical trials showing that the lipid formulations have superior efficacy.[38]

Itraconazole has good activity against *Aspergillus* organisms in vitro and has often been used as sequential oral therapy after initial therapy with amphotericin B. For oral therapy, the suspension is preferred because absorption is better than with the capsules. An intravenous formulation is also available.

Voriconazole is a broad-spectrum triazole agent with activity against *Aspergillus*. Among pediatric patients with invasive

aspergillosis who were intolerant to amphotericin B or failed to respond, 45% had a complete or partial response to voriconazole.[39] In a large clinical trial in adults, voriconazole showed superior efficacy compared to amphotericin B for primary therapy of invasive aspergillosis.[40] Voriconazole is now approved for first-line therapy of invasive aspergillosis, and many experts consider it the drug of choice. The recommended dose for adults is 4 mg/kg/dose every 12 hours, although pharmacokinetic data suggest that higher doses, up to 8 mg/kg/dose, may be needed in children to achieve adequate concentrations.[31]

Posaconazole is another extended spectrum triazole with activity against *Aspergillus*. Clinical trials have documented efficacy as prophylaxis in patients with neutropenia[31a] and as salvage therapy for patients with invasive aspergillosis.[31b] Data researching the use of posaconazole in children are limited. The echinocandins are fungistatic against *Aspergillus*, and caspofungin is approved for patients with invasive aspergillosis who are refractory to or intolerant of other therapies.[41] Caspofungin is dosed in children at 50 mg/m^2/day.[31,42] Anidulafungin and micafungin have in vitro activity against *Aspergillus*, but there are very limited clinical data.[43] There also are limited data regarding the use of micafungin[44] and anidulafungin[45] in children.

Because of the high mortality associated with invasive aspergillosis, combination antifungal therapy has been considered (e.g. voriconazole and caspofungin), but there are no definitive data to support its use.[30,34]

The duration of treatment depends on the patient's clinical and radiographic response, immune status, and the severity of infection, but it should be at least 12 weeks.[34]

The role of surgical intervention in critically ill patients with invasive pulmonary aspergillosis is limited. Surgical resection should be considered for patients with well-defined lesions or those with an aspergilloma that does not respond to conventional antifungal therapy.

The definitive therapy for an aspergilloma is surgical resection, but surgery may be associated with significant morbidity and even mortality. The major threat of the aspergilloma is life-threatening hemoptysis; therefore, the risks and benefits of potential curative surgery must be considered.

CRYPTOCOCCOSIS

Cryptococcus neoformans is an encapsulated yeast with a worldwide distribution. It can be isolated from trees, fruits, and soil contaminated with bird droppings, especially those of pigeons. The disease is acquired through the inhalation of airborne particles containing the yeast. Infection is typically subclinical or is limited to the lungs. Dissemination to other organs, such as the central nervous system, bones, and skin, is rare in children unless they are immunocompromised. Although cryptococcosis is a frequent opportunistic infection in adults with AIDS, it is rare in pediatric AIDS patients.

Clinical Features

The lungs and the central nervous system are the two primary sites of infection with C. *neoformans*.[46] At least one third of patients with pulmonary cryptococcosis are asymptomatic. Symptomatic children present with headache, fever, chest pain, and cough. The chest radiograph is variable and may reveal a solitary nodule, multiple nodules, cavities, hilar adenopathy, or focal or diffuse infiltrates usually involving the lower lung fields.

In the immunocompromised patient with cryptococcal pneumonia, disease can progress rapidly. The chest radiograph can show a variety of features as with normal hosts, but can also reveal diffuse or focal interstitial infiltrates that may be confused with *Pneumocystis* pneumonia.

Diagnosis

The diagnosis of cryptococcosis is often made by the demonstration of budding, encapsulated yeast in India ink or wet-mount preparations of clinical specimens (Figs. 42-12 and 42-13). C. *neoformans* can be isolated from culture of blood, body fluid, or tissue specimens. The lysis centrifugation method should be used for blood cultures.[47] The latex agglutination test for detection of cryptococcal capsular antigen remains highly sensitive and specific, especially in patients with meningitis or disseminated forms of cryptococcosis, but serum cryptococcal antigen is generally negative if disease is limited to the lungs.

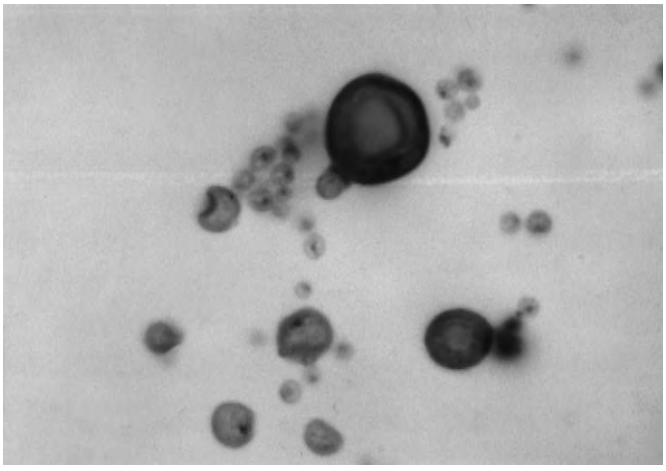

Figure 42-12 *Cryptococcus neoformans* isolated from cerebrospinal fluid (original magnification, ×400).

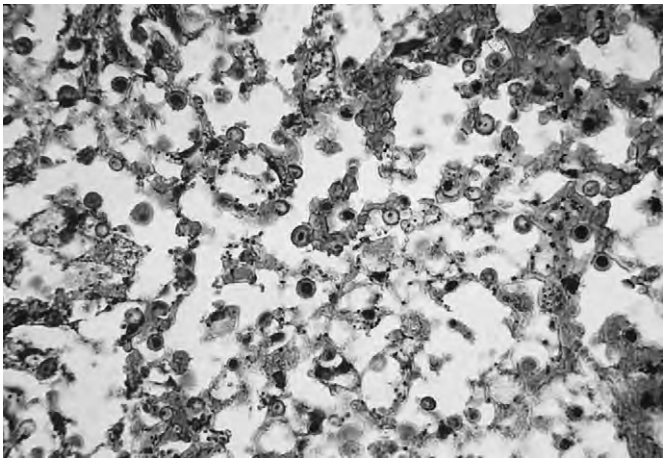

Figure 42-13 Pulmonary cryptococcosis (original magnification, ×100).

Treatment

For severe infections and meningitis, amphotericin B (or one of the lipid based amphotericin B preparations) in combination with oral flucytosine, is the initial therapy of choice.[46] After two weeks of combination therapy, fluconazole can be used as continuing therapy if the response is adequate (see Table 42-1).

The azole antibiotics, such as fluconazole or itraconazole, are probably the drugs of choice for pulmonary cryptococcosis. Children with HIV infection should be continued on lifelong suppressive therapy with fluconazole after completing treatment.[47]

UNCOMMON PULMONARY MYCOSES

In severely immunocompromised patients, a variety of fungi can cause invasive disease, including *Candida* species, the Zygomycetes, *Sporothrix schenckii*, *Fusarium* species, and *Pseudallescheria boydii*.

Pulmonary candidiasis as a primary disease is extremely rare, although it sometimes occurs as one manifestation of disseminated candidiasis. Patients with disseminated candidiasis can appear septic with various degrees of dyspnea. The chest radiograph may show multiple septic emboli or interstitial or lobar disease. Isolation of *Candida* species from the sputum or bronchoalveolar lavage fluid almost always reflects oropharyngeal colonization. Therefore, histologic demonstration of invasive disease is required to confirm the diagnosis.

Mucormycosis (or zygomycosis) most commonly occurs in immunocompromised patients, such as those with malignancies, those receiving immunosuppressive therapy including long-term corticosteroids, or those with diabetes mellitus. The clinical picture is similar to that of aspergillosis and it can be confused with *Aspergillus* on histologic examination of tissues. Therefore, cultures are important to distinguish between the fungi. As mucormycosis is not susceptible to voriconazole, high doses of a lipid-based amphotericin B drug should be used if there is any question whether the diagnosis is mucormycosis or aspergillosis.

Pulmonary sporotrichosis is probably underdiagnosed because its radiographic and clinical courses are similar to those of other granulomatous lung infections (such as tuberculosis) and because it is difficult to diagnose. Pulmonary sporotrichosis can occur as a primary infection or secondary to disseminated disease. The most reliable method of diagnosis is by culturing the organism from infected tissues. Amphotericin B or itraconazole are the drugs of choice and surgical resection is important in well-localized disease.

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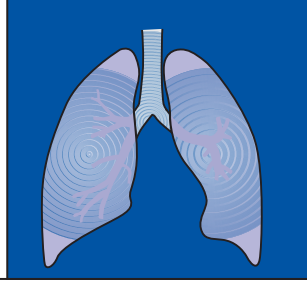


CHAPTER 43 Other Infectious Agents

Geoffrey A. Weinberg and Ann M. Buchanan

TEACHING POINTS

Pneumocystis carinii

- This is an opportunistic atypical fungus that causes pneumonia in immunodeficient hosts.
- Risk factors include T-lymphocyte deficiencies (HIV infection, cancer chemotherapy, organ transplantation, primary immunodeficiency, connective tissue disorders, marked protein-calorie malnutrition), and, rarely, humoral immunodeficiency (hypogammaglobulinemia).
- Typical manifestations are tachypnea, dyspnea, fever, nonproductive cough, and hypoxemia, all in association with relatively normal auscultation of the chest. There are diffuse interstitial infiltrates on chest radiography.
- Diagnosis is best made by silver staining or immunologic staining of bronchoalveolar lavage fluid or lung tissue.
- Antibiotic therapy of choice is trimethoprim-sulfamethoxazole for 14 to 21 days (plus adjunctive prednisone for moderate to severe pneumonia).
- Prophylactic therapy of choice is trimethoprim-sulfamethoxazole for 3 to 7 days per week.

Legionella pneumophila

- This is a rare cause of pediatric community-acquired pneumonia requiring hospitalization.
- Risk factors are organ transplantation and immunodeficiency.
- Typical manifestations include acute fever, patchy alveolar pneumonia unresponsive to β-lactam antibiotics, progressive lung consolidation, diarrhea, mental status changes, hyponatremia, and elevated transaminase levels.
- Diagnosis is best made by culture of bronchoalveolar lavage fluid, lung tissue, or pleural fluid; urinary antigen test is available for *L. pneumophila* serogroup 1.
- Antibiotic therapy of choice is azithromycin for 14 to 21 days (with or without adjunctive rifampin) or a fluoroquinolone.

A number of infectious agents of several types (beyond those discussed in other chapters of this textbook) can cause infections of the lung in childhood. Perhaps the most commonly considered unusual infectious etiologies for pediatric pneumonia in children in the developed world are *Pneumocystis carinii* and *Legionella pneumophila*. Less commonly, pulmonary infections caused by *Toxoplasma gondii*, *Echinococcus*, *Paragonimus westermani*, *Ascaris lumbricoides*, hookworms, *Toxocara*, *Strongyloides stercoralis*, *Schistosoma*, and other parasites might be encountered. It is beyond the scope of this chapter to include full sections on each of these unusual pediatric pulmonary pathogens, but *P. carinii* and *L. pneumophila* are addressed in detail, and salient features of several of the parasitic causes of pneumonia are summarized.

PNEUMOCYSTIS CARINII

P. carinii is one of the most common causes of pneumonia in the immunocompromised host, whether the immunocompromise results from a congenital defect (e.g., severe combined immunodeficiency syndrome), an acquired defect (e.g., human immunodeficiency virus [HIV] infection), or an iatrogenic cause (e.g., immune suppression associated with therapy of malignancy or prevention of organ transplant rejection).[1-11] Recognized infection with *P. carinii* was once uncommon, but as the prevalence and survival of immunocompromised hosts have increased over the past several decades, so has the incidence of *Pneumocystis* disease. The occurrence of several consecutive cases of *P. carinii* pneumonia among apparently healthy young men in Los Angeles and New York City led to the rapid recognition of acquired immunodeficiency syndrome (AIDS) as a new diagnostic entity in the early 1980s. With the spread of the HIV pandemic, the importance of accurate diagnosis of and effective therapy for *P. carinii* disease has greatly increased.

Epidemiology, Risk Factors, and Pathogenesis

ORGANISM

P. carinii is an extracellular eukaryotic pathogen whose taxonomic classification has been a matter of controversy since its description in 1909. Chagas originally thought that the organism was a variant form of *Trypanosoma cruzi* infecting animals, but by 1912 this assignment was shown to be incorrect.[1,6] In the 1950s the organism was found to be the cause of interstitial plasma cell pneumonia in infants and children, most of whom were malnourished residents of orphanages and foundling homes following World War II.[1,6] Over the past 50 years, the pathogen has been classified alternately as a protozoan because of its morphologic structural properties and susceptibility to antiprotozoal agents or as a fungus because of its subcellular organelle structure, cell wall biochemistry, and staining characteristics.[1] Molecular biologic studies have shown that *P. carinii* exhibits the greatest genomic homology with fungal rather than protozoal lineages at a number of loci (ribosomal RNA, β-tubulin, folate metabolism pathway, and mitochondrial enzyme genes, among others); thus, the organism is best classified as an unusual

fungus that infects both humans and animals, yet retains many biologic features more typical of protozoa.[1,6,8-12] Recent attempts at synthesizing both phenotypic and genotypic data have led to a trinomial system of names to distinguish among *P. carinii* from human and animal hosts,[13] and some investigators have suggested renaming the human form of *P. carinii* as *P. jiroveci*.[14,15] However, the renaming of the organism is controversial and not universally accepted.[16-19] For the sake of simplicity, here we refer to all *P. carinii* organisms with the older binomial system.

Three developmental stages of *P. carinii* have been identified: trophozoites, cysts, and precysts.[1,2,8] Trophozoites are small (1 to 5 μm), are pleomorphic, and commonly exist in large clusters in lung tissue or respiratory secretions. This form is identified on Giemsa stain, rapid Giemsa stain variants such as the Diff-Quik stain, or Wright stain, by its dot-like reddish nucleus with surrounding blue cytoplasm[1,6] (Fig. 43-1). It is thought that trophozoites reproduce via binary fission. Cysts appear as spherical or crescent-shaped structures about 5 μm in size, often with a fold that gives them a parentheses-like or cup-shaped appearance. The cyst wall will not be visualized with Giemsa stain, but up to eight round or spindle-shaped intracystic bodies may be seen, surrounded by a clear halo. The cyst wall is readily stained by the Gomori methenamine silver nitrate procedure (Fig. 43-2), the more rapid Grocott silver stain, or other cell wall stains such as toluidine blue O, cresyl echt violet, or calcofluor white.[1,6] The precyst is an intermediate stage of reproduction, about 4 to 6 μm in size, which may represent a parent cell undergoing encystment. All three *P. carinii* forms reside in the alveoli.

Attempts at long-term or continuous cultures of rat *P. carinii* or short-term culture of *P. carinii* from humans have not been successful, although a few laboratories have successfully propagated rat and mouse *P. carinii* for a short period (7 to 14 days) in cell culture using epithelial or fibroblast cells such as HEL and WI-38 cells.[1,20]

EPIDEMIOLOGY

Many questions about the natural habitat, modes of transmission, and attack rates of *P. carinii* remain unanswered. It is well established that *P. carinii* infects a wide variety of wild, domestic, and laboratory animals, as well as humans, in a worldwide distribution.[2] Airborne transmission of infection has been shown to occur among infected rats in the laboratory,[21,22] and *P. carinii* DNA has been amplified by the polymerase chain reaction (PCR) from filtered ambient air samples.[23] Thus, while circumstantial evidence indicates that *P. carinii* might be an opportunistic zoonosis in humans, no firm evidence of animal-to-human transmission has been found, and the substantial chromosomal and DNA sequence diversity among *P. carinii* recovered from humans, rats, mice, and ferrets makes zoonotic transmission seem unlikely.[24,25] In addition, attempts to produce experimental infections between different mammalian species have been unsuccessful.[26] It is currently thought that several *P. carinii* lineages (perhaps distinct species of the genus *Pneumocystis*) infect different mammals, perhaps with transmission only to homologous hosts.

It is generally accepted that most children and adults have been asymptomatically infected with *P. carinii*, based on seropositivity rates of 75% in children and 90% in adults.[1,2,27] Reactivation of latent organisms when the host becomes immunosuppressed was thought to explain subsequent disease appearance.[3] However, animal studies question the existence of *P. carinii* latency.[28] The transmission of new infection from one animal to another (within the same host species),[29] and the occurrence of apparent outbreaks of *P. carinii* pneumonia in some (but not all) nurseries and orphanages in central and eastern Europe after World War II, in some children's hospitals in the United States, and in outpatient clinics for immunocompromised patients in Europe,[6] suggests that transmission of *P. carinii* from person to person, even if uncommon, is more likely than reactivation as a source of disease among immunosuppressed hosts.

RISK FACTORS

Whether *P. carinii* disease is manifested after acquisition of new infection or after reactivation of latent infection, it is clear that the infection is opportunistic, occurring in patients with immunodeficiency disorders, especially those involving cell-mediated immunity. Before the beginning of the HIV pandemic, the disease was rare and was found almost exclusively in hosts with malnourishment, malignancy, or primary immunodeficiency disorders or those undergoing immunosuppressive therapy for malignancies, connective tissue disease, or organ transplantation.[30] In contrast, without che-

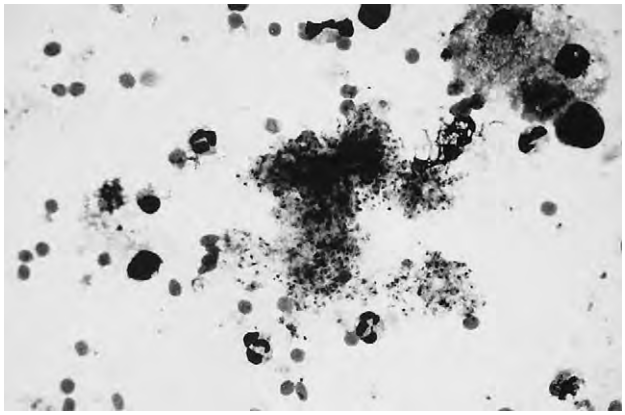


Figure 43-1 *Pneumocystis carinii* trophozoites in bronchoalveolar lavage fluid (Giemsa stain, original magnification ×1000).

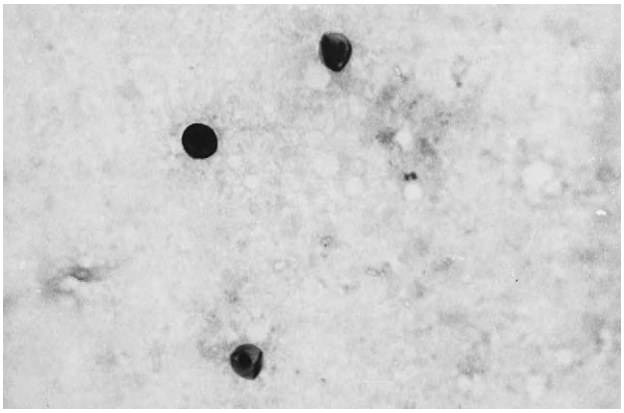


Figure 43-2 *Pneumocystis carinii* cysts in bronchoalveolar lavage fluid (modified Gomori methenamine silver stain, original magnification ×1000).

moprophylaxis, *P. carinii* pneumonia will affect about 75% of adults with AIDS and at least 50% of children with AIDS.[3,4] Initially, *P. carinii* pneumonia was said to be much less common in patients with AIDS in central Africa than in North America and Europe;[6] however, when modern diagnostic techniques are applied, the infection is found globally.[31,32]

PATHOLOGY AND PATHOGENESIS

After the presumed airborne acquisition of organisms, *P. carinii* adheres to type I alveolar cells via binding to fibronectin, vitronectin, or other host components.[33,34] Reproduction of the organisms takes place in the alveolus. Malnutrition, hypogammaglobulinemia, and severe combined immunodeficiency (SCID) have all been associated with *P. carinii* disease, although $CD4^+$ T-lymphocyte immune defects appear to be most important in the pathogenesis of *P. carinii* pneumonia, as manifested by its prominent occurrence in patients with AIDS. The central role of T cells is borne out by the resolution of *P. carinii* pneumonia in nude mice and SCID mice after adoptive transfer of splenic helper T cells from normal heterozygote mice.[1,28] However, the humoral immune system does seem to play a role in protection against *P. carinii*, because the disease has been found in hypogammaglobulinemic children, and experimental animal studies show that passive protection can be afforded by monoclonal antibodies and also that $CD4^+$ T cells alone are not required for protection in previously immunized animals.[1,35] The $CD8^+$ T-cell subset is postulated to contribute more to host pulmonary inflammation than protection against *P. carinii*.[36,37]

Alterations in both amount and distribution of pulmonary surfactant occur during *P. carinii* pneumonia.[4,9,38] Surfactant protein A binds to *P. carinii* surface glycoproteins, which could possibly enhance attachment of the organisms to the alveolus and retard phagocytosis by alveolar macrophages. The alteration in surfactant phospholipids might contribute to ventilation-perfusion mismatches and altered lung compliance.[1,4,9,39] Pulmonary surfactant is inactivated also by $CD8^+$ T-lymphocyte–mediated inflammation.[38]

In children and adults alike, the classic histopathologic appearance of *P. carinii* pneumonia is a prominent eosinophilic foamy intra-alveolar exudate with a mild interstitial pneumonitis[1] (Fig. 43-3). Upon staining with Giemsa or silver stains, organisms are seen within the exudate. Organizing diffuse alveolar damage with interstitial fibrosis is commonly seen (63%) in HIV-infected patients with *P. carinii* pneumonia. Less common findings include absence of foamy exudate (20% of patients with AIDS, nearly 50% in those without AIDS), granuloma formation (5% to 10%), calcification (2%), and cyst formation (2%).[1] Extrapulmonary disease is uncommon (1% to 3%) but well described in adults with AIDS; dissemination in pediatric AIDS patients and in non-AIDS patients appears to be much rarer.[1,40]

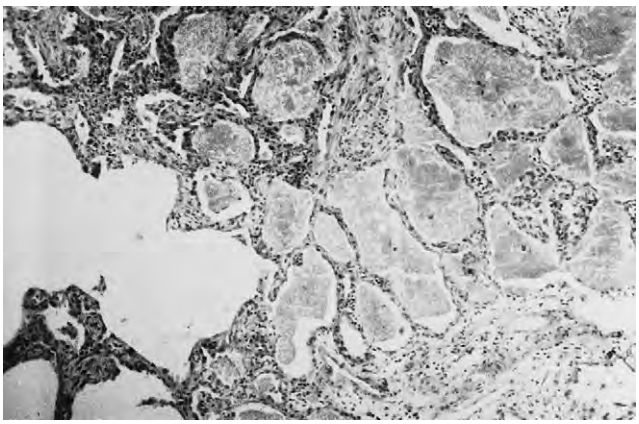


Figure 43-3 Foamy alveolar exudate and mild interstitial fibrosis characteristic of *P. carinii* pneumonia (hematoxylin and eosin stain, original magnification ×450).

Clinical Manifestations

P. carinii pneumonia is characterized by tachypnea, dyspnea, fever, and nonproductive cough.[1] The course of the disease is variable, however, and symptoms distressing enough to bring the patient to medical attention may not occur until late in the infection. This is particularly true in patients with HIV infection, in which the onset of disease is more insidious (over several weeks) than in the pediatric cancer patient, in whom fever and respiratory distress occur over a period of days.[41,42] Crackles are conspicuously absent in most cases (60% to 70%) of *P. carinii* pneumonia; few abnormalities on physical examination are evident beyond tachypnea and respiratory distress.[3,4,41] The mortality of *P. carinii* pneumonia among immunosuppressed patients approaches 100% without therapy.[3] Most infants with perinatally acquired HIV infection (not receiving antimicrobial prophylaxis) have onset of *P. carinii* pneumonia between 3 and 6 months of age.[43,44]

Epidemic interstitial plasma cell pneumonia in malnourished babies, now a rarely recognized condition, was associated with an even more insidious onset, often following weight loss and chronic diarrhea. Fever was less prominent to absent; the mortality rate was at least 50%.[1]

RADIOLOGY

Chest radiographs typically show interstitial infiltrates, beginning in the perihilar regions and spreading to the periphery, becoming more homogeneous and alveolar as the disease progresses[1] (Fig. 43-4). The apices are usually spared until late in the disease. Less commonly, atypical lesions are found, such as asymmetric lobar or segmental consolidation (Fig. 43-5), cavitary, nodular, or upper lobe disease (the latter is especially noted in patients receiving aerosolized pentamidine chemoprophylaxis).[1]

Computed tomography (CT) scans of the chest have shown diffuse interstitial and alveolar consolidation in some cases in which chest radiographs appeared normal, but CT has limited added diagnostic value in most children. Similarly, gallium nuclear imaging has been suggested to be of value in the diagnosis of *P. carinii* in adults with AIDS, but the sensitivity and specificity of the test have varied between 50% and 90%, and the test takes up to 72 hours to perform. In addition, data among pediatric populations (who might have other conditions yielding abnormal gallium uptake, such as lymphoid interstitial pneumonia) are limited, making gallium imaging much less useful.[3]

LABORATORY DIAGNOSIS

The most important indirect marker of *P. carinii* pneumonia is hypoxemia (i.e., a PaO_2 in room air of <80 mm Hg or an

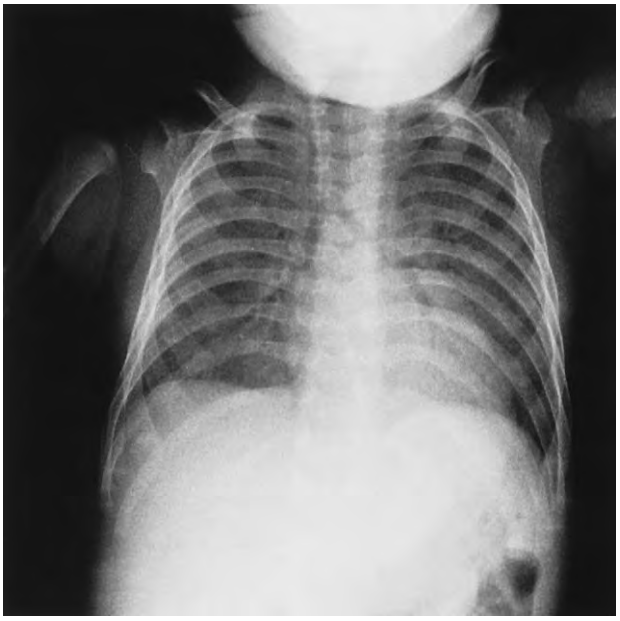


Figure 43-4 Chest radiograph showing diffuse interstitial infiltrates in a 7-month-old child with AIDS and *Pneumocystis carinii* pneumonia.

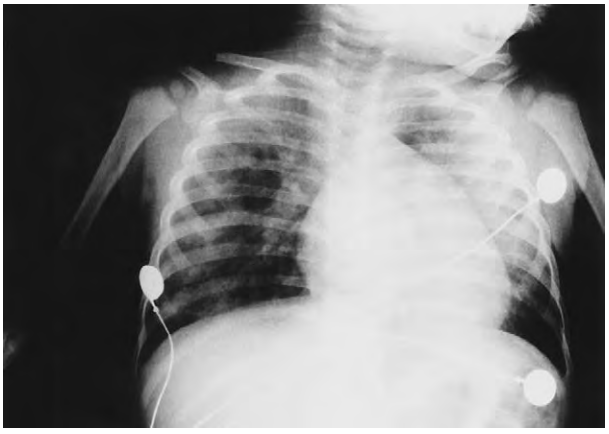


Figure 43-5 Chest radiograph showing right lung interstitial infiltrates and left lung consolidation in an 18-month-old child with AIDS and *Pneumocystis carinii* pneumonia.

alveolar-arterial oxygen gradient of >35 mm Hg).[4] Although more difficult to measure, carbon monoxide diffusion capacity is below 70% of predicted values in nearly all patients with *P. carinii* disease. Serum lactate dehydrogenase (LDH) levels are elevated in both children and adults with AIDS and *P. carinii*, but the finding has limited specificity (75%).[3,4] Serum antibody tests for *P. carinii* are useful in epidemiologic work but not for diagnosis, because low antibody titers are found in normal hosts, and the immunosuppressed host may not be competent enough to show increases in antibody titers.[2] Serum antigen tests were studied at one time but were prohibitively nonspecific.[2] Detection of serum (or sputum) *P. carinii* DNA, which has been amplified by PCR in several laboratories, may become a useful diagnostic technique when better standardized.[45-47]

When an immunocompromised child has tachypnea, cough, dyspnea, fever, and diffuse interstitial infiltrates on chest radiographs, *P. carinii* disease must be considered, along with a number of other etiologies, including cytomegalovirus, *Mycobacterium tuberculosis*, *M. avium-intracellulare*, *Histoplasma capsulatum*, and lymphoid interstitial pneumonitis. Effective therapy depends on definitive tissue diagnosis, which in turn currently depends on demonstration of organisms in lower respiratory secretions or lung tissue.

A staged approach is useful to maximize diagnostic information and minimize patient risk. Techniques that have been advocated include sputum induction, bronchial biopsy, bronchial wash, bronchoalveolar lavage (BAL), and open lung biopsy.[1,3,4] Sputum induced by ultrasonic nebulization and then subjected to Giemsa staining, silver staining, and immunologic staining has been useful for adults with HIV infection/AIDS at medical centers familiar with the technique. However, the procedure is labor intensive when done correctly, experience with children has been limited, and the predictive values have ranged widely (between 40% and 90%). Bronchial washes (suctioning secretions through the bronchoscope) increase sensitivity somewhat, and transbronchial biopsy can be very sensitive if 20 to 25 alveoli are obtained without crushing; however, the risk of bleeding and pneumothorax approaches 10%.

The cornerstone of diagnostic procedures in adults and children is the BAL.[3,4,10,11] In this procedure, aliquots of sterile, preservative-free saline are instilled in a peripheral nondependent airway (e.g., right middle lobe) after the bronchoscope is wedged. After a few seconds, the saline is aspirated and the procedure repeated several times. The yield of BAL is often 85% to 95%. Some success has been achieved with non–bronchoscopic lavage via a small feeding tube placed through the endotracheal tube in patients already undergoing mechanical ventilation.

When the BAL is nondiagnostic, when controlled hemostasis is desirable because of bleeding disorders or when diffuse nodular infiltrates are present that may not yield a diagnosis by BAL, the open lung biopsy is performed. This procedure remains the most sensitive and specific, but it involves the most risk, requiring general anesthesia and the risk of some impairment of pulmonary function. It is possible that open lung biopsy might even be superior to BAL for the non-AIDS patient, because the organism load in this case is lower than that seen in the AIDS patient.[42]

Once BAL fluid or lung tissue is obtained for diagnosis, the material should be examined by experienced personnel, ideally using multiple staining techniques to detect both cysts and trophozoites, although many laboratories will feel most comfortable with careful examinations of specimens for cysts alone.[1,3,4,6] The Gomori or Grocott methenamine silver stain for cysts is widely used. It has sensitivity and specificity exceeding 95%, and the cysts are relatively easy to see.[1,4] Disadvantages include a more intensive procedure, which can take 6 to 24 hours to perform. However, several rapid modifications exist that can cut down the preparation time to a few hours and utilize a microwave oven rather than boiling water baths. Other cyst stains used less widely include toluidine blue O, crystal echt violet, and calcofluor white.[1,4]

Trophozoites are stained by the Giemsa stain and its derivatives such as Diff-Quik. The cost of these stains is minimal, and they require only a few minutes to an hour to perform. However, the sensitivity and specificity are slightly less than silver stains (perhaps 85% to 90% each), and more experience

is needed to recognize the trophozoites among the stained host cells and debris.[1,4] Papanicolaou stain can be useful but is more labor intensive and slightly less sensitive in detecting trophozoites.

Immunologic stains (direct and indirect immunofluorescent antibodies) are now commercially available and may be a reasonable choice for some laboratories. The diagnostic sensitivity exceeds 90% in BAL fluid, and these stains may be useful for induced sputum as well. However, the kits are costly and require considerable experience to discern false positives from true positives.[1,4] Molecular techniques (PCR amplification and oligonucleotide probing) have the potential for exquisite sensitivity, but possibly at the cost of decreased specificity, depending upon the laboratory's experience.[10,11,45-47]

Treatment

ANTIMICROBIAL THERAPY

A number of agents are currently available for the therapy of *P. carinii* pneumonia[1-4,48-54] (Table 43-1). Most have been tested only in adults with *P. carinii* disease, and substantially fewer controlled data are available to provide guidelines for appropriate pediatric use. Thus, the published pediatric experience primarily concerns trimethoprim-sulfamethoxazole (TMP-SMX), pentamidine, and, to a lesser extent, dapsone. Because the incidence of *P. carinii* infection in children and adults with HIV infection has fallen so remarkably in the era of highly active antiretroviral therapy, it is doubtful that further randomized comparative therapy trials will be forthcoming.

Table 43-1
Therapy of *Pneumocystis carinii* Pneumonia*

Medication	Total Daily Dosage
Trimethoprim-sulfamethoxazole	IV: 15-20 TMP + 75-100 SMX mg/kg/day divided q6h-q8h PO: 15-20 TMP + 75-100 SMX mg/kg/day divided q8h
Prednisone (adjunctive)†	PO or IV: 2 mg/kg/day divided q12h for 5 days, followed by 1 mg/kg/day q24h for 5 days, followed by 0.5 mg/kg/day q24h for 11 days
Pentamidine	IV: 4 mg/kg/day q24h, infused over 60 min
Atovaquone	PO: 30-45 mg/kg/day divided q12h administered with food (maximum dose 750 mg PO q12h)
Trimetrexate and leucovorin	IV: trimetrexate 45 mg/m^2 body surface area/day divided q24h plus leucovorin (IV or PO) 20 mg/m^2 body surface area/day divided q6h (leucovorin must be continued for 3 days following completion of trimetrexate)
Primaquine and clindamycin	PO: primaquine base 0.3 mg/kg/day q24h plus clindamycin (IV or PO) 40 mg/kg/day divided q6h (maximum dose primaquine 30 mg/day and clindamycin 600 mg IV or 300-450 mg PO q6h)
Dapsone and trimethoprim	PO: dapsone 2 mg/kg/day q24h (maximum dose 100 mg) plus trimethoprim (IV or PO) 15 mg/kg/day divided q8h)

*Duration of therapy: 21 days for HIV-infected patients, 14 days for non–HIV-infected patients, generally followed by suppressive therapy (secondary prophylaxis); see text and Tables 43-2 and 43-3. Medications are listed roughly in order of choice—see text.
†Prednisone adjunctive therapy suggested for patients with moderate to severe disease, as defined by room air Pa_{O_2} < 70 mm Hg or $P(A-a)_{O_2}$ gradient >35 mm Hg.

The mortality rate of *P. carinii* pneumonia has been strongly correlated (in adults) with the degree of hypoxemia at presentation. Patients with either Pa_{O_2} values less than 70 mm Hg or alveolar-arterial $[P(A-a)_{O_2}]$ gradients greater than 35 mm Hg while inspiring room air experience 20% to 30% mortality rates even with rapid, aggressive therapy, whereas those who have less severe hypoxemia experience a 5% or less mortality rate. Thus many authorities differentiate moderate to severe disease [room air Pa_{O_2} < 70 mm Hg or $P(A-a)_{O_2}$ gradient >35 mm Hg] from mild to moderate disease [room air Pa_{O_2} > 70 mm Hg or $P(A-a)_{O_2}$ gradient <35 mm Hg] in planning therapy.[4,10,11,53,54]

For the initial therapy of moderate to severe disease, parenteral TMP-SMX remains the drug of first choice, and parenteral pentamidine is the most suitable alternative for those intolerant of or not responding to TMP-SMX.[3,4,10,11,53,54] For initial therapy of mild to moderate disease in adults and older adolescents, a number of alternatives exist, including oral or intravenous TMP-SMX, oral TMP-dapsone, oral atovaquone, and intravenous or oral clindamycin with oral primaquine.[4,10,11,53,54] Experience with therapy of mild disease in younger children and infants is limited to TMP-SMX for the most part.[3,54]

It is often noted that the response to therapy seems delayed for 4 to 8 days, and that patients may in fact worsen initially (presumably from pulmonary inflammation incited by dying organisms). Thus determining whether a patient has failed initial therapy, is simply slow to respond, or whether antibiotic resistance has developed, is difficult, and further therapeutic options ("salvage therapy") are uncertain.[48,53,54] For those patients failing TMP-SMX, intravenous pentamidine is generally added or used as a single replacement agent. For those given pentamidine initially, TMP-SMX is used if tolerated. For those patients failing or intolerant to both TMP-SMX and pentamidine, the next best studied agent is parenteral trimetrexate in combination with leucovorin rescue; the combination of clindamycin and primaquine may also have a role in salvage therapy.[4,48]

Therapy for *P. carinii* pneumonia in patients with HIV infection is given for 21 days. In non–HIV-infected individuals, 14 days of therapy generally will suffice.

Specific Agents (see Table 43-1)

TMP-SMX remains the preferred drug for all patients (children and adults) who can tolerate it, because it is the most effective agent, is generally safe, is inexpensive, and is available in both oral and intravenous formulations.[4,48,52-55] The drug combination inhibits two sequential steps in *P. carinii* folate metabolism; TMP inhibits the enzyme dihydrofolate reductase and SMX inhibits dihydropteroate synthetase. Therapy is given intravenously at the onset for all but very mild disease; oral therapy can be used to finish a course of parenteral therapy for those who have responded well. The intravenous infusion should be infused over at least 60 minutes, and the dose must be adjusted for renal failure. It

is possible (but not established) that holding the dose to 15 mg/kg/day (to provide trough serum levels of 5 to 8 μg/ml of TMP and 100 to 150 μg/ml of SMX) may reduce toxicity while providing efficacy.[4,48] TMP-SMX is generally well tolerated, although adult patients with HIV infection (and, to a lesser extent, children with HIV infection) have a much higher rate of adverse effects than do other patients.[3,4] Many of the adverse effects are thought to be due to the SMX component or its metabolites; desensitization of individuals with a history of adverse reactions has been advocated by some authorities but has not been studied in a controlled manner.[3,4,48] Mild adverse effects are not necessarily contraindications for further therapy, because they can be managed with antihistamines or antipyretics, or may even resolve and not recur if the drug is temporarily withdrawn.[4,49,50] Such side effects include transient maculopapular rashes, itching, nausea, and fever; neutropenia can also occur. Urticaria, the Stevens-Johnson syndrome, or hepatitis may contraindicate further therapy.

Pentamidine isethionate is the most commonly used alternative to TMP-SMX.[3,4,48,52-54] It is an antiparasitic agent whose mechanism of action is not well established. For moderate to severe *P. carinii* disease in children or adults, pentamidine is best administered once daily as a slow (60 to 120 minutes) intravenous infusion. In the past, intramuscular injections were used, but these led to the development of painful sterile abscesses. Pentamidine is a toxic drug in both patients with and without coexisting HIV infection. Nephrotoxicity, pancreatitis, hypotension, and hypoglycemia can develop during therapy or even days to weeks later. Azotemia and hypoglycemia tend to occur in the second and third weeks of therapy; the latter is thought to be due to pancreatic injury with subsequent release of insulin. Some patients develop insulin deficiency resulting in hyperglycemia. An aerosolized form of pentamidine was developed in an attempt to deliver medication to the lung while reducing toxicity. Aerosolized pentamidine is an effective agent for prophylaxis but is less effective for therapy of established disease than intravenous pentamidine or TMP-SMX, and thus it can be used for therapy of only very mild disease.[4,48] Aerosolized pentamidine has rarely been associated with pancreatitis, nephrotoxicity, and hypoglycemia, but it is commonly associated with cough due to bronchospasm.

Trimetrexate is a powerful inhibitor of *P. carinii* dihydrofolate reductase. It is perhaps 1500 times more avid in binding the enzyme than is TMP but is far less selective for the *P. carinii* protein than the mammalian protein.[4] Thus, trimetrexate must be given with leucovorin (folinic acid, which *P. carinii* cannot use as an extrinsic source for folate metabolism) to attenuate potentially severe trimetrexate-induced hematologic toxicity. When careful attention is paid to adjustment of the trimetrexate dosing and leucovorin dosing depending on observed hematologic toxicities, trimetrexate can serve as a better tolerated (but somewhat less effective) agent for severe *P. carinii* pneumonia than TMP-SMX.[56] It is critical to extend the leucovorin administration for 3 days beyond the last administered dose of trimetrexate. A few children have been treated using this protocol as well, but data are limited.

Dapsone, like SMX, is a dihydropteroate synthetase inhibitor that is reportedly somewhat better tolerated than SMX. The drug is potentially useful because it is orally bioavailable, is inexpensive, and has a long half-life. However, it is not clear whether dapsone's efficacy when administered with TMP equals that of TMP-SMX or whether it is indeed less toxic.[4,48] Dapsone can cause methemoglobinemia (almost uniformly, but rarely to a treatment-limiting degree), anemia (especially if glucose-6-phosphate dehydrogenase deficiency is present), rash, and vomiting. Dapsone has been used in adults as daily therapy for mild *P. carinii* pneumonia in combination with daily TMP (dapsone is not acceptable as single-agent therapy).[4] Perhaps a better role for dapsone is as a prophylactic agent (see discussion later in this chapter).

Atovaquone is an antimalarial hydroxynaphthoquinone. It inhibits protozoan mitochondrial electron transport, but the mechanism of action against *P. carinii* is unknown. The drug has a long serum half-life and is bioavailable orally (especially if ingested with fat-rich food, and if no diarrhea or gastrointestinal disease is present), lending itself to use in mild to moderate *P. carinii* pneumonia. In a randomized, double-blind study of oral atovaquone versus oral TMP-SMX conducted in 322 adults with mild to moderate *P. carinii* pneumonia, there were more therapeutic failures with atovaquone (20% versus 7%, $p = 0.002$), but fewer patients required change of therapy because of treatment-limiting side effects (7% versus 20%, $p = 0.001$).[57] Overall success rates were similar between the two groups. Thus atovaquone might serve as an alternative agent for mild *P. carinii* pneumonia in those patients who cannot tolerate TMP-SMX. Limited pharmacokinetic data in children suggest that 30 mg/kg/day of the suspension yields serum concentrations comparable with those found in adults given 750 mg twice daily Palatability of atovaquone suspension has been problematic for some children and adults.

The combination of clindamycin and primaquine shows excellent activity in cell culture and experimental animal models of *P. carinii* infection, although neither agent is effective if used alone.[58] This alternative regimen is attractive because of the relative inexpense of the drugs, their oral bioavailability, and the fact that each appears to concentrate in lung tissue. Several studies have been performed in adults using clindamycin-primaquine as either salvage therapy for patients not responding to or intolerant of conventional agents (TMP-SMX or pentamidine) and as primary therapy in mild to moderate *P. carinii* disease.[4] In one prospective noncomparative study, 20 (91%) of 22 patients given intravenous clindamycin and oral primaquine, followed by oral clindamycin and primaquine responded to therapy, and 16 (73%) completed therapy.[59] In a follow-up trial, 38 adults were treated for the entire course with oral medication; 92% responded and 79% completed therapy.[59] In these and other studies, the primary toxicity was a macular or maculopapular erythematous rash developing in about 60% of patients around day 10 of therapy, which often subsequently regressed, rarely necessitating limitation of therapy. About 10% of patients experienced diarrhea; because clindamycin has been associated with pseudomembranous colitis, therapy may need to be altered if severe diarrhea occurs. Like dapsone, primaquine causes methemoglobinemia (40% incidence in the previously mentioned study, but none requiring treatment or with serum methemoglobin >20%), and it can cause hemolytic anemia in patients with glucose-6-phosphate dehy-

drogenase deficiency. Although there is no theoretical reason why the combination should not also be effective in children, few data are available to guide its use.

Several classes of experimental therapeutic agents for *P. carinii* have been studied, including inhibitors of dihydrofolate reductase,[60,61] novel pentamidine analogs,[62] echinocandin antifungal agents,[1,63] inhibitors of enzymes or proteins required for *P. carinii* growth,[64,65] antimalarials,[64,66] and iron chelators.[67-69] None of these agents, however, has been shown to be safe and effective for *P. carinii* therapy in humans.

ADJUNCTIVE THERAPY

Anti–*P. carinii* therapy is often associated with a decline in PaO_2 of 10 to 30 mm Hg during the first few days, especially in patients with AIDS. Such a decline may be tolerated in those with mild disease, but it can be harmful in moderate to severely ill patients who already have PaO_2 values below 70 mm Hg. It is not certain whether the decline in oxygenation is part of the natural progression of *P. carinii* pneumonia, or whether dying organisms incite further pulmonary inflammation. The possibility that pulmonary inflammation might significantly contribute to lung damage in *P. carinii* pneumonia, along with the observation that *P. carinii* pneumonia in cancer patients often developed while corticosteroids were being tapered, suggested that corticosteroid therapy could serve as a useful adjunct to antimicrobial therapy.

Five controlled trials assessing the efficacy of adjunctive corticosteroid therapy in reducing pulmonary morbidity and mortality in adults with moderate to severe *P. carinii* pneumonia have been reviewed by a National Institutes of Health–University of California Expert Panel.[70] All four trials in which steroids were begun within 72 hours of anti–*P. carinii* therapy showed improved outcome, as documented by (in various combinations) prevention of initial decline in oxygenation, reduced need for mechanical ventilation, and reduced mortality rate (from 22% to 11% overall mortality rate in the largest trial).[53,70] Adverse effects of steroid therapy were uncommon, but included an excess of oral thrush and development of mucocutaneous herpes; there was no observed increase in Kaposi's sarcoma or life-threatening opportunistic fungal or mycobacterial infections.

The Expert Panel consensus, now recommended as standard by most experts, was that for adults and adolescents over 13 years of age with moderate to severe *P. carinii* pneumonia, as defined by PaO_2 below 70 mm Hg or $P(A-a)O_2$ gradient above 35 mm Hg, adjunctive corticosteroid therapy should be begun as soon as possible after anti–*P. carinii* therapy is instituted.[70] The dosage regimen recommended for adults was that used by the largest published study, as follows: on days 1 through 5 of therapy, 40 mg of oral prednisone twice daily; on days 6 through 10, 40 mg of prednisone once daily; and on days 11 through 21, 20 mg of oral prednisone once daily.[10,11,53,70]

Four reports have described the use of steroids in children with *P. carinii* pneumonia to be beneficial, but each study has been an open, nonrandomized trial without concurrent controls, using different dosages of medications among a combined study population of fewer than 50 children.[71-74] Despite these statistical limitations, it seems reasonable to consider using steroids as adjunctive therapy for children with moderate to severe *P. carinii*.

Other supportive measures are to maintain the PaO_2 greater than 70 mm Hg and, if possible, to limit the FIO_2 to <50%. Assisted ventilation, packed red blood cell transfusion, and parenteral alimentation are frequently indicated in severe infection.

ANTIMICROBIAL PROPHYLAXIS

Antimicrobial prophylaxis is highly effective in preventing the development of *P. carinii* pneumonia and is indicated for any group of patients with a high incidence of the disease resulting from immunosuppressive therapy or primary immune dysfunction.[2-4,10,11,48-52] Such groups include children with T-lymphocyte dysfunction, such as those with acute lymphocytic leukemia, those with severe combined immunodeficiency syndromes, children undergoing intensive chemotherapy for lymphomas or solid tumors, and recipients of solid organ and bone marrow transplants.[2,30,48] A few children with humoral immune defects have also developed *P. carinii* pneumonia and may warrant prophylaxis, as have children with connective tissue diseases such as rheumatoid arthritis or systemic lupus erythematosus who are undergoing high-dose corticosteroid therapy.[2,30] Finally, the most susceptible group of immunodeficient patients recognized is the HIV-infected population, who require chronic primary and secondary prophylaxis against *P. carinii* pneumonia during advanced immunosuppresson.[10,11,52] Primary prophylaxis refers to the use of medication to prevent the initial episode of *P. carinii* pneumonia; secondary prophylaxis refers to the use of medication to prevent recurrences of disease.

Seminal controlled studies by Hughes and colleagues[75] in 1977 showed that the incidence of *P. carinii* pneumonia in children with acute lymphocytic leukemia undergoing chemotherapy could be reduced from 21% to 0% by daily oral administration of TMP-SMX (150 mg/m^2 TMP and 750 mg/m^2 SMX divided in two daily doses). Subsequent studies by the same workers showed that TMP-SMX could be given on three consecutive days per week rather than daily, with equivalent efficacy.[76] These results now have been generalized to other groups of patients. Although controlled studies are lacking in other groups of patients, a number of retrospective analyses and a large body of clinical experience have indicated that a number of different dosage regimens of TMP-SMX (once or twice daily, 3 or 7 days per week) effectively prevent the development (primary prophylaxis) and recurrence (secondary prophylaxis) of *P. carinii* pneumonia in children and adults with both primary and acquired immunodeficiency, including those with HIV infection.[3,4,48-52]

Prophylaxis with TMP-SMX is simple, safe, inexpensive, and highly effective in patients with immunosuppression of any cause. Unfortunately, in the HIV-infected individual, the incidence of adverse effects is much higher than in other immunocompromised patients, especially in the HIV-infected adult.[3,4] Thus, many adults and some children cannot tolerate TMP-SMX because of the development of substantial pruritus, rash, leukopenia, transaminase elevation, and nausea. For these individuals, the development of aerosolized pentamidine was an important advance. Aerosolized pentamidine delivered by the Respirgard II nebulizer at a monthly dose of 300 mg was shown to be effective in two controlled trials in

Table 43-2
Indications for Prophylaxis of *Pneumocystis carinii* Pneumonia*

Indication	Begin Prophylaxis	Discontinue Prophylaxis
Any immunosuppressive therapy for cancer or connective tissue disease	With immunosuppression	After immunosuppressive therapy ends
HIV infection, no previous history of *P. carinii*	0-1 yr: From 1 mo through 12 mo of age 1-5 yr: Begin if $CD4^+ < 500$ cells/μL or <15% 6-18 yr: Begin if $CD4^+ < 200$ cells/μL or <15%	Prophylaxis may be discontinued for adolescents and adults undergoing highly active antiretroviral therapy whose $CD4^+$ counts are ≥200 cells/μL or ≥15% for ≥3 mo; prophylaxis is restarted if cell counts again fall below these levels. The safety of discontinuing prophylaxis in children has not yet been adequately studied.
HIV infection, previous *P. carinii* disease, any age	As soon as therapy for primary infection ends	Prophylaxis may be discontinued for adolescents and adults undergoing highly active antiretroviral therapy whose $CD4^+$ counts are ≥200 cells/μL or ≥15% for ≥3 mo; prophylaxis is restarted if cell counts again fall below these levels. The safety of discontinuing prophylaxis in children has not yet been adequately studied.
Infants born to HIV-infected women	From 1 mo until 4-6 mo or longer (until time that HIV infection is reliably excluded)	Discontinue at 12 mo, unless HIV excluded earlier by serially negative HIV PCR tests (i.e., negative PCR tests at a minimum of 1 mo and 4-6 mo of age)

*Choice and dosages of prophylactic medications in Table 43-3.

adults with HIV infection (one trial was a primary prophylaxis study and the other a secondary prophylaxis study).[4,49,50] Two other controlled trials in Canada also demonstrated the effectiveness of aerosolized pentamidine, 60 mg every 2 weeks delivered by the Fisoneb ultrasonic nebulizer (a product not currently available in the United States).[4,49,50] The toxicity of aerosolized pentamidine is primarily limited to bad taste and bronchospasm and coughing. The latter complications can be reduced by administration of β-agonists such as albuterol, but they are of concern because of the possibility of coughing increasing the transmission of other coinfecting opportunistic pathogens (such as *M. tuberculosis*). Systemic toxicity of aerosolized pentamidine is rare, but it has been described. In addition, a limitation of aerosolized pentamidine is the development of atypical *P. carinii* disease (upper lobe pneumonia, extrapulmonary disease, etc.), complicating diagnosis and management. Finally, the medication is expensive and requires a source of compressed air.

Controlled trials in adults with AIDS have shown that aerosolized pentamidine is less effective than TMP-SMX for primary and secondary prophylaxis.[77,78] Thus, when TMP-SMX is tolerated, it is the first choice for both children and adults. A randomized controlled trial of TMP-SMX, aerosolized pentamidine, and oral dapsone as primary prophylaxis in adults with advanced HIV infection showed that all three regimens were similarly effective for patients with 100 to 200 $CD4^+$ lymphocytes/μL, but that aerosolized pentamidine was inferior for those patients with fewer than 100 $CD4^+$ lymphocytes/μL. Aerosolized pentamidine was better tolerated than systemic therapy.[79] If TMP-SMX, pentamidine, and dapsone are not tolerated, many theoretical options exist, but few have been subjected to large controlled trials. Dapsone with pyrimethamine, dapsone with TMP, sulfadoxine with pyrimethamine, and intermittent parenteral pentamidine also have been tried in adults with HIV infection.[4] Limited data exist on the use of dapsone in children. Atovaquone and clindamycin-primaquine have theoretical attractiveness for children, but no data allow firm conclusions about their use in primary or secondary prophylaxis; in addition, atovaquone is substantially more expensive.[52]

The U.S. Public Health Service/Infectious Diseases Society of America Prevention of Opportunistic Infections Working Group issues periodically updated comprehensive guidelines on therapy and prevention of opportunistic infections, including those caused by *P. carinii*, in adults and children with HIV infection.[52-54] These important documents (and any future publications from the groups) should be consulted for detailed recommendations on therapeutic and prophylactic agents, choice of regimens, monitoring of patients, and treatment of breakthrough *P. carinii* disease. A summary of the guidelines is presented below and in Tables 43-2 and 43-3.

Because of the recognized advantages of TMP-SMX (efficacy against pulmonary and extrapulmonary *P. carinii*, low cost, cross-protection against toxoplasmosis and bacterial infections), the guidelines call for consideration of rechallenge with TMP-SMX in case of non–life-threatening adverse effects, because many patients seem to tolerate rechallenge and can thus be continued on TMP-SMX.[50,52,53] Preliminary data suggest that TMP-SMX is better tolerated by HIV-infected children than adults and that TMP-SMX prophylaxis is better tolerated than therapy.[3]

In the HIV-infected adolescent and adult, the $CD4^+$ lymphocyte count below 200 cells/μL or the previous occurrence of *P. carinii* disease indicates high susceptibility to infection and mandates primary prophylaxis[50,52] (see Table 43-2). The preferred regimen for both primary and secondary prophylaxis is TMP-SMX for those who can tolerate it.[50,52] Similar recommendations, utilizing age-appropriate $CD4^+$ T-lymphocyte levels, are made for HIV-infected children.[52] Prophylaxis against *P. carinii* is often given for the lifetime of an immunosuppressed patient, but recent guidelines suggest that prophylaxis may be discontinued for certain patients with HIV infection, i.e., adults and adolescents receiving highly active antiretroviral therapy whose $CD4^+$ T-lymphocyte counts have increased and remained greater than 200

Table 43-3
Medications for Prophylaxis against *Pneumocystis carinii* Pneumonia*

Medication	Dosage
Trimethoprim-sulfamethoxazole	150 TMP + 750 SMX mg/m^2 body surface area/day divided q12h administered PO 3 times weekly on consecutive days. (Acceptable alternative regimens include the above dosage given as a single dose 3 times weekly on consecutive days; given as 2 divided doses daily; or given as 2 divided doses 3 times weekly on alternate days. The standard adult dose, which should not be exceeded for children, is 1 DS tablet [160 TMP + 800 SMX mg] once daily.)
Dapsone	2 mg/kg/day as a single dose (maximum dose 100 mg/day)
Aerosolized pentamidine	300 mg by inhalation via Respirgard II nebulizer (Marquest, Englewood, CO) once monthly
Atovaquone	30-45 mg/kg/day as a single dose (maximum dosage 1500 mg/day)

*Medications are listed roughly in order of choice—see text.

cells/μL for longer than 3 months.[52] Prophylaxis is restarted if CD4$^+$ T-lymphocyte counts decrease to less than 200 cells/μL. The safety of discontinuing *P. carinii* prophylaxis in HIV-infected children is less certain but might be considered if age-appropriate CD4$^+$ T-lymphocyte reconstitution has taken place for 3 to 6 months[52] (see Table 43-2).

Universal prophylaxis for HIV-exposed infants is provided until such time that HIV infection is reasonably excluded.[51,52] The preferred regimen is TMP-SMX in two divided doses, three times weekly; acceptable alternatives include once-daily TMP-SMX three times a week or twice-daily TMP-SMX seven times a week[51,52] (see Table 43-3). Aerosolized pentamidine, oral dapsone, and (least desirable) intravenous pentamidine are suggested alternatives for TMP-SMX–intolerant patients.[51,52]

The prophylactic drug regimens shown in Table 43-3 may be used for the primary prophylaxis of *P. carinii* disease in children with non–HIV-related immunocompromise (e.g., cancer and cancer chemotherapy, congenital immunodeficiency, transplant recipients) as well. All children and adults with a previous episode of *P. carinii* disease likely require secondary prophylaxis, although again, discontinuation in immune-reconstituted, HIV-infected adults and adolescents may be considered.[52]

LEGIONELLA PNEUMOPHILA

A number of species of genus *Legionella* of the family Legionellaceae are responsible for causing infection in humans.[80] *Legionella pneumophila*, the cause of legionnaires' disease, was the first species to be associated with fatal pneumonia and is the one most commonly implicated in human legionellosis.[81] Legionnaires' disease is uncommon in children. The illness is often grouped with the "atypical pneumonias" caused by *Chlamydia* or *Mycoplasma*, but this classification is unsatisfactory because the clinical features of legionellosis are much more variable.

Epidemiology, Risk Factors, and Pathogenesis

ORGANISM

Legionella organisms are pleomorphic, thin, faintly staining gram-negative rods that are aerobic, motile, and nutritionally fastidious. Growth of *Legionella* depends on the presence of L-cysteine and iron in specialized growth media, which often results in unsuccessful bacterial isolation unless the laboratory is forewarned that *Legionella* infection is suspected; this most likely plays a role in the underdiagnosis of *Legionella* infection. Similar to other gram-negative rods, the outer membrane of *Legionella* is primarily lipopolysaccharide, and the serogroup-specific antigen of the lipopolysaccharide is used for serotyping of the organism. *Legionella* species are saprophytic aquatic microorganisms that rarely become human pathogens. Most cases of *Legionella* infection are caused by only a few of the 70 or so serogroups among the nearly 50 known species.[82,83] The *L. pneumophila* serogroup 1 is responsible for up to 85% to 90% of *Legionella* infection in healthy individuals, and *L. pneumophila* serogroups 4 and 6, along with *L. longbeachae* and *L. bozemanii*, are responsible for much of the rest.[82,83]

EPIDEMIOLOGY

Legionella organisms are most commonly found in water sources; the natural reservoir may be freshwater amebae.[84] The organism has been isolated both from natural (freshwater streams and lakes, water reservoirs) and artificial (cooling towers, potable-water distribution systems) aquatic habitats. The optimal temperature for growth is between 28° C and 40° C, a range present in both natural and artificial habitats.

RISK FACTORS

In the initial period after the recognition of *Legionella* as a cause of pulmonary disease, the infection was most often identified in point-source epidemics. Sporadic individual infections often went unrecognized. However, more recent data from studies performed in adults suggest that *Legionella* may be responsible for up to 15% of community-acquired pneumonias and 40% of nosocomial pneumonias in some areas.[85-88] Immunodeficiency, corticosteroid and other immunosuppressive therapy, old age, chronic obstructive pulmonary disease, and cigarette smoking have been considered risks for *Legionella* infection in adults. Surgery also appears to be a risk factor in nosocomial infection,[89,90] and transplant patients are among the patients at the highest risk for *Legionella* infection.[91-93]

In children, immunologic and pulmonary compromise have also been considered risks for *Legionella* infection, but sound data regarding the actual incidence of pediatric *Legionella* are lacking. Most of the information has been obtained by serologic surveys of specific groups of patients under medical care and therefore may be biased. In one study from Iceland, 14% of children showed serologic evidence of previous *Legionella* infection.[94] Legionnaires' disease has been documented in children with immunosuppression, but large

studies of this population have not been completed.[95-99] Nevertheless, as in adults, immunosuppression must be considered one of the most important factors assumed to increase the risk of *Legionella* infection in childhood.

PREVALENCE

Legionella infection in children appears to be uncommon, being responsible for only about 1% of cases of pneumonia in seven surveys involving a total of 742 children (range, 0% to 6% in individual studies).[100-106] In contrast, at least 2% of community-acquired pneumonia in adults, 5% of pneumonia in adults causing hospitalization, and 8% of pneumonia in adults requiring ICU admission are thought to be due to legionnaires' disease.[82] A number of reports of nosocomial transmission of *Legionella* infection in children have been published.[107-109] These reports have most often been linked to contaminated water supplies, and aerosol-generating respiratory equipment has been implicated in outbreaks. Sporadic infection in infants younger than 2 weeks has been associated with contaminated water both at home and in the hospital.[110,111] Person-to-person transmission probably does not play a role in the nosocomial spread of *Legionella*.

PATHOLOGY AND PATHOGENESIS

Legionella organisms are facultative intracellular pathogens that cause acute fibrinopurulent pneumonia with alveolitis and bronchiolitis. Histologically, organisms can be seen both intracellularly and extracellularly along with inflammatory cells in the purulent exudate. Besides the lungs, *Legionella* has also been found in the lymph nodes, brain, kidney, liver, spleen, bone marrow, and myocardium.[112] *Legionella* is cleared from the upper respiratory tract by the mucociliary action. Therefore, any process that compromises mucociliary clearance (such as tobacco smoke) will increase the risk of legionellosis. It is phagocytosed by local pulmonary macrophages but is not actively killed, and macrophages may actually support the growth of *Legionella* (thereby allowing the organism to evade one of the first lines of pulmonary host defense). *Legionella* multiplies intracellularly and kills infected macrophages, and then spreads to infect other macrophages. Cell-mediated immunity appears to be the primary protective host defense mechanism, although the roles of neutrophils and humoral immunity have not yet been well characterized. The mode of acquisition of original infection in humans is uncertain but is likely to be airborne inhalation of contaminated aerosols, or perhaps aspiration of contaminated water or oropharyngeal secretions.

Clinical Features

Most of the information regarding the classic clinical features of *Legionella* infection is from studies of adults, because of the rarity of documented pediatric legionellosis. *Legionella* infection in adults has a wide spectrum of clinical manifestations ranging from serious and fatal pneumonia to a self-limiting viral-like illness, but typically the infection manifests as one of two clinical syndromes: Pontiac fever or legionnaires' disease.

Pontiac fever is a viral-like illness with high fever, headache, malaise, and myalgia. The illness is self-limiting, with a short incubation period (24 to 48 hours) and recovery in 7 to 10 days, usually without sequelae. Pneumonia is not usually a part of Pontiac fever, although nonproductive cough may be present. Antibiotic therapy is not necessarily required.

Legionnaires' disease is a multisystem disease that primarily affects lungs. The onset of illness may be acute or insidious. Although pneumonia is the predominant feature of this disease, respiratory symptoms may be absent initially. After an incubation period (which can be as short as 48 hours or as long as 10 days) patients have weakness, lethargy, fatigability, myalgia, and malaise. High fevers (>40° C) and chills are not uncommon. Almost all patients are febrile, although initially fever may be absent or low grade.[80] Relative bradycardia may be present in febrile patients. A dry cough is present in almost all patients. Most adults develop purulent sputum and sometimes hemoptysis. Patients may complain of pleuritic chest pain and shaking chills. Neurologic and gastrointestinal symptoms may also be prominent in some patients, including headache, lethargy, confusion, cerebellar ataxia, agitation, mental status changes, encephalopathy and watery, nonbloody diarrhea. Anorexia may be present, and some patients may complain of abdominal cramps.[90] Hyponatremia and elevated serum transaminase levels are seen more commonly with *Legionella* than pneumonias caused by other organisms. A number of extrapulmonary sites of *Legionella* infection occur as a result of bacteremic dissemination. Although isolation of *Legionella* from the cerebrospinal fluid (CSF) has not been successful, CSF pleocytosis and elevated protein concentrations have been described.[113]

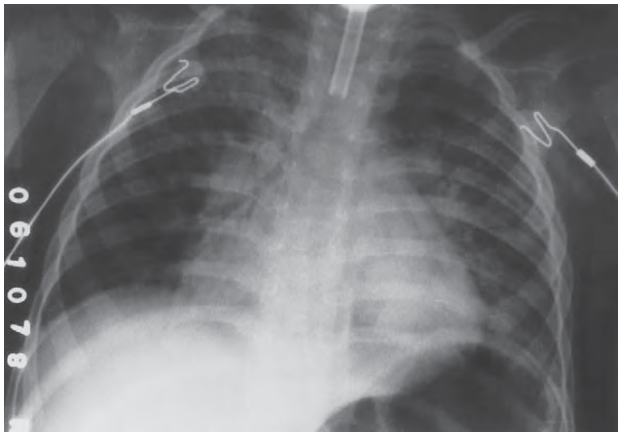
In short, the triad of pneumonia, confusion, and diarrhea, especially if accompanied by hyponatremia and elevated serum transaminase levels, should raise the suspicion of legionnaires' disease. Unfortunately, several prospective studies have noted that it is not possible to distinguish between legionnaires' disease and other causes of pneumonia on the basis of one or more of these findings alone.

Radiographic findings of legionellosis are variable and nonspecific, from patchy alveolar infiltration to a consolidated pneumonia (Fig. 43-6). Pleural effusions may be seen, and cavitary lesions develop occasionally.[114] The usual progression is from patchy areas or nodules to multilobar, almost homogeneous infiltrates. A somewhat typical feature is the centripetal progression of *L. pneumophila* pneumonia. Initially the pneumonia is present in the peripheral lung regions and then becomes sublobar and finally lobar, involving contiguous lobes on the same side.[116-118] This progression may be complicated by adenopathy, abscess, or atelectasis.[119,120] The majority of patients with legionnaires' disease develop radiographic evidence of pneumonia.[114]

Patients who are healthy before the infection will most likely recover in 7 to 10 days. Immunocompromised or debilitated patients may develop multiorgan failure and die of respiratory failure. Some patients may have other complications of one of the organ systems involved (such as colitis or peritonitis) that may take weeks to resolve.

LABORATORY DIAGNOSIS

Various methods are available for laboratory diagnosis of *Legionella* infection, but the diagnosis of *Legionella* infection cannot be excluded on the basis of any single test.[82,115] However, diagnostic tests can be complementary, elevating



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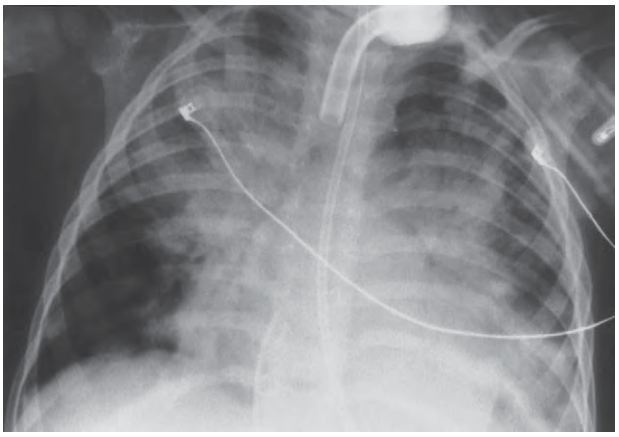

B

Figure 43-6 Serial radiographs of a 19-month-old who developed lipoid-like pneumonia after the ingestion of oil of cloves, followed by induced emesis and aspiration. Subsequently this child required a tracheostomy, steroid therapy, and multiple antimicrobial agents. One month after the aspiration the patient died from respiratory failure secondary to *Legionella pneumophila* serogroup 6 pneumonia. **A,** Chest radiograph 26 days after aspiration and 1 day after onset of fever and increasing respiratory distress. **B,** Chest radiograph 2 days later, showing increasing infiltrates. One day later the child died. (Radiographs courtesy of Leland L. Fan, MD, National Jewish Center for Immunology and Respiratory Medicine and Department of Pathology, Children's Hospital, Denver, CO.)

the diagnostic yield for the diagnosis of *Legionella* infection.

Culture is currently considered the gold standard but requires special media, as noted earlier. When *Legionella* is suspected, the clinical laboratory may also "decontaminate" the specimen with a brief acid treatment before inoculation of the specialized growth medium, again to reduce the overgrowth of other organisms. Even with these specialized techniques, it may take up to 5 days to isolate the slow-growing *Legionella*. Although the specificity of culture is 100%, its sensitivity ranges from 10% to 80%.

Direct fluorescent antibody (DFA) staining for *Legionella* is a rapid test requiring as few as 2 to 4 hours for results. However, the sensitivity of DFA can vary from 25% to 70%, depending upon the experience of the technician and quality of the specimen.[115] Therefore, a negative DFA does not exclude *Legionella* infection. Newer monoclonal antibody reagents appear more specific than the polyclonal anti-*Legionella* antibody preparations for diagnosis of *Legionella*, yielding 95% specificity; false positives result from cross-reaction with other bacteria or operator error in reading fluorescence.

Specimens for culture and DFA stain commonly must be obtained by bronchoscopy, because sputum specimens are usually not available from children. Bronchoalveolar lavage is the method of choice, because the yield of bronchial washings and induced sputum samples is low. Pleural fluid, if available, may be sent for culture and DFA stain for diagnosis of *Legionella* infection.

Serologic assays for *Legionella* antibodies are not generally useful in clinical decision making, although are valuable for epidemiologic research. The antibody detected by indirect immunofluorescence tests is produced against the lipopolysaccharide in the outer membrane of *Legionella*. Diagnosis is based on a 4-fold or greater rise in antibody titer, between acute and convalescent serum specimens, to at least 1:128. This seroconversion may take up to 4 to 8 weeks to develop. In epidemics, a single titer of 1:256 or greater, with supporting clinical illness, has been considered sufficient to make a presumptive diagnosis of legionellosis,[121] but this definition has been questioned.[122]

The urinary antigen test for the diagnosis of *Legionella* infection is commonly used in clinical practice because of its rapid turnaround time with high sensitivity (70% to 99%) and specificity (>99%).[115,122] The major disadvantage of the urinary antigen test is that it detects antigen only from serogroup 1 *Legionella*. However, this limited cross-reactivity is less of a problem clinically because serogroup 1 organisms are the cause of most clinical disease. Nucleic acid amplification tests (PCR, etc.) have been used to identify *Legionella* species in research laboratories; if these become commercially available, their theoretical sensitivity should be very high for many serogroups and species, but specificity will depend upon the characteristics of the tests and laboratories performing them.

At the present time, the best combination of diagnostic tests appears to be the urinary antigen test combined with culture of respiratory tract material (BAL fluid, lung tissue, or possibly pleural fluid), especially in geographic areas where *L. pneumophila* serogroup 1 infection is predominant.

Treatment

Many antibiotics inhibit the growth of *Legionella* in vitro, but only those that concentrate well inside cells are clinically useful to combat this intracellular pathogen.[123] Thus, only macrolides, fluoroquinolones, doxycycline, TMP-SMX, and rifampin should be considered as potential therapeutic agents; β-lactams and aminoglycosides will not be clinically effective, despite the in vitro activity of the latter.

Azithromycin (10 mg/kg/day in children, up to the adult dose of 500 mg/day) has replaced erythromycin as the antibiotic of choice for *Legionella* infection. This choice is not based on carefully controlled clinical trials, but rather on good in vitro and animal model activity against *Legionella*, and clinical experience in isolated legionellosis, nosocomial infections, and outbreaks of legionnaires' disease.[82,123] Addition of rifampin to azithromycin (or erythromycin) may be beneficial

in some patients with severe legionellosis.[82,123] In adolescents older than 18 years or in children younger than 18 years in whom the benefits of use outweigh the theoretical risks of cartilage toxicity, a fluoroquinolone such as levofloxacin, ciprofloxacin, moxifloxacin, or gatifloxacin may be used (some experts prefer to treat severely ill adults with fluoroquinolones rather than macrolides).[124-128]

The initial antibiotic therapy of severe *Legionella* infection should be given intravenously, and when clinical improvement occurs antibiotic administration may be changed to the oral route to complete at least 14 days of therapy. Azithromycin and several of the fluoroquinolones are available for intravenous use and are also well absorbed by mouth. Severely ill patients, as well as those who are immunosuppressed, may require longer courses of antibiotic therapy, up to 21 days. Length of the antibiotic therapy should not be gauged solely by radiologic manifestations, because the radiograph may show progression, even when the patient is receiving adequate antibiotic therapy (similar to what occurs during the therapy of pneumococcal pneumonia).

Alternative drugs for legionellosis, if neither macrolides nor fluoroquinolones are used, include TMP-SMX and doxycycline, although experience is limited, and doxycycline may not be suitable for therapy of children younger than 7 to 9 years of age.

PREVENTION

Potable water systems in hospitals and clinics should be maintained in such a fashion to minimize nosocomial *Legionella* (generally a combination of superheating, hyperchlorination, or copper-silver ionization treatment followed by periodic routine water culturing and patient surveillance).[82]

PARASITIC INFECTIONS

Parasitic infections are common worldwide, but pulmonary complications are relatively rare. This section reviews notable pulmonary disease caused by intestinal, tissue, and blood protozoa; helminthic pulmonary infections will be discussed individually. Table 43-4 presents the antiparasitic drugs of choice and suggested dosages for the most common parasitic infections of the lungs.

Table 43-4
Therapy of Selected Pediatric Parasitic Pulmonary Infections

Parasite	Therapy of Choice (maximum daily adult dose shown in [brackets]; all given by mouth)
Protozoa	
Entamoeba histolytica	Metronidazole 35-50 mg/kg/day divided q8h × 7-10 days [750 mg PO q8h] ***Or*** Tinidazole 50 mg/kg/day q24h × 5 days [2 g once daily × 5 days]
Toxoplasma gondii	Pyrimethamine 2 mg/kg/day × 3 days, then 1 mg/kg/day × 4 wk [25-100 mg/day × 4 wk] **plus** sulfadiazine 100-200 mg/kg/day divided q6h × 4 wk [1-1.5 g q6h × 4 wk] **plus** leucovorin 10-25 mg/day [all ages; combination therapy for congenital infection prolonged to 12 mo]
Helminths	
Echinococcus species	Albendazole 15 mg/kg/day divided q12h × 1-6 mo [400 mg q12h × 1-6 mo] (and/or surgery; see text)
Paragonimus species	Praziquantel 75 mg/kg/day divided q8h × 2 days [all ages]
Schistosoma species	Praziquantel 40-60 mg/kg/day divided q8h × 2 days [all ages; exact dose depends on infecting species]
Ascaris lumbricoides	Mebendazole 200 mg/day divided q12h × 3 days [all ages] **OR** Albendazole 400 mg once [all ages]
Hookworm	Mebendazole 200 mg/day divided q12h × 3 days [all ages] **OR** Albendazole 400 mg once [all ages]
Strongyloides stercoralis	Ivermectin 0.2 mg/kg/day × 2 days [all ages] ***or*** Albendazole 400 mg q12h × 7 days [all ages]
Toxocara canis	Albendazole 400 mg q12h × 5 days [all ages] ***or*** Mebendazole 200 mg q12h × 5 days [all ages]

Intestinal, Blood, and Tissue Protozoa

INTESTINAL PROTOZOA

Entamoeba histolytica. Amebiasis is endemic worldwide, but the prevalence of disease is highest in areas with poorer sanitation systems, including nearly all developing countries. Although a large number of species infect humans, most human disease is associated with *E. histolytica*. Recent evidence suggests that even most organisms identified as *E. histolytica* are not actually pathogenic; rather, a minority of strains that contain a number of virulence genes cause nearly all clinical disease. Cysts are shed in the stools of individuals with intestinal infection (90% of which is asymptomatic) and are ingested by others via contaminated food or water. Direct person-to-person transmission can also occur. Although intestinal amebic disease causes dysentery, most patients with the less common extraintestinal disease do not have dysentery. The most common extraintestinal manifestation is amebic liver abscess, which typically causes fever, abdominal pain or tenderness, and leukocytosis.

Pleuropulmonary involvement is seen in only 0.1% of cases of amebiasis and usually represents a complication of amebic liver abscess.[129] An inflammatory reaction may develop adjacent to an abscess in the liver or subphrenic space, causing pleural effusion or pneumonitis. Hepatic abscesses can also rupture into the pleural space, causing localized empyema, pneumonitis, or lung abscess.[129,130] Erosion into the airways may lead to chocolate-colored sputum or even to a bronchobiliary fistula. Pericardial involvement is rarely noted. Only rarely are *E. histolytica* trophozoites identified in aspirated or expectorated material. Thus diagnosis is usually based on demonstration of serum antibodies. Extraintestinal amebiasis usually responds to treatment with antiparasitic agents such as metronidazole or tinidazole, followed by therapy with an agent directed at cysts such as paromomycin or iodoquinol to clear intestinal cyst carriage. Surgical drainage may be used as an adjunct to therapy in some cases of hepatic abscesses.

BLOOD PROTOZOA

***Plasmodium* species.** Malaria is a common infection worldwide, with more than 300 million persons infected and at least 1 million deaths per year. Uncomplicated malaria is characterized by fever, chills, and hemolysis. Malaria can be complicated by involvement of the central nervous system, kidneys, or lungs. Pulmonary involvement is thought to result from a combination of cytokine-associated damage and perhaps localized ischemia caused by vessels occluded with adherent parasitized erythrocytes.[131] The clinical picture of bilateral infiltrates and hypoxia resembles that seen in other causes of noncardiac pulmonary edema, such as the adult respiratory distress syndrome. Management involves aggressive therapy for the parasitemia with chemotherapeutic agents and possibly exchange transfusion. In addition, ventilatory support is often required.

TISSUE PROTOZOA

Toxoplasma gondii can cause clinically and radiologically discernible pneumonia, or it can be found as a silent component in patients with clinical toxoplasmosis of other organ systems.[132] Pulmonary toxoplasmosis is rare among infections in immunocompetent hosts (probably much less than 1%), but it is increasingly reported among immunosuppressed adults with malignancy or advanced AIDS.[132,133] The symptoms, signs, and radiographic findings provide few clues to the diagnosis and may easily be confused with those of *P. carinii* or cytomegalovirus disease (dyspnea, cough, fever, crackles, and interstitial infiltrates). Serologic diagnosis can be difficult in immunocompromised hosts who may not produce antibody, and thus BAL or lung biopsy may be required. Pyrimethamine combined with sulfadiazine is the standard therapeutic regimen for severe toxoplasmosis, as summarized elsewhere.[134-136] Both the mortality rate and the relapse rate among survivors have been reported to be high,[132] although the lack of prospective contemporary data may have biased these estimates.

Leishmania donovani and ***Cryptosporidium parvum*** have been identified in pleuropulmonary infections in a few cases.[129] Most of these patients had depressed immunity, most often from advanced AIDS.

Helminthic Infections

ECHINOCOCCOSIS

Epidemiology, Risk Factors, and Pathogenesis

Echinococcosis, also known as hydatid disease, is caused by the cestode parasites of the genus *Echinococcus*. The two major species that infect humans, *Echinococcus granulosus*, and *E. multilocularis*, differ in geographic location, host specificity, and disease manifestations.[137,138]

Different genetic strains of *E. granulosus* have separate domestic and wild animal (sylvatic) life cycles.[137-138] In the domestic cycle, the definitive host (i.e., the host harboring the intestinal tapeworm form) is the domestic dog. The most common intermediate host (i.e., the host harboring the tissue cyst) is sheep. Other intermediate hosts include goats, swine, cattle, buffalo, horses, and camels. In the sylvatic cycle, wild carnivores, such as wolves, coyotes, jackals, and dingoes, are the normal definitive hosts. The intermediate hosts include moose, elk, and deer. Thus, both domestic and sylvatic hydatid disease is usually acquired from domestic dogs, which are in turn infected by ingestion of either contaminated mutton/lamb/beef or game, respectively.

Human disease caused by *E. granulosus* is termed *cystic hydatid disease*. Cystic hydatid disease has a wide geographic distribution and is endemic in most areas where sheep are raised. Highly endemic areas include eastern and southern Europe, the Middle East, North Africa, Australia, and southern portions of South America. There are also endemic foci in North America. The domestic cycle has been described in sheep-raising areas of the American Southwest, such as Navajo and Zuni Indians in Arizona and New Mexico, among Mormons in Utah, and among Basque shepherds in California. The sylvatic cycle most often occurs in Alaska and Canada.

Human disease caused by *E. multilocularis* is termed *alveolar hydatid disease*. Alveolar hydatid disease is a more serious, but somewhat more geographically limited, infection in the colder portions of the Northern Hemisphere, including most of the arctic and subarctic regions, the alpine regions of central Europe, and much of Russia and central Asia. In North America, endemic areas include the subarctic tundra and scattered areas in the north central plains. The usual definitive hosts are foxes. Dogs and cats can serve as definitive hosts as well. The most important intermediate hosts are small rodents such as mice and voles.

Rarely, human hydatid disease is caused by two other species, *E. vogeli* and *E. oligarthrus*, and is known as *polycystic or multicystic hydatid disease*. These species are limited to parts of lower Central America and upper South America. The normal definitive hosts are wild dogs or cats (e.g., bush dogs, ocelots, or pumas) and the intermediate host is the paca.

After a person is infected by ingestion of parasite eggs from infected dogs, the eggs hatch in the intestines, and the larvae penetrate the intestinal mucosa into the portal veins and lodge in the liver or in some cases the lung. The cysts do not cause symptoms until they have enlarged to several centimeters in diameter. Symptoms usually result from mass effects of the expanding cyst. The rate of cyst expansion is determined in part by the tissue infected. Cysts in the liver typically expand at a rate of 1 to 5 cm in diameter per year and require years to decades before causing symptoms; thus, symptomatic pediatric disease is uncommon. Lung tissue offers less resistance than liver, such that pulmonary cysts may expand more rapidly and cause clinical symptoms earlier in life. In one recent series, one third of patients with pulmonary cysts were 20 years of age or younger.[139] Cyst rupture is associated with localized inflammation, allergic manifestations, and the formation of daughter cysts. Bacterial superinfection of the cyst may lead to symptoms suggestive of bacterial infections, such as fever and leukocytosis.

Clinical Features

Most patients with intact pulmonary hydatid cysts are asymptomatic and are discovered incidentally at autopsy or by radiographic studies. Signs and symptoms vary with the location, number, and size of cysts. Typical cystic hydatid disease causes solitary cysts in the lungs (25%), liver (60% to 70%), and rarely in other organs including muscle, spleen, brain, and bone (<5%). Isolated pulmonary disease has been reported

to be more common in children and in adults with sylvatic disease, but this finding is likely confounded by genetic strain variation among *E. granulosus*.[137,140,141] Cough, hemoptysis, and chest pain are the most common symptoms in patients with hydatid disease of the lungs. In the case of cyst rupture, patients may note abrupt onset of cough and expectoration of cyst fluid, parasite membranes (described as "grape skins"), or even scolices. Cyst rupture may also be associated with allergic manifestations, including urticaria, pruritus, and anaphylactic shock, and may lead to pneumothorax or empyema. Secondary bacterial infection is common and causes fever and purulent sputum.

One fourth of patients with pulmonary hydatid cysts also have liver involvement. Symptoms of liver disease include epigastric pain, bloating, and indigestion, and signs include hepatomegaly and obstructive jaundice. If cysts are secondarily infected, patients may have signs and symptoms of liver abscess.

Alveolar hydatid disease (caused by *E. multilocularis*) invariably involves the liver; pulmonary disease, when present, is due to metastatic lesions. Clinical disease generally is limited to adults.[142]

Radiographic Features

Pulmonary cysts are unilateral in 80% and bilateral in 20% of cases. There is a predilection for the lower lobes and the right lung over the left. Intact cysts appear as well-defined, rounded masses on chest radiographs (Fig. 43-7). Cysts adjacent to the pleura may conform to the shape of adjoining structures. On CT scan the cyst fluid is at water density, and the cyst wall may vary in thickness. Daughter cysts are occasionally seen within the cyst. If the cysts have eroded into bronchioles, air can be introduced between the pericyst and the parasite membrane, resulting in the appearance of a thin lucent crescent in the upper portion of the cyst: the "air meniscus" or "crescent" sign.[137,143-145] When the cyst has collapsed, the collapsed endocyst membrane may appear floating freely in the remaining fluid, producing an irregular air-fluid level ("water lily sign")[137,143-145] (see Fig. 43-7). Ruptured cysts may be associated with surrounding bronchopneumonia or may be secondarily infected, appearing as a lung abscess with thickened walls and an air-fluid level. Collapsed or detached endocysts or daughter cysts are more readily visualized by CT scan.[146] The role of magnetic resonance imaging (MRI) in pulmonary hydatid disease is as yet undefined.

Laboratory Diagnosis

Laboratory findings in all forms of hydatid disease are nonspecific. Only 30% or less of patients manifest eosinophilia. Serologic tests can be used to confirm a clinical diagnosis of hydatid disease. Indirect hemagglutination and enzyme-linked immunosorbent assay (ELISA) techniques are about

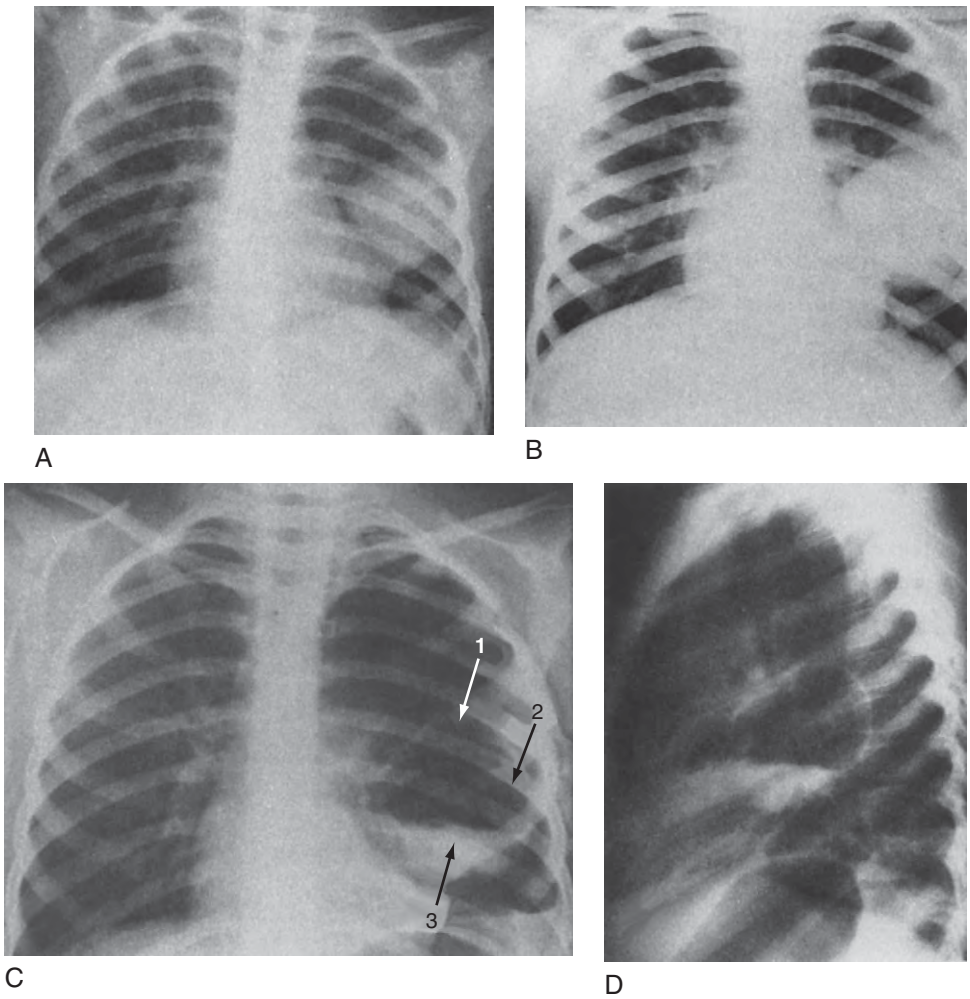

Figure 43-7 Serial chest radiographs of a 4-year-old girl with cystic hydatid disease caused by *Echinococcus granulosus*. **A,** Chest radiograph taken during asymptomatic period reveals large solitary left-lung lesion. **B,** Subsequent film taken 1 year later shows growth of cyst. **C,** The cyst has now ruptured, producing a left hydropneumothorax; the characteristic "air meniscus" or "crescent" sign is seen when air is introduced between the cyst and the host adventitia (arrow 1). The remnants of the cyst (arrow 2) appear inside the pericyst, and the irregular air-fluid level caused by the floating collapsed endocyst membrane ("water-lily sign") is also seen (arrow 3). **D,** Lateral view of the chest corresponding to **C.** (Figure reproduced from Reeder MM, Palmer PES [eds]: The Radiology of Tropical Diseases with Epidemiological, Pathological, and Clinical Correlation. Baltimore, Williams & Wilkins, 1981.)

90% sensitive.[137,147] The sensitivity of these assays is lower for isolated pulmonary disease.[137,138] Specificity can be improved by employing multiple simultaneous antigens, but currently there is no standardized highly sensitive and specific antibody test for cystic hydatid disease. For alveolar hydatid disease, assays employing semipurified antigens from *E. multilocularis* (e.g., Em2 ELISA) are suggested rather than using tests employing *E. granulosus* antigens.

In the setting of a ruptured or carefully aspirated pulmonary cyst, parasite membranes or hooks may be visualized in unstained sputum or fluid; hooks also stain well with the Ziehl-Neelsen acid-fast stain. Cyst aspiration solely for confirmation of diagnosis should not be performed in most cases of hydatid disease because of the potential risks of producing metastatic infection from, and anaphylactic reactions to, leaked fluid. In some patients, however, a definitive diagnosis may be possible only at surgery or by employing percutaneous aspiration under ultrasound or CT guidance (PAIR procedure, see later).[137,141,148,150]

Treatment

Surgical resection is the best-established therapy for pulmonary cystic hydatid disease when treatment is necessary. Until recently, all cases were believed to require radical surgery to avoid spillage of cyst contents and associated risk of anaphylaxis or the development of metastatic cysts. However, many authorities are now using a combined approach to therapy involving surgery, preoperative and postoperative antiparasitic chemotherapy, or even careful monitoring with time alone, depending on the presumed *Echinococcus* organism strain, the number and location of lesions, symptomatology, and underlying health of the patient.

If surgery is indicated (either at the onset of therapy or after a trial of chemotherapy to reduce worm viability), care is taken to avoid rupture and release of cyst contents.[151-154] For pulmonary cysts, the usual approach is to remove the entire cyst, pericyst, and a margin of normal lung. Scolicidal agents such as 70% to 90% ethanol or 10% to 15% (hypertonic) saline may be instilled into cysts before completing resection. Preoperative and perioperative chemotherapy with antiparasitic agents (e.g., albendazole) may be used to kill the scolices and prevent intraoperative spread from spillage of cyst contents.[137,138,155] *P*ercutaneous *a*spiration, *i*nstillation of scolicidal agents, and *r*e-aspiration (known as the *PAIR procedure*) has been very useful for the therapy of isolated hepatic cysts.[148,149] At present, however, there are too few data to comment on the safety or efficacy of the PAIR procedure for therapy of pulmonary cysts in adults and children, or hepatic cysts of children or pregnant women.[148,149]

The benzimidazole antiparasitic drug albendazole (and, to a lesser extent, mebendazole) is active against *Echinococcus*. Most patients will respond to antiparasitic agents, although many of the responses are only partial (i.e., reduction in size of the cysts rather than disappearance).[137,156-158] Albendazole therapy is indicated as an adjunct to surgery, or as sole therapy for those patients with inoperable, widespread, or numerous cysts, as well as for those patients who are judged to be unsuitable for surgery because of complicated medical problems.[137,155]

Alveolar hydatid disease caused by *E. multilocularis* is probably best managed by prolonged albendazole chemotherapy, because only a minority of cases of this metastatic infection can be cured by radical surgery.[137,138,142,155]

PARAGONIMIASIS

Human paragonimiasis is caused by infection with trematode lung flukes of the genus *Paragonimus*, most commonly *P. westermani*. Infection is acquired by ingesting undercooked crustaceans. Eastern Asia is the primary endemic region, but there are also foci in western Africa and, less commonly, in Latin and North America.[159,160] In endemic areas, paragonimiasis is a common cause of bronchitis and hemoptysis, and it must be differentiated from tuberculosis, which may cause similar clinical and radiographic findings.

Epidemiology, Risk Factors, and Pathogenesis

The adult parasites live within cystic lesions in the lung parenchyma.[159] The eggs are passed via tunnels into the bronchi and are either expectorated in sputum or swallowed and eventually passed in the stools. In fresh water, the eggs embryonate, hatch into miracidia, and invade snails (the first intermediate host). After a cycle of asexual reproduction, the cercarial form can either emerge from the snail and invade freshwater crabs (or sometimes crayfish) or be ingested with the snail by the crab. Infectious metacercariae form in the tissues of the crabs. Mammalian hosts are infected by ingesting raw or undercooked crab (or crayfish). In humans, the metacercariae excyst and penetrate the duodenum and, after a period of further development in the liver, penetrate the diaphragm into the lung. Over 5 to 6 weeks the parasites mature into adults, which can begin to lay eggs as early as 8 to 10 weeks after infection. The adult worms may persist in the lungs for up to 20 years.

In the lung, the parasite cysts are 1 to 4 cm nodules, typically located within a few centimeters of the pleura, adjacent to bronchi or bronchioles. The cysts consist of a pseudocapsule of host granulation tissue and contain one or two adult worms (7 to 12 mm × 4 to 7 mm). Parasite eggs and Charcot-Leyden crystals are also present within the cyst. Associated pathology may include bronchopneumonia, bronchitis and bronchiectasis, fibrosis, or angiitis. There are often tunnels, egg granulomas, and calcified eggs in the vicinity of the cysts.

Each of the three endemic regions for paragonimiasis is associated with different species of parasite and minor differences in epidemiology and clinical manifestations. The major factors necessary for transmission include the presence of large numbers of the snail and crustacean intermediate hosts and local customs in which raw or lightly cooked crustaceans are ingested. The prevalence of infection has been estimated to range from 15% to 45% in endemic regions in China and 0.3% to 78% in Korea.

Clinical Features

Acute infection is typically asymptomatic, but it may be associated with abdominal pain, diarrhea, urticaria, cough, fever, or chest pain.[159,160] Chronic pulmonary infection usually follows an incubation period of about 6 months; chronic infections may be asymptomatic or associated with symptoms of bronchitis (cough, sputum production, and chest discomfort). Many patients will complain of dyspnea and wheezing. Pleuritic chest pain and production of rusty brown ("golden flake") sputum or even frank hemoptysis are

typically present. Mild fever may be present also. Symptoms are usually episodic and are frequently associated with exertion. Some patients primarily manifest with pleural disease. Pleural effusions are exudative, frequently contain numerous eosinophils, and may be quite large. Ectopic worms sometimes can be found in the brain and abdominal cavity.

Radiographic Features

Up to 20% of patients with pulmonary paragonimiasis will have normal chest radiographs.[129] One third of patients have patchy infiltrates and one third have well-defined homogeneous densities. Many of the chest radiographs show either cystic lesions or streaks within the infiltrates, depending on the stage of the infection. Early in infection when the larvae first arrive in the lung, poorly defined cottonwool shadows are seen. Later, when the mature worms produce eggs, characteristic ring shadows with a corona (thin-walled cysts with crescent-shaped opacities along one edge) are noted.[161] Linear worm burrows may be seen adjacent to the cysts (Fig. 43-8). Pleural abnormalities are noted in up to half of all cases and may occasionally be the only abnormality.[161,162] The main CT feature of pleuropulmonary paragonimiasis is the presence of pulmonary nodules with poorly defined margins, frequently associated with adjacent areas of ground-glass consolidation and subpleural linear opacities.[163] Late in the infection after the death of the parasite, cysts often become calcified, simulating the radiographic appearance of tuberculosis (Fig. 43-8).

Laboratory Diagnosis

Laboratory tests often reveal eosinophilia. Sputum examination may reveal ova, necrotic tissue, erythrocytes, leukocytes, or Charcot-Leyden crystals. Definitive diagnosis requires demonstration of the operculated eggs in sputum or stools. Because the eggs are shed intermittently, multiple specimens or 24-hour collections are often required to demonstrate the eggs. Body fluids from involved sites, such as cerebrospinal fluid or pleural fluid, may occasionally contain eggs, but demonstration of eggs is usually not possible. A number of serologic assays have been employed and may be required to make a firm diagnosis in cases in which eggs cannot be identified, such as in extrapulmonary disease.

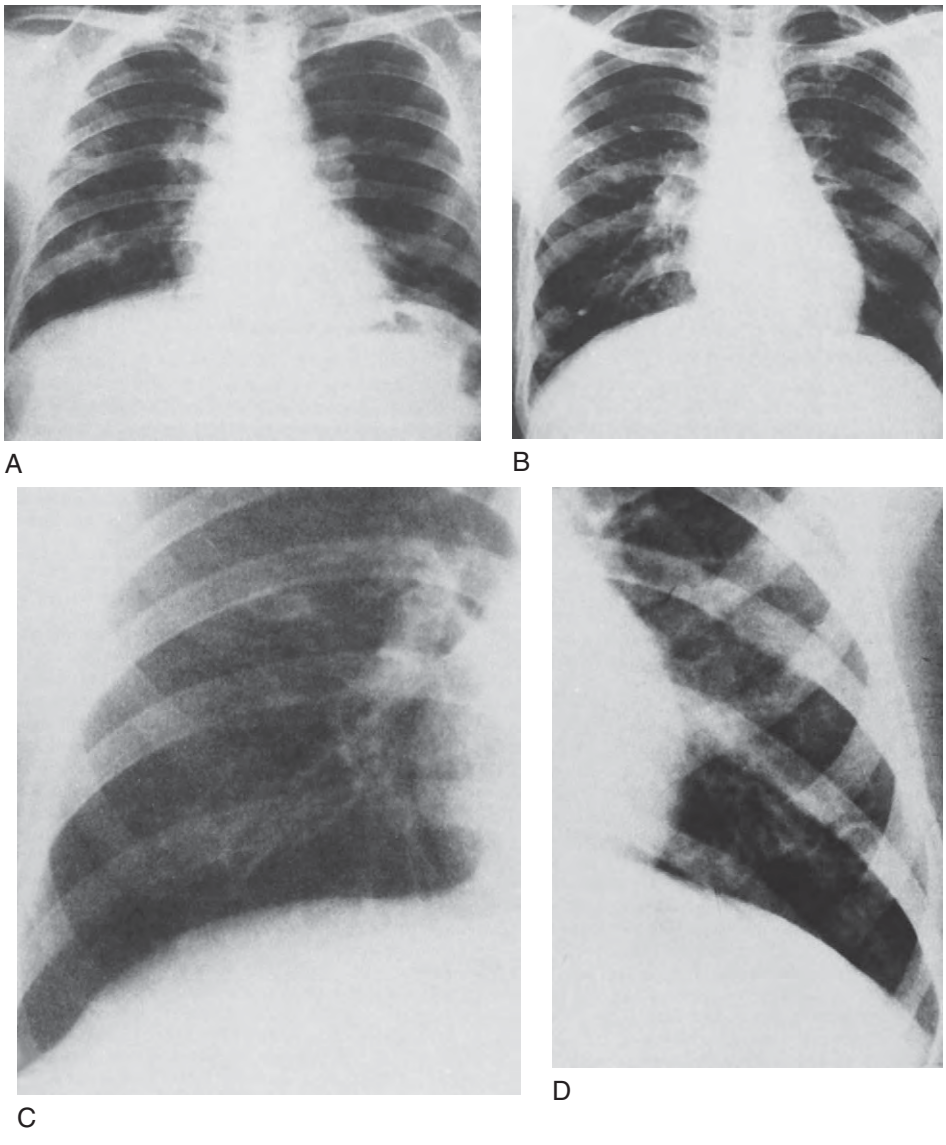

Figure 43-8 Chest radiographs from four different Korean adults with *Paragonimus westermani* infection. **A,** Multiple cystic cavities of 1 to 2 cm are seen in the right midlung and lower lung. **B,** Aggregates of 5-mm ringlike cysts appear in the right midlung, right base, and left upper lobe (especially under the left clavicle). Older calcified lesions appear in the right lung also. **C,** A single ring shadow with medial corona is seen in the right midlung. **D,** Numerous cystic cavities, some of which show coronas as well as adjacent linear tracts representing worm burrows. (Figure reproduced from Reeder MM, Palmer PES [eds]: The Radiology of Tropical Diseases with Epidemiological, Pathological, and Clinical Correlation. Baltimore, Williams & Wilkins, 1981.)

Treatment

Praziquantel is the drug of choice for treating paragonimiasis.[160,164] Symptoms improve rapidly, and eggs typically clear from the sputum in a matter of weeks, but radiographic clearing may be slower.

STRONGYLOIDIASIS

Strongyloides stercoralis is the cause of human strongyloidiasis. *Strongyloides* has a wide geographic distribution, including most of the developing world, parts of Europe, and scattered foci in the United States, especially in the Appalachian region.[165] The clinical presentation of strongyloidiasis can vary from asymptomatic infection and mild intestinal disease to fatal disseminated disease with multiple organ involvement. Unlike other nematode parasites, *Strongyloides* larvae can mature into free-living adults in the soil; furthermore, the worms also can multiply in humans without passing through the soil or any other host via an autoinfectious cycle. The *Strongyloides* hyperinfection syndrome continues to be found in immunosuppressed older adults who were infected decades earlier as a result of serving in the military in Asia during World War II, or who have immigrated from endemic areas of Asia.[166]

Epidemiology, Risk Factors, and Pathogenesis

The *Strongyloides* life cycle is more complex than that of other nematodes. It begins when infective filariform larvae in the soil penetrate intact skin. After passive migration (via the bloodstream) to the lungs, the parasites exit the capillaries into the alveoli. After further maturation in the lung, the larvae migrate up the trachea and are swallowed. The adult females attach to the small intestine and produce eggs, which are laid in the lamina propria. The eggs hatch within the lumen of the gut, and rhabditiform larvae are excreted into the soil, where they either molt into infective filariform larvae or mature into free-living adults. The free-living adults, unique among the pathogenic nematodes, can lay eggs in the soil that will hatch into rhabditiform larvae; these larvae will subsequently molt into infective filariform larvae. The "autoinfective cycle" of *Strongyloides* arises when some of the rhabditiform larvae in the intestines or perianal area molt into filariform larvae before reaching the soil. These filariform larvae can directly reinfect the host by penetrating either the colonic mucosa or the perianal skin. It is the autoinfective cycle that is thought to be responsible for chronic infection (which can last for many decades) as well as significant illness in the subsequently immunocompromised host.

Strongyloidiasis is primarily acquired by skin contact with contaminated soil. There is no clear evidence of direct person-to-person transmission. Fecal-oral spread is thought to occur rarely.[167]

In most cases, strongyloidiasis is only mildly symptomatic. Intestinal infection is associated with congestion and mononuclear cell infiltration. There are descriptions of rare cases with sprue-like malabsorption. Migration of the larvae through the lungs may stimulate a hypersensitivity response presenting as asthma and eosinophilia (Loeffler's pneumonia).

In uncomplicated cases of chronic infection, low numbers of parasites are in equilibrium with the host. Disease is primarily abdominal and cutaneous in nature; respiratory complaints are distinctly unusual, but asthma and chronic obstructive lung disease have been reported.

The symptomatic *Strongyloides hyperinfection syndrome* occurs primarily in immunocompromised hosts. Although the hyperinfection syndrome has been associated with various malignancies, renal disease, asthma, and autoimmune diseases, in industrialized countries the majority of cases occur after corticosteroid treatment.[168,169] In areas of the world in which the human T-cell lymphotrophic virus-1 (HTLV-1) and strongyloidiasis are co-endemic (much of Africa, the Caribbean, South America, and Asia), there is an increase in the prevalence of severe hyperinfection syndrome, refractory to treatment, among persons with HTLV-1 infection.[169,170] HTLV-1 infection appears to shift the immune response toward activation of Th-1 cells, with greater production of interferon-γ and decreased production of interleukins 4 and 13. This is the reverse of the Th-2 predominant profile thought important in controlling *Strongyloides* replication and inducing anti–*S. stercoralis*–specific IgE antibody.[170] Whether *Strongyloides* infection reciprocally worsens HTLV-1 clinical disease in addition is unclear from the current conflicting data.[170] In the past, it was thought that hyperinfection primarily resulted from failure of the host response (e.g., eosinophils, IgE, mast cells) to kill migratory larvae. More recently, it has been hypothesized that hyperinfection instead may result from a direct effect of corticosteroids or HTLV-1 infection on larvae, via acceleration of molting and parasite maturation.[168-170] This theory would explain why patients with HIV infection–induced immunocompromise living in endemic areas for strongyloidiasis do not commonly develop the *Strongyloides* hyperinfection syndrome, unless treated with corticosteroids or coinfected with HTLV-1.[168-170]

Patients with the *Strongyloides* hyperinfection syndrome have massive worm burdens, with hundreds of thousands of adult parasites in the intestines.[167] The lung is the primary extraintestinal organ involved. Damage to the lung is in part mechanical. Passage of larvae from the bloodstream to the alveoli causes microhemorrhages. When there are low numbers of larvae the microhemorrhages are of little consequence. With hyperinfection and dissemination, however, innumerable microhemorrhages may lead to massive pulmonary hemorrhage, manifested as hemoptysis, pulmonary infiltrates, and respiratory distress. Because alveolar hemorrhage may occur after treatment, some have speculated that immunologic mechanisms may also be involved. Larval migration from the intestines may be associated with invasion of the bloodstream by bacteria, either because of breaks in the mucosa or in association with the parasite cuticle.

Clinical Features

Chronic strongyloidiasis may be asymptomatic. When symptoms are present, they are often nonspecific: abdominal pain, bloating, heartburn, diarrhea, constipation, and chronic urticaria.[167,171] When the filariform larvae migrate through the skin, serpiginous urticarial lesions termed larva currens may be noted. These lesions appear to reflect both direct parasite migration and an associated hypersensitivity response. Cough, dyspnea, wheezing, and fleeting pulmonary infiltrates also have been described in association with larval migration, as have asthma and chronic obstructive lung disease. Although the role the parasite plays in the pathogenesis is not clear,

strongyloidiasis should thus be considered in patients with asthma and significant concomitant eosinophilia.

The *Strongyloides* hyperinfection syndrome, which may occur days to months after the initiation of immunosuppression, primarily causes gastrointestinal and pulmonary manifestations.[167,171] In contrast to uncomplicated disease, most patients with hyperinfection do not have eosinophilia. In addition to severe abdominal pain, nausea, vomiting, and diarrhea, hyperinfection may progress to intestinal obstruction, paralytic ileus, gastrointestinal bleeding, protein-losing enteropathy, peritonitis, and shock. The pulmonary symptoms of hyperinfection are nonspecific. A minority of patients will have only bronchospasm, but most patients will have pulmonary infiltrates (which may be focal or diffuse), opacities with or without cavitation, or consolidation. Common symptoms include cough productive of sputum, hemoptysis, dyspnea, and wheezing. Respiratory failure may develop in severe cases. In nearly one third of cases, hyperinfection is accompanied by severe bacterial infections.[166,167] These infections include pneumonia, lung abscess, sepsis, meningitis, and brain abscess. The most common bacterial isolates are enteric gram-negative bacilli and group D streptococci (including *Enterococcus*).[166] The source of enteric bacteria may be damaged intestinal mucosa, organisms associated with the surface of the filariform larvae, or even organisms from the parasites' intestinal tracts. Other systems commonly affected include skin, liver, and biliary tract.

Radiographic Features

The results of intestinal radiographs are typically nondiagnostic but may show gastritis, duodenitis, and mucosal thickening, spasm, and transverse folds in the duodenum. In hyperinfection, there may be disruption of the mucosa, ulcerations, or ileus.[167]

Chest radiographs are usually normal in uncomplicated disease. In contrast, hyperinfection is usually accompanied by changes on chest radiographs.[167] Pulmonary infiltrates are typically diffuse but may be focal. Lobar consolidation may occur with or without accompanying bacterial superinfection. Some patients have localized nodules. Cavitation and abscess formation have been associated with both infiltrates and nodules.

Laboratory Diagnosis

Uncomplicated strongyloidiasis is usually diagnosed by examination of three separate stool specimens for rhabditiform larvae. Because the burden of organisms is low, larvae may be difficult to detect, however, and a positive diagnosis cannot always be obtained even with multiple specimens.[167] Additional methods of diagnosing infection include sampling of duodenal fluid for larvae (string test), duodenal biopsy, and serologic assays for antibody. ELISA titers are available from the Centers for Disease Control and Prevention.

For patients with hyperinfection, demonstration of parasites is less difficult. The key is to consider the diagnosis of strongyloidiasis in immunocompromised hosts with nonspecific symptoms. The burden of parasites in the stool is high.

Treatment

Ivermectin is the drug of choice for the treatment of strongyloidiasis.[168-173] For nondisseminated strongyloidiasis, ivermectin is given on each of 2 days; for disseminated strongyloidiasis (hyperinfection syndrome), prolonged or repeated courses of therapy may be required (data are lacking to determine the optimal regimen). Albendazole, a broad-spectrum benzimidazole antiparasitic agent, is an alternative to ivermectin.[169,171,172] The older, more toxic alternative (thiabendazole) is generally no longer recommended if ivermectin or albendazole is available.

VISCERAL LARVA MIGRANS

Migration of larvae of several nematode species through the liver, lung, and central nervous system can give rise to the syndrome of visceral larva migrans, causing pulmonary manifestations such as asthma and eosinophilic pneumonitis. Although most of the infections are due to *Toxocara canis*, the canine roundworm, a similar clinical picture can be seen with *Toxocara cati*, the cat roundworm, *Ascaris suum*, a pig roundworm, and, rarely, *Baylisascaris procyonis*, a raccoon ascarid (although the latter is much more associated with severe meningoencephalitis rather than pulmonary disease).[174,175]

Toxocara is endemic worldwide, and human toxocariasis has been recognized in nearly every country. In the United States, most of the 52 million domestic dogs are infected with *Toxocara*, usually from perinatal exposure.[176] Up to one third of puppies and dogs at any one time pass *Toxocara* ova into the soil. The eggs can withstand a wide variety of environmental conditions and remain infective for years. *Toxocara* eggs can be recovered from yards of homes, parks, and playgrounds frequented by children. The seroprevalence of antibodies to *Toxocara* in the United States is 2.8%, with rates of 4.6% to 7.3% in children aged 1 to 11 years.[177] In contrast, seroprevalence rates in developing countries are typically 50% to 80%.[176] Infection is most associated with pica and geophagia.

Epidemiology, Risk Factors, and Pathogenesis

The life cycle of *T. canis* in dogs is similar to that of *Ascaris* in humans. After ingestion of the ova, the larvae hatch, migrate through the lungs, are swallowed, and develop into adult worms in the canine intestines. Ova are shed in the stool but must embryonate in the soil over a period of weeks before they are infectious. In general, humans are infected after ingesting embryonated eggs from the soil (e.g., young children with geophagia or pica). A recent report of an adolescent with pulmonary and abdominal visceral larva migrans after ingestion of an earthworm showed that *Toxocara* eggs can be transmitted by soil-contaminated objects as well.[178] The *Toxocara* ova hatch in the intestines and penetrate the intestinal wall. Humans are an abnormal host, however, and the larvae are unable to complete their migration and maturation into adult worms. Instead, the larvae continue to migrate through the tissues of the liver, the lungs, and, to a lesser extent, the eye and the central nervous system. The larvae can continue to migrate for years within the human viscera.

Migratory larvae and their excretory products induce a strong local inflammatory response, with eosinophils as the predominant cell. Most patients also have a prominent peripheral eosinophilia. Hemorrhages may be noted at sites where the larvae exit the host venules. Asthma and urticaria are associated with an elevated IgE response. When the larvae

become trapped in the host tissues, they typically induce an eosinophilic granulomatous response, which may subsequently lead to fibrosis and calcification. Thus disease is related to both parasite migration and host inflammation.

The pathogenesis of *Toxocara* infections is thought to be related to the number of infecting organisms.[179] Thus infections with low numbers of organisms evoke only a minimal immune response. In these cases, disease may not be apparent until the larvae migrate to the eye (causing the ocular larva migrans syndrome). Heavier infections elicit a stronger host response, with larvae trapped and destroyed in the liver and lungs causing symptoms of visceral larva migrans. Rarely, as the numbers of larvae increase still further (e.g., a large inoculum in a very young child), the host is unable to trap the migratory larvae, and patients may have both visceral and ocular larva migrans.

Clinical Features

The clinical presentation of visceral larva migrans varies with the number of larvae and the organs infected. Most infected patients are asymptomatic, but some have pulmonary symptoms and signs.[174,176,178-181] Cough is the most common symptom, and wheezing is reported in over half of cases. Examination may reveal wheezes, crepitations, or signs of consolidation. One third to one half of patients have pulmonary infiltrates. Visceral larva migrans should be considered in children with asthma of unknown cause, especially with a history of pica. Eosinophilia is usually present and may be pronounced. However, recent descriptions note normal eosinophil counts in up to 27% of patients with elevated *Toxocara* titers.[180] Other common clinical manifestations of visceral larva migrans relate to involvement of the abdomen: abdominal pain, hepatomegaly, anorexia, nausea, and vomiting. Lethargy and sleep and behavior disturbances are also common. Only a minority of patients have cervical lymphadenopathy or fever.

Ocular larva migrans is generally distinct from visceral larva migrans, and takes the form of leukocoria and posterior granulomas (mimicking retinoblastoma), chronic endophthalmitis, retinal detachment, and uveitis. It is distinctly unusual to see any visceral signs or symptoms in children with ocular disease, and such patients are generally older (mean age, 8 years versus 2 years for visceral disease) and have normal eosinophil counts and lower antibody titers.

Occasional involvement of the nervous system may take the form of seizures, eosinophilic meningitis, or one of a variety of focal neurologic symptoms.[181]

Radiographic Features

The chest radiograph will be abnormal in 30% to 50% of cases of visceral larva migrans. Abnormalities are described as alveolar, interstitial, or miliary. The infiltrates may be unilateral or bilateral, patchy or diffuse. Infiltrates are often migratory. Hilar adenopathy may be present.

Laboratory Diagnosis

It is difficult to make a definitive specific diagnosis of visceral larva migrans. Definitive diagnosis requires the demonstration of larvae in biopsy specimens, especially from the liver. A presumptive diagnosis, however, can be made based on a consistent clinical picture in a child with a history of soil, grass, or feces pica. Because the human host does not allow the worms to mature, no ova are found in the stool.

Eosinophilia, hyperglobulinemia (IgG, IgM, and IgE), and elevated isohemagglutinin titers (due to worm surface components that cross-react serologically with blood-group antigens) are often found in children with visceral larva migrans. Anti-*Toxocara* antibody tests also aid in diagnosis. An ELISA assay employing *Toxocara* larval excretory-secretory antigens has been shown to be a specific indicator of *Toxocara* infection (using a cutoff of 1:32, sensitivity in visceral larva migrans of 73% to 78%, and specificity >90%).[174,179] Many of the "negative" specimens nonetheless showed low but detectable titers of antibody (1:8 to 1:16). There are some cross-reactions to other species of ascarids. A positive ELISA does not ensure that a patient's illness is due to *Toxocara*, because a small percentage of normals will also have antibody titers.

Treatment

The symptoms usually regress spontaneously over a period of months to years such that mild disease may not require specific treatment. Treatments include measures aimed at decreasing the host inflammatory response in addition to antihelminthic drugs. Antihistamines have been used to diminish symptoms in some cases. Corticosteroids may dramatically reduce pulmonary inflammation and are indicated in life-threatening infection, including severe bronchospasm and disease of the myocardium or central nervous system.

A course of oral albendazole for 5 to 21 days, often supplemented by prednisone for symptomatic children, is generally suggested for therapy of visceral larva migrans. Older alternative agents include the less bioavailable mebendazole, and the more toxic (and perhaps less effective) agents thiabendazole and diethylcarbamazine.[174,176,182,183]

OTHER HELMINTHIC INFECTIONS

Tropical pulmonary eosinophilia is one of the causes of the syndrome of pulmonary infiltrates with eosinophilia.[129,184] The disease is thought to represent an unusual immunologic reaction to the microfilariae of parasites more commonly associated with lymphatic filariasis (*Wuchereria bancrofti* and *Brugia malayi*). The clinical presentation includes cough, wheezing, and peripheral blood eosinophilia. Patients have a gradual onset of cough and paroxysms of wheezing and breathlessness mimicking asthmatic attacks. Systemic complaints can include fever, weight loss, and fatigue. Chest radiographs show increased vascular markings, diffuse interstitial nodular lesions, and mottled opacities. Pulmonary function tests usually show restrictive defects, although obstructive defects are also noted. Antifilarial antibodies are present and can be used to confirm the diagnosis. Patients usually respond to treatment with diethylcarbamazine given for 3 weeks, although several courses may be required.

Pulmonary symptoms can also be identified during larval migration through the lungs for *Ascaris lumbricoides*, hookworm, and other roundworms.[129,185] The symptoms and pathogenesis are similar to those seen with *Toxocara* infection. However, because the larvae are able to complete their normal migration, symptoms are self-limited (i.e., there is no chronic larva migrans stage), and ova do later appear in the stool. *Ascaris* infections with low numbers of organisms are usually asymptomatic. Symptoms may develop 9 to 12 days

after ingestion of large numbers of ova and include cough, chest discomfort, wheezing, and hemoptysis. Some patients have urticaria or pruritic skin lesions. Low-grade fever is common. On examination, there may be wheezing and crepitations, but signs of consolidation are absent. Chest radiographs may reveal oval infiltrates, which are migratory. Eosinophilia is characteristic. Symptoms resolve spontaneously in 5 to 10 days. Diagnosis at the time of chest symptomatology requires demonstration of the larvae in sputum or gastric aspirate, because ova passed in the stool are not produced until weeks after pulmonary symptoms resolve. Occasionally, coincidental worm migration through endotracheal tubes has been noted during induction of anesthesia in otherwise asymptomatic children (G. A. Weinberg, unpublished observations). Therapy of ascariasis is given with mebendazole for 3 days or albendazole once. After therapy, migrating worms may be expelled orally and adult worms rectally.

Schistosomiasis is caused by infection with the blood flukes *Schistosoma mansoni*, *S. japonicum*, *S. hematobium*, *S. mekongi*, and *S. intercalatum*.[129] Approximately 200 million people are infected worldwide, with endemic areas in Asia, the Middle East, Africa, and Latin America.[186] Schistosomiasis has become an infection noted in industrialized countries among returning travelers.[186-188] Human infection is acquired by penetration of the skin by cercaria released from freshwater snails. The adult worms live in the mesenteric (most species) or vesical (*S. hematobium*) venules. Disease results from a granulomatous reaction to the released, embolized eggs, resulting in portal hypertension or fibrosis of the urinary tract. Eggs may also migrate to the lungs, where chronic granulomatous inflammation may cause an obliterative arteriolitis that may result in pulmonary hypertension. Schistosomiasis is treated with praziquantel.

Rarely, the canine heartworm, *Dirofilaria immitis*, can cause solitary pulmonary nodules in humans (zoonotic filariasis), most of which are asymptomatic and often coincidentally discovered.[129,189] This infection has only been described in adults, despite the fact that pediatric contact with dogs is frequent. The clinical significance of these nodules is their frequent diagnostic confusion with malignancy; no specific antiparasitic therapy is required.

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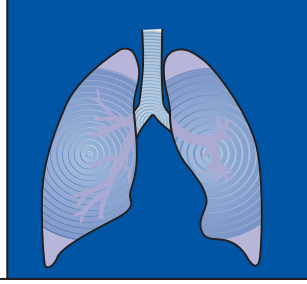

CHAPTER 44 Interstitial Lung Disease

Gregory J. Redding, Robin R. Deterding, and Leland L. Fan

TEACHING POINTS

- Many etiologies for interstitial lung disease in infants and young children do not produce inflammation or fibrosis by lung histology. In these cases, use of corticosteroid therapy may have no role.
- Genetic mutations in genes that influence surfactant metabolism, including surfactant proteins B and C and genes for ABCA3, can produce several forms of histologic interstitial lung disease.
- Noninvasive diagnostic techniques can identify a specific etiology of childhood interstitial lung disease (chILD) syndrome in up to one fourth of cases.
- Lung biopsy is the current standard for diagnosis of primary pulmonary etiologies for chILD syndrome.
- Mutations in the genes for surfactant protein C and ABCA3 proteins tend to produce severe lung disease in newborns but can also produce milder disease with onset later in childhood.

Concepts about pediatric interstitial lung disease (ILD) have undergone dramatic changes with new nomenclature and the recognition of new clinical entities not encountered in adults. In fact, the term ILD has become controversial because it includes a variety of rare and heterogeneous pulmonary disorders involving the lung parenchyma and not exclusively the pulmonary interstitium. Radiographic changes associated with ILD, including ground glass, reticular, nodular patterns, reflect alveolar, vascular, and interstitial involvement on histology. Changes in lung function associated with ILD are not specific to the pulmonary interstitium. As a result, a new term, "childhood interstitial lung disease" syndrome (chILD syndrome) has been coined to include pulmonary disorders involving the acinar regions of the lung.[1] Importantly, many of the entities included under the chILD syndrome do not result from interstitial inflammation or the propensity for fibrosis cited in adult literature.[2] Consideration of chILD syndrome is raised in children who present with acute or chronic respiratory symptoms, respiratory signs on physical examination, hypoxemia, and diffuse radiographic changes in the absence of known causes of lung disease. A combination of any three of these four features identified 91% of 336 children with ILD in a recent retrospective chart review.[3] Clinical algorithms for diagnostic evaluations have been expanded to include this broader group of disorders.

ILD in children is rare compared to other forms of pediatric lung disease and is less common in children than ILD in adults. A descriptive study from the United Kingdom estimated a prevalence of 3.6 cases per 1,000,000 children less than 16 years of age based on a survey among physicians.[4] However, the definitions and nomenclature are dated and may under-represent the true prevalence among infants and children. In contrast, Coultas and colleagues reported an incidence of ILD to be 31.5 and 26.1/100,000 per year in adult men and women, respectively, in a population-based study over a 2-year period.[5] The categories of etiologies that cause ILD in infants and children are listed in Box 44-1. This chapter focuses on primary pulmonary etiologies for pediatric ILD and chILD syndrome. It does not describe etiologies associated with known exposures such as hypersensitivity pneumonitis or radiation-induced injury, recurrent aspiration, drug responses, and pulmonary hemorrhage; nor does it address the pulmonary complications of systemic disease such as connective tissue disorders, sarcoidosis, histiocytosis, inflammatory bowel disease, or immunodeficiencies.

NOMENCLATURE AND CLASSIFICATION OF ILD IN CHILDREN

The American Thoracic Society (ATS)/European Respiratory Society (ERS) consensus statement in 2002 standardized common histologic patterns of ILD in adults.[6] However, these patterns often do not resemble pathologic features of lung tissue from infants and children with chILD syndrome. Consequently, a new histologic classification system is being developed based on review of 187 pediatric lung biopsies of children with diffuse lung disease by a pathology cooperative from 11 medical centers in North America.[7] This classification, pertaining to immunocompetent children <2 years of age, includes disorders of lung growth (e.g., pulmonary hypoplasia), lung development (e.g., alveolar capillary dysplasia), and genetic disorders of surfactant metabolism. Importantly, many of these conditions are not associated with inflammation or fibrosis, and underscore the need for a specific histologic diagnosis before considering anti-inflammatory therapy. A detailed version of this classification system is in preparation for publication. Over the last decade, conditions specific to infants and young children have been described and then

BOX 44-1 General Etiologies for ILD in Children

- Infections (viral, *Pneumocystis,* fungal)
- Inhalation injury
  - Aspiration
  - Hypersensitivity pneumonitis
- Exposures
  - Drug reactions
  - Radiation injury
- Congenital or acquired immunosuppression-associated disease
  - Post–bone marrow transplantation (noninfectious)
- Systemic diseases
  - Connective tissue disease
  - Storage and metabolic diseases
  - Post-transplantation disease
  - Leukemia, histiocytosis
  - Lymphoproliferative disorders
  - Sarcoidosis
  - Churg-Strauss vasculitis
  - Eosinophilic pneumonia
- Pulmonary hemorrhage syndromes
  - Pulmonary hemosiderosis
  - Pulmonary capillary hemangiomatosis
  - Diffuse capillaritis
- Cardiovascular disease
  - Post–pulmonary capillary obstructions, e.g., anomalous pulmonary venous return
- Structural abnormalities
  - Lymphangiectasia
  - Lymphangiomatosis
- Metabolic disease
  - Lysinuric protein intolerance
  - Lysosomal storage disease
  - Neurofibromatosis
  - Gaucher disease
  - Niemann-Pick disease
  - Farber lipogranulomatosis
  - Pulmonary alveolar microlithiasis
  - Inborn errors of surfactant metabolism

renamed after further study. Persistent tachypnea of infancy, described in 2001,[8] is likely the same condition as neuroendocrine cell hyperplasia (NEHI) syndrome, described in 2004.[9] Cellular interstitial pneumonitis (1992)[10] represents pulmonary interstitial glycogenosis, described in 2002.[11] Chronic pneumonitis of infancy (1995)[12] includes some children with underlying genetic mutations in the gene for surfactant protein C and the ABCA3 gene.[13] Notably missing is usual interstitial pneumonitis (UIP), also known as cryptogenic fibrosing alveolitis or idiopathic pulmonary fibrosis. Katzenstien described fibroblastic foci within the leading edges of the fibrotic regions in UIP from adults, but these foci have not been identified in several case series of children previously diagnosed with UIP.[14-16] Although a recent large series identified 46 children with idiopathic pulmonary fibrosis, it is unclear if this represented UIP or other forms of ILD (e.g., nonspecific interstitial pneumonitis [NSIP]), that progressed to a fibrotic stage.[17] Further prospective and retrospective reevaluation of histology in children diagnosed with UIP should resolve this controversy.

Table 44-1
Clinical Presentation of 185 Infants and Children with Interstitial Lung Disease

	All Patients	Patients Aged <2 Yr
Patients (no.)	233	58
Symptoms		
Cough	78%	73%
Tachypnea/dyspnea	76%	84%
Failure to thrive	36%	62%
Fever	16%	29%
Physical Findings		
Cyanosis	26%	54%
Clubbing	16%	9%
Crackles	47%	57%

From Clement A: Task force on chronic interstitial lung disease in immunocompetent children. Eur Respir J 24:868-697, 2004; and Fan LL, Mullen ALW, Brugman SM, et al: Clinical spectrum of chronic interstitial lung disease in children. J Pediatr 121:867-872, 1992.

In addition, different histologic diagnoses of ILD can result from a single genetic abnormality. Surfactant protein C deficiency causes pediatric ILD that can appear on histology as DIP, UIP, NSIP, or chronic pneumonitis of infancy.[18-21] Conversely, the histologic pattern of pulmonary alveolar proteinosis can result from mutations in the genes encoding surfactant B or C proteins, the ABAC3 gene, a transmembrane protein and member of the ATP binding cassette family, or the beta c chain of the receptors for GMCSF/IL-3/IL-5.[22-24] Although pulmonary histopathology remains the standard for diagnoses of ILD in children, genetic diagnoses may prove to be a more cohesive classification system for some of these disorders in the future. Further understanding as to how specific genetic mutations produce different histologic patterns of ILD will also improve the current classification system of chILD syndrome.

CLINICAL PRESENTATION AND ASSESSMENT OF SEVERITY OF ILD IN CHILDREN

Clinical symptoms at presentation include nonproductive cough, fatigue, and dyspnea with exertion, such as during feeding in infants and exercise in older children.[17,25,26] Less common symptoms include fever, wheezing, anorexia, chest pain, and poor growth. In severe cases, cyanosis and dyspnea at rest may also be present. Symptoms of chILD syndrome can begin at any age. Onset of symptoms can be acute and life-threatening, particularly in the neonatal period. Although acute ILD occurs in older children, an insidious onset of symptoms is more common in this age group and the specific onset of symptoms may be difficult to ascertain. Consequently, children may present initially with severe disease because they have adapted to the gradual progression of disease over months and years.[25-27] "Chronic" ILD has been defined as greater than 1 and 3 months' duration by U.S. and European literature, respectively.[17,28]

Common physical findings in children with ILD in two case series are listed in Table 44-1 according to relative frequencies and age at diagnosis.[17,25] Infants in particular present

with failure to thrive and tachypnea. Other reported physical findings were chest wall retractions in 22 of 48 children (46%) and wheezes in 9 children (22%).[25]

Pulmonary function and lung imaging studies are abnormal in most children with chILD. The characteristic features produced by chILD syndrome in older children are restrictive lung mechanics and hypoxemia, first evident during exercise and later at rest. Vital capacity is reduced more than functional residual capacity and residual volume.[29] Total lung capacity is therefore reduced but less so than vital capacity. Lung compliance, measured as a rightward shift in the static expiratory pressure-volume curve, is also reduced.[30] Some children have mixed obstructive-restrictive abnormalities, with reduced flows or elevated FRC. Recent data using infant lung function tests showed that infants with neuroendocrine cell hyperplasia (NEHI) have significant air trapping and reduced forced expiratory flows, whereas infants with surfactant protein C deficiency and pulmonary interstitial glycogenosis (PIG) have reduced vital capacities with minimal air trapping.[31] Hypoxemia without hypercapnia is the most common gas exchange abnormality in children with chILD syndrome. Cardiopulmonary exercise testing is useful to establish baseline functional limitations in older children when disease is mild. In adults, a simpler and useful method is measurement of oxyhemoglobin saturation during a standardized 6-minute walk test.[32] Lung diffusion capacity corrected for hemoglobin and alveolar volume may be reduced if alveolar-capillary surface area is reduced, but it also can be normal or even increased if significant pulmonary parenchymal bleeding has occurred.

Typical chest radiographic abnormalities among children with chILD include hazy parenchymal densities in reticular, nodular, or ground-glass patterns. The densities are usually bilateral and often diffuse. Normal-appearing chest radiographs have been reported in symptomatic adults and children with ILD.[33,34] However, the plain chest radiograph has been replaced by high resolution computed tomography (HRCT) as the imaging technique of choice owing to improved sensitivity in detecting disease and more precise definition of the distribution and pattern of disease. Common pulmonary patterns by HRCT in children with chILD include ground-glass densities, nodules, cystic changes, and tissue consolidation—all of which can be either patchy or diffuse.[35] HRCT scans in young children and infants who cannot hold their breath are obtained at controlled lung volumes at full inspiration and passive expiration, often under anesthesia or sedation, and in some cases while patients are intubated.[36] HRCTs at low lung volumes identify areas of air trapping, suggesting the presence of airway disease. In children with radiographic densities in dependent regions, HRCTs are obtained in both the prone and supine positions. The use of helical or spiral HRCT tailored to the size of the child and performed only in regions of interest reduces the delivered radiation dose.[37]

Among infants with severe ILD, pulmonary hypertension can be life threatening and produce refractory hypoxemia because of right-to-left shunting through the ductus arteriosus or foramen ovale. In two case series of 74 infants and children presenting with ILD, 45% had evidence of pulmonary hypertension, reflecting the insidious progression of disease and severity at the time of diagnosis.[25,26] In older children, elevated pulmonary artery pressures, measured by echocardiography, may exist during and immediately after exercise before progressing to pulmonary hypertension at rest.[38] Pulmonary hypertension may reflect, in part, the involvement of the pulmonary vasculature with an underlying disease, as is seen in connective tissue disorders. Alternatively, it reflects the extent to which the lung is involved with the underlying process and represents a marker of severity.

Assessment

The pace of evaluation and choice of diagnostic tests depends on age at presentation, immunocompetence, chronicity and severity of disease, and trend over time toward improvement. These features particularly influence the choice to use invasive techniques (e.g., lung biopsies) early. Presentation of chILD in the newborn period mandates a more aggressive approach because many infants with chILD are extremely ill and may have lethal conditions. Given the broad range of clinical considerations, there is no universally accepted algorithm for diagnosis.

Laboratory evaluations are used for two purposes: (1) to quantify functional severity, changes in severity over time, and changes in response to therapy and (2) to identify an etiology for the chILD syndrome. Spirometry and total lung volumes, diffusion capacity, exercise tests, and hemodynamic assessments are more useful to assess functional severity than to identify a diagnosis. Imaging studies are used to diagnose and assess extent of disease, identify sites to biopsy, and monitor changes in patterns and extent of disease over time. Both imaging and lung function studies are used to monitor patients with chILD syndrome but trends in these studies do not necessarily correlate with one another or coincide over time.[17] This poses a challenge of defining responses to therapy.

In contrast to the manifesting clinical features of chILD syndrome, the characteristics that portend shortened survival are symptoms and hypoxemia at rest and pulmonary hypertension.[39] Aside from neonates, age of onset of symptoms and duration of symptoms do not predict longevity, nor do physical findings of crackles, clubbing, or weight less than 5% than predicted.[39] Specific histologic diagnoses clearly influence prognosis, and values for spirometry (FVC) and lung diffusion capacity associated with ILD in adults have been used to predict survival.[40] However, functional assessments, apart from gas exchange and pulmonary hemodynamics that predict longevity, have not been described in children.

Most children with chILD who present with symptoms after 1 month of age have features of a chronic pulmonary process. Exceptions include children with pulmonary hemorrhage, acute interstitial pneumonia, and acute eosinophilic pneumonia. Among both adults and children with chronic ILD, a noninvasive evaluation followed by selective invasive techniques usually yields a specific diagnosis and minimizes the use of unnecessary procedures.[41,42] Fan and colleagues reported that one fourth of children with ILD were successfully diagnosed without use of invasive procedures.[41] The initial choice of tests follows medical history of exposure, recurrent infections, known immunodeficiencies, known underlying conditions, such as rheumatologic or oncologic disease, and past medical treatments such as radiation or

organ transplantation. A family history should include any early infant deaths, use of prolonged oxygen by family members, and any chronic childhood or adult disease. A history of extrapulmonary organ involvement, such as renal disease (Goodpasture syndrome), inflammatory bowel disease (ulcerative colitis and Crohn disease), skin rash (Churg-Strauss disease), and sinus disease (Wegener granulomatosis), may lead to diagnosis by evaluating these affected organs. Gastroesophageal reflux with or without aspiration can represent either an etiology for chILD syndrome or the consequence of increased work of breathing associated with the underlying ILD, or both.

When a diagnosis is not suggested by history, certain screening procedures are necessary to address broad categories of etiologies of chILD syndrome. An echocardiogram will identify occult congenital heart disease and obstructed pulmonary veins. An evaluation for occult congenital or acquired immunodeficiency and a screen for rheumatologic and autoimmune diseases (in older children) are necessary, as the lung may be the first organ affected in some patients. The HRCT scan may be suggestive (e.g., subpleural cysts in association with connective tissue disorders [Fig. 44-1][43]) or sufficiently characteristic to avoid a lung biopsy. Examples of the latter are bronchiolitis obliterans, lymphangiectasia, and NEHI syndrome (Fig. 44-2).[9]

When these tests are not revealing, bronchoalveolar lavage (BAL) is used to sample the lung for infectious etiologies, parenchymal cell populations, and noncellular material, such as that found in pulmonary alveolar proteinosis. A few cell types in BAL, such as Langerhans cells staining for S100 and CD1a, are pathognomonic of histiocytosis.[44] Erythrocytes and hemosiderin-laden macrophages in BAL are very suggestive of pulmonary hemorrhage but do not indicate the nature of pulmonary bleeding (e.g., vasculitis versus idiopathic etiology). Lipid-laden macrophages in BAL may be found with aspiration events but also can reflect nonspecific lung injury due to other etiologies. BAL has been most useful in immunocompromised hosts to identify common and opportunistic infections, identifying infection in 50% to 75% of patients with HIV and pulmonary symptoms.[45,46] In the future, additional markers of lung pathology in BAL, such as cytokine profiles, may direct clinicians toward specific etiologies or pathologic pulmonary processes.[47]

Lung histology remains the gold standard to make a definitive diagnosis in most immunocompetent patients with chILD. That said, up to 40% of technically adequate biopsy specimens do not reveal diagnostic characteristics.[48] With the new classification of disorders and concomitant gene testing, this percentage may be lower. In addition, new standardized methods for lung tissue processing have been described that will reduce the technical reasons for nondiagnostic results.[49] This processing includes electron microscopy to assess for ultrastructural changes consistent with genetic diseases affecting lipid and surfactant protein function. The choice of optimal site(s) for lung biopsy by the surgeon has not been studied. Fan and associates reported that among 27 patients with lung biopsies, 7/12 (58%) with single sites biopsied were nondiagnostic compared to 5/15 (33%) who were biopsied in multiple sites.[48] This was not a statistically different proportion between the groups, but a larger series may have led to different statistical conclusions. Where to biopsy and how many sites to sample remain controversial.

Transbronchial biopsy has been used to assess organ rejection in lung transplant recipients, but its use in infants and older children with chILD syndrome is less common. Video-assisted thoracoscopic surgery (VATS) has become the procedure of choice to sample lung tissue for chILD syndrome. Lung biopsies using VATS are as safe and useful as the open

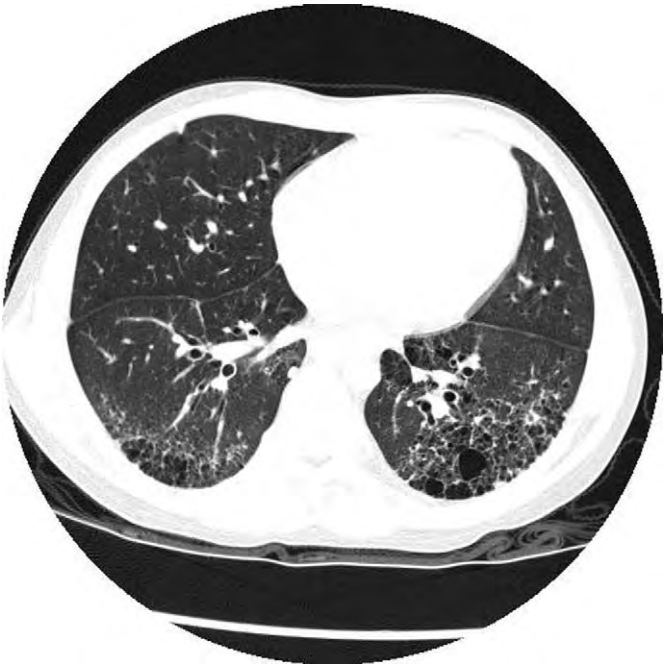

Figure 44-1 High resolution CT scan of 9-year-old girl with systemic sclerosis. The pattern is one of peripheral cystic changes in multiple lobes.

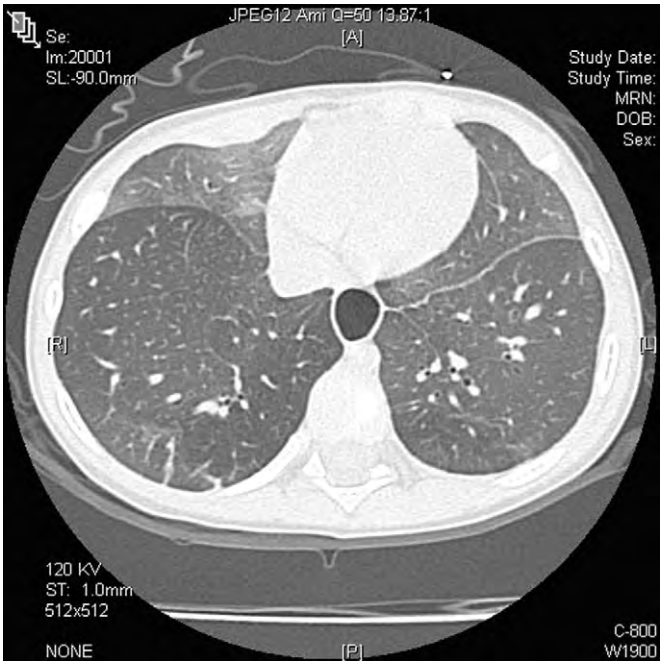

Figure 44-2 High resolution CT scan of lungs of a young child with neuroendocrine cell hyperplasia. Note the patchy nature of the ground-glass appearance characteristic of this condition.

mini-thoracotomy approach and carry less postoperative morbidity.[50] Children receiving VATS to obtain lung biopsies for chILD have reduced use of chest tube drainage and reduced length of hospital stay postoperatively compared to children undergoing open lung biopsies. The lung biopsy may transiently worsen pulmonary function as a result of the anesthesia, air leak, or bleeding in children who are severely ill.[51] However, the potential benefit, even in infants and children receiving ventilator support, may outweigh the risks.

EVALUATION OF THE NEONATE WITH chILD SYNDROME

The clinical presentation of chILD syndrome in the newborn period may be similar to that of common etiologies for neonatal respiratory distress, such as pneumonia or meconium aspiration. Some newborns develop mild to moderate chronic tachypnea and persistent pulmonary infiltrates in the first month of life, do not progress rapidly, and are diagnosed later in infancy. However, the typical neonate with chILD is a full-term neonate with persistent, severe parenchymal lung disease requiring oxygen, mechanical ventilation, or extracorporeal membrane oxygenation who does not improve. Pulmonary hypertension commonly coexists and may reflect either primary pulmonary vascular disease, the severity of the lung disease, or both. Evaluation should include family history, assessment for immunodeficiency, a search for pulmonary infection, and extrapulmonary manifestations of systemic disease. Specific entities causing severe neonatal onset of the chILD syndrome are listed in Table 44-2. Most of these entities require a lung biopsy for diagnosis despite the severity of the pulmonary disease.[52] Conditions such as surfactant B protein deficiency and alveolar capillary dysplasia are lethal newborn pulmonary entities, and early histologic diagnosis will influence philosophy of care and consideration for early lung transplantation. Tests for mutations in genes for surfactant protein B and ABCA3 should be performed early if they are to influence duration of supportive care.

Entities Producing chILD in Children Less Than 2 Years of Age

The common etiologies of chILD with onsets in children <2 years of age are listed in Table 44-2. Not all conditions are associated with an inflammatory process, and treatment of some of these disorders with steroids is neither effective nor indicated. Importantly, the prognosis varies greatly among these entities despite the fact that they are clinically similar. Gene analysis of ABCA3 and SPC mutations suggests that the age at clinical presentation may dictate the prognosis of the child, with more severe disease developing in the neonatal period. Currently there are no predictable genotype/phenotype relations, although cases with combinations of mutations in both SPC and ABCA3 genes reportedly lead to more severe disease.[13] The list also includes disorders of the pulmonary vasculature and pulmonary lymphatics. Brief summaries of some of the conditions producing chILD in neonates, infants, and children less than age 2 are listed subsequently.

Alveolar capillary dysplasia (ACD) with or without misalignment of pulmonary veins is a uniformly fatal condition manifesting in the newborn period with refractory severe pulmonary hypertension, diffuse radiographic infiltrates, and in some cases, with other congenital anomalies of the heart, duodenum, eye, and spleen.[53] In the more than 100 reported cases in the literature, this disorder has been uniformly fatal despite mechanical ventilation, inhaled nitric oxide, and extracorporeal membrane oxygenation (ECMO).[54] "Prolonged" survival of several months on intensive supportive care has been described.[55] Diagnosis is made at autopsy or with lung biopsy. In five reported families, multiple children have been born with ACD, suggesting a rare familial form.

Surfactant protein B deficiency manifests in the newborn period and is almost always fatal within the first few months of life despite intensive supportive care and exogenous surfactant replacement. The only current effective therapy is lung transplantation. There are many mutations of the gene

Table 44-2
Entities Causing chILD in Children <2 Years of Age

	Onset	Inflammatory Cells	Mortality*	Clinical Course
Neonatal Onset chILD				
Alveolar dysplasia	A	–	100%?	Pro
Alveolar/capillary dysplasia	A	–	100%	–
Surfactant protein B gene mutations	A	+/–	95%+	–
ABCA3	A/C	+/–	Variable	Per/Pro
Pulmonary interstitial glycogenosis (PIG)	A/C	–	16%	Imp
Pulmonary hypoplasia	A/C	–	Variable	Per/Imp/Pro
Pulmonary venous disease	A/C	–	Variable	Per/Pro
Pulmonary hemorrhage	A	+/–	Variable	Rec/Per/Pro
Onset in Infancy and Older				
Chronic pneumonitis of infancy	C	+	33%+	Per/Pro
Neuroendocrine cell hyperplasia (NEHI)	C	–	0%	Imp
Follicular bronchitis	C	+	0%	Per/Imp
Surfactant protein C gene mutations	C	+	Variable	Per/Pro
Diffuse capillaritis	A/C		Variable	Per/Pro/Imp

*Without lung transplantation.
A, acute; C, chronic; chILD, childhood interstitial lung disease; Imp, Improving; Per, persistent; Pro, progressive; Rec, recurrent.

on chromosome 2 that reduce its transcription or compromise intracellular transport of the gene product into lamellar bodies. The 121ins2 mutation is most common, accounting for 65% to 75% of mutations.[56,57] Surfactant protein B deficiency is transmitted as an autosomal recessive disorder. There are case reports of transient surfactant protein B deficiency and a mutation that did not reduce the protein enough to cause lung disease later in childhood.[58,59] However, the most common presentation is acute severe neonatal respiratory distress with diffuse ground-glass densities on chest radiographs similar to IRDS and, less frequently, neonatal pneumothoraces.[60] The histology includes extracellular material which stains positively with periodic acid–Schiff stain, consistent with alveolar proteinosis, type II pneumocyte hyperplasia, and interstitial inflammation and fibrosis.[22,61] Genetic testing for this disorder should be conducted on any neonate with a diagnosis of congenital alveolar proteinosis.

ABCA3 gene mutations are associated with severe neonatal chILD syndrome and also chronic ILD which can be either mild or severe in older children. The gene for ABCA3 on chromosome 16 contains 30 exons and encodes a large protein with 170 amino acids. The ABCA3 transmembrane protein is highly expressed in alveolar type II cells and localizes to lamellar body membranes. Missense, frame shift, insertion, and splice site mutations have all been described.[62] ABCA3 mutations are transmitted as an autosomal recessive trait. Disease onset in the neonatal period occurs hours to days after birth and progresses to death within a month despite intensive supportive care.[63] The clinical presentation in neonates is similar to surfactant protein B deficiency. One case out of 16 reported in the newborn period survived and was followed through age 6 years with chronic lung disease.[63] Histology in neonatal lungs includes hyperplasia of alveolar type II cells, accumulation of alveolar macrophages and proteinaceous material in the airspaces, and interstitial thickening—previously diagnosed as neonatal DIP or pulmonary alveolar proteinosis. Lamellar bodies are abnormal, small, and densely packed on electron microscopy of lung tissue.

In contrast to the neonatal presentation, Bullard and coworkers described 11 older children with ABCA3 mutations who had milder ILD.[64] Seven had symptoms as neonates, two within the first year of life, but two with onset of symptoms at 5 and 7 years of age. HRCT scans demonstrated nonspecific diffuse ground-glass densities. Four of the 11 had lung biopsies consistent with DIP. Ten of the children had a common missense mutation (E292V). Older children with chILD who have ABCA3 mutations or surfactant protein C deficiency present similarly.

Pulmonary interstitial glycogenosis (PIG) has been described in 12 infants presenting with radiographically diffuse infiltrates, chronic tachypnea, cough, and wheeze beginning between birth and 1 month of life in both premature and full-term infants.[11,10] Two of 12 children died but the others improved gradually over a period of 6 to 18 months. Three children assessed at age 6 years were asymptomatic with normal exercise tolerance but required intermittent inhaled therapy. PIG is also associated with neonatal lung injury such as bronchopulmonary dysplasia but is not encountered on lung biopsies after 6 months of age (C. Langston MD, personal communication). HRCT patterns have diffuse nonspecific densities. Previously described as *cellular interstitial pneumonitis of infancy,* Canakis and colleagues found abnormalities on lung biopsies consisting of spindle-shaped histiocytic immature interstitial cells containing mono-particulate glycogen, and diffuse interstitial thickening but no inflammation or collagen deposition.[11] Mature lymphocytes occur in small numbers within the interstitial spaces. The typical histologic appearance of PIG is depicted in Fig. 44-3. The condition may be a developmental adaptation to lung injury. Treatment is supportive, although bronchodilators and corticosteroids have been used empirically.

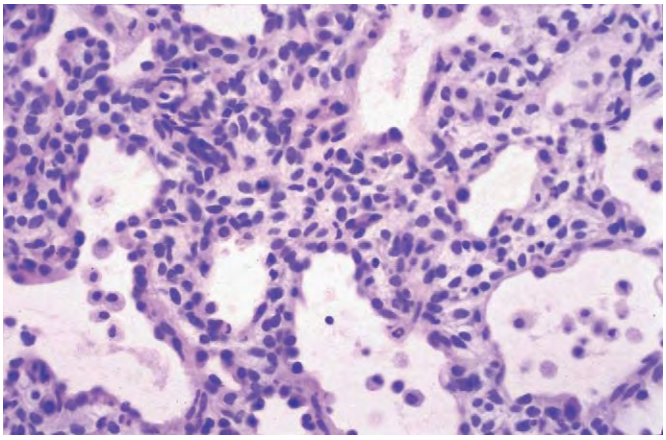

Figure 44-3 In pulmonary interstitial glycogenosis, alveolar walls are widened by a proliferation of glycogen containing bland interstitial cells with round to ovoid nuclei and clearing to bubbly cytoplasm on routine hematoxylin and eosin stain. The alveolar epithelium is not generally hyperplastic.

Chronic pneumonitis of infancy begins 2 weeks to 9 months after an uneventful birth and neonatal course. It produces chronic cough, tachypnea, and respiratory distress associated with ground-glass densities, consolidation, and hyperinflation on a chest radiograph.[12] HRCT findings, limited to a few case reports, show diffuse ground-glass appearance.[65] Lung biopsies in Katzenstein's original series were obtained at 2 to 16 months. Histologic features are portrayed in Fig. 44-4 and

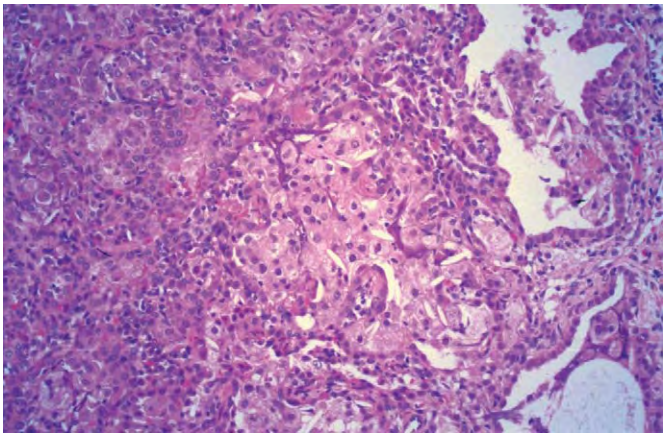

Figure 44-4 Chronic pneumonitis of infancy is one of the histologic patterns associated with surfactant dysfunction mutations in Sp-C and to a lesser extent in ABCA3 deficiency. It is characterized by diffuse alveolar epithelial hyperplasia and lobular remodeling with the addition of mild interstitial inflammation and occasional cholesterol clefts and eosinophilic hyaline globules in airspace. All of these features, except for the hyaline globules, are seen in this image.

include striking cellularity, with pneumocyte hyperplasia in the alveolar septa and macrophages in the air spaces. Multifocal alveolar proteinosis-like material also fills the airspace. Reported outcomes include 9 children in the original description, several individual case reports, and a series of 12 children with autopsy findings.[12,66,67] Mortality is at least 33% if not higher. Of the four children followed up to 3 years after biopsy, all had significant persistent respiratory impairment.[12] Genetic testing was not performed in the original series, but the pathology is similar to changes associated with ABCA3 and surfactant C protein gene mutations.

Neuroendocrine cell hyperplasia of infancy (NEHI) manifests in infancy with tachypnea, crackles, hypoxemia, and hyperinflation on physical examination and chest radiograph. It can manifest in the first week of life or within the first two years of life.[9] The HRCT of NEHI is almost pathognomonic (see Fig. 44-2). Biopsies of both the lucent and dense areas show remarkably normal lung, which may lead one to believe that diseased lung was missed at the time of sampling. However, with Bombesin staining, hyperplasia of neuroendocrine cells along the distal airways and in aggregates in the lung parenchyma are identified.[9] This is illustrated in Figure 44-5. NEHI persists over years and improves gradually, but is not responsive to prolonged steroid therapy. Fatalities have not been reported despite clinically severe pulmonary manifestations.[9] Supportive care with oxygen is indicated, particularly at night and with intercurrent illness. Previously called *persistent tachypnea of infancy*, the pathogenesis of NEHI is not understood.

Follicular bronchitis of infancy has been reported in 13 cases from two series of children.[68,69] Some investigators believe this is part of the continuum of lymphoproliferative disorders that include lymphocytic interstitial pneumonitis (LIP).[16] Symptoms of cough and tachypnea develop by 4 to 6 weeks of age in most cases and persist for years. Chest radiographs have diffuse infiltrates and hyperinflation. Lung biopsies show follicular lymphocytic infiltrates around and invading bronchial walls but no alveolar or interstitial cellularity or fibrosis. Children do not respond to steroid therapy despite the presence of lymphocytes on lung biopsy.[68] No one died in these two series and most children improved dramatically between 3 to 4 years of age. The longest reported follow-up in three patients, age 8 to 15 years, revealed mild to moderate obstructive lung disease by spirometry and persistent crackles on examination.[69]

Surfactant protein C deficiency results from missense and frameshift mutations in a 6 exon gene located on chromosome 8.[23,62] These mutations result in abnormal processing of the pro-SPC protein after transcription, leading to accumulation of pro-SPC within the cell and absent SPC production and secretion. SPC deficiency has produced ILD in all age groups including severe neonatal lung disease consistent with alveolar proteinosis.[22] Unlike surfactant protein B deficiency or mutations in the ABCA3 gene, surfactant protein C deficiency in newborns may not be as lethal a condition and the lung disease may clinically improve over time with chronic respiratory support (R. Deterding, personal communication); however, it is more commonly diagnosed in infants and older children than in newborns. SPC mutations are inherited as an autosomal dominant trait with variable penetrance. In one family kindred of 97 members, 14 people had ILD with a single mutation.[20] The lung disease on histology appeared as usual interstitial pneumonitis (UIP) in adults and nonspecific interstitial pneumonitis (NSIP) in two children who were 4 and 17 months old. Two adults in this kindred with the mutation had no respiratory symptoms, demonstrating incomplete penetrance. SPC deficiency has also been associated with lung histology in children consistent with DIP and chronic pneumonitis of infancy.[19,21] Clinical and radiographic features of SPC deficiency in infants and older children are indistinguishable from children with ABCA3 mutations and both gene studies should be obtained in this age group.

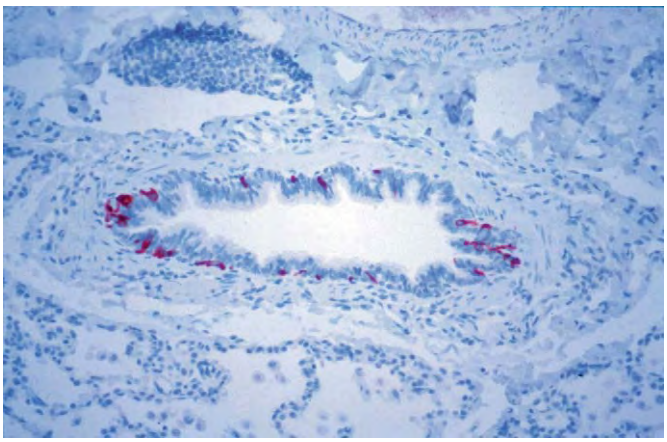

Figure 44-5 In neuroendocrine hyperplasia of infancy (NEHI) the lung histology is near normal; only immunostaining for neuroendocrine cells, here with immunostain for Bombesin, shows the increased numbers of neuroendocrine cells in clusters in bronchioles.

Interstitial Lung Disease Common to Adults and Children

Several forms of ILD described in the ATS/ERS Consensus Statement on ILD are common to both adults and children. They include lymphocytic interstitial pneumonitis, cryptogenic acute interstitial pneumonitis (Hamman-Rich syndrome), desquamative interstitial pneumonitis, organizing pneumonia, and nonspecific interstitial pneumonitis.[6] Despite identical histology, certain clinical characteristics differ between adults and children.

Lymphocytic interstitial pneumonitis (LIP) is a distinct form of ILD that can occur at any age alone or in conjunction with an underlying disorder. Familial forms of LIP have been reported.[70] LIP represents a form of lymphoproliferative pulmonary disease rather than a primary inflammatory or fibrotic process and it occurs in conjunction with congenital or acquired immunodeficiency, autoimmune disease, and dysproteinemia.[71] Clinical features of LIP are identical to other chILD conditions but are also associated with features of underlying conditions, for example,. weight loss and lymphadenopathy in HIV infection. Radiographic features on HRCT include ground-glass densities, reticulonodular or nodular densities, and (less often) bronchovascular thickening and thin wall cysts. Histologic features of the lung include diffuse infiltrates of B and T cell lymphocytes within the interstitial spaces, along lymphatics, and occasionally around airways.

Nodules of cells with germinal centers and noncaseating granulomas can also be seen. Pulmonary fibrosis rarely develops. The lymphocytes are usually polyclonal but oligo- and monoclonal populations can occur, suggesting malignant potential.[72]

LIP has been associated with Epstein-Barr virus in the lungs and by serology among children with HIV infection and following organ transplantation without HIV.[71,73] Among patients with HIV infection, noninfectious interstitial pneumonitis is presumed to be LIP and biopsy may not be necessary for diagnosis.[74] Whether EBV contributes to the lung pathology or dictates the clinical course of LIP is unclear.[73,75] LIP occurs in up to 30% of children with perinatal acquisition of HIV infection and manifests 5 to 60 months after birth.[76] LIP can improve, persist, or progress, and can be fatal. LIP is responsive to corticosteroids in many cases but controlled therapeutic trials have not been performed. The prognosis among children with LIP in the absence of immune defects has not been described.

Acute interstitial pneumonitis (AIP) is an acute and rapidly progressive form of parenchymal lung disease that results from diffuse alveolar damage. Very little has been published about AIP, specifically in children. It is strikingly similar to the fibrotic phase of adult respiratory distress syndrome (ARDS) but without a known inciting event (e.g., sepsis). Histologic features include temporally homogeneous lesions with hyaline membrane remnants, fibroblast proliferation, mononuclear cell infiltrates, and increased collagen deposition. It differs from acute eosinophilic pneumonia where eosinophils predominate.[77] Up to 25% of adults have a subacute course with symptoms developing over a period of more than 30 days—similar to the original case reports of Hamman and Rich.[78,79] Mortality is 70% for adults; similar data are not published in children. There are no proven therapies for this disorder.

Desquamative interstitial pneumonitis (DIP) has common histologic features among adults and children but different predisposing circumstances and different prognoses. The clinical presentation is similar to other etiologies of the chILD syndrome. Findings on HRCT are reticular or ground-glass densities that can be diffuse or regionally distributed, often in a basal or peripheral distribution.[80] Lung biopsies show a consistent pattern of airspaces filled with alveolar macrophages (previously considered epithelial desquamation [erroneously]), thickened alveolar septa, scattered mixed inflammatory cells, and minimal fibrosis.

In adults, DIP is associated with smoking and respiratory bronchiolitis-associated interstitial lung disease (RBILD).[81] Some experts consider these entities to represent a continuum of the same condition. DIP is considered relatively benign with a better prognosis than other etiologies of ILD in adults.[82] In contrast, DIP is not associated with smoking in children, can occur in families, and carries a high mortality rate, particularly in children with onset of symptoms in the first year of life.[26] The recent association of DIP with surfactant protein C deficiency and mutations in the ABCA3 gene may explain why DIP in infants is so much more severe.[21,64] Clinical improvement in response to corticosteroid therapy occurs short-term in almost one half of children.[25] However, mortality among children is 50% among 42 reported cases and higher among children with familial DIP.[83]

Cryptogenic organizing pneumonia (COP) was previously known as bronchiolitis obliterans and organizing pneumonia (BOOP). It occurs in both adults and children, and is usually associated with infections, drug exposure, myelodysplastic syndromes, bone marrow transplantation, or autoimmune disease.[84-86] In the largest series of 112 adults with COP, King and coworkers reported dyspnea, cough, and restrictive lung disease in one half of the patients. Fever and elevated erythrocyte sedimentation rate were common.[87] HRCT features are different from other radiographic features of the chILD syndrome, with patchy focal or bilateral consolidation that can migrate, ill-defined nodules, or a reticular pattern.[88] The histopathologic features include organization of the alveolar spaces and respiratory bronchioles with a fibromyxoid appearance and temporally uniform features, suggesting response to a single insult.[89] COG carries a good prognosis and is steroid responsive in adults and in the majority of case reports of children.[86,90]

Nonspecific interstitial pneumonitis (NSIP) was recognized by the ATS/ERS classification of interstitial lung disease as separate from UIP/IPF in 2002.[6] NSIP differs from UIP primarily because its histologic pattern is temporally homogeneous, unlike UIP, which has lesions in various stages of fibrosis. However UIP and NSIP have been diagnosed in the same patients with multiple biopsies.[91] NSIP has either cellular or fibrotic predominance on biopsy. The cellular form is associated with up to 80% improvement on therapy in adults; the fibrotic NSIP carries a progress of 45% survival over 5 years.[92] Both the cellular and fibrotic forms have been described in children.[16] NSIP is a prevalent form of ILD in adults. However, it is rare in children and there are insufficient numbers of cases to describe prognosis or responses to therapy. NSIP has been associated with surfactant protein C deficiency in several children but mutations have not been evaluated in most reported cases.[18] NSIP also occurs with a variety of underlying conditions, including occupational or drug exposure, and collagen vascular diseases (dermatomyositis, polymyositis, and systemic sclerosis).

THERAPY

Specific therapies for chILD syndrome clearly relate to the etiology identified for a particular patient, and vary from anti-infective and immunosuppressive agents to observation and supportive care. In patients with pulmonary alveolar proteinosis, lung lavage is still the treatment of choice with or without subcutaneous or aerosolized GM-CSF.[93,94] Interventions should also include alterations in the environment if the environment is contributing to the disease (e.g., hypersensitivity to bird antigens). Importantly, in those conditions where inflammation does not exist, the use of agents such as corticosteroids may create or increase rather than reduce morbidity.

In all cases, supportive care should include reducing irritant exposure (e.g., tobacco smoke, immunization against preventable infections, and assurance of adequate nutrition, sleep, and oxygenation). Models of care for idiopathic chILD should include a team approach to chronic severe lung disease in centers that can provide serial physiologic and radiographic assessments in addition to supportive care. Psychosocial support of families, genetic counseling, and

serial nutritional assessments are all necessary for most patients.

The most common treatment of ILD in children remains corticosteroids, administered orally or by monthly intravenous delivery.[95,96] The latter treatment was initially reported for treatment of adults with ILD in 1982 and has been extended to children with ILD using 15 to 30 mg/kg/day of methylprednisolone administered monthly. The period of time between intravenous treatments may be lengthened when improvement occurs.[95,96] There is some evidence that higher dose parenterally administered corticosteroids may more effectively reduce neutrophilia in the lung when inflammation is present.[96] In addition, intravenous intermittent steroid therapy may reduce the severity of side effects associated with prolonged use of high-dose oral corticosteroids. When oral steroids are used, an initial dose of 2 mg/kg/day twice daily is used for 3 to 6 months as a therapeutic trial, despite anticipated side effects. Choices about route, initial dose, and duration of therapy are at best empirical because no controlled studies of children with the chILD syndrome have been conducted to assess the efficacy of different regimens for different clinical entities.

In addition, the amount of improvement may be modest and slow in developing on corticosteroid treatment alone, and a choice between magnitude of improvement and development of therapy-induced side effects will influence considerations for further drug therapy. Reducing the dose of oral corticosteroids when improvement has reached a plateau is equally empirical. Equally important is a reduction in corticosteroid dosage when no improvement has occurred. There are reports in children of rapid steroid weaning leading to flares of disease activity that are not easily reversed.[27] Cautious reductions in steroid therapy are, therefore, prudent.

Hydroxychloroquine has been used as a second line agent when corticosteroids produce significant morbidity or minimal improvement and as a concurrent first line agent in children who are very ill.[97] Hydroxychloroquine is preferred to chloroquine to minimize the risk of retinopathy associated with both drugs.[98] As with corticosteroids, no placebo-controlled trials have been conducted and experience with this agent remains anecdotal, based on case reports.[99] The dose used initially is 5 to 10 mg/kg/day and trials of therapy usually last 3 to 6 months.[30] Additional anti-inflammatory immunosuppressive agents that have been used in selected cases include azathioprine, cyclophosphamide, methotrexate, cyclosporine, rituximab, and chlorambucil. All have been used empirically when corticosteroid therapy is ineffective and all produce unpredictable results.

Lung transplantation is a last treatment option when chILD syndrome is severe and disease is progressive or life threatening. It has been used successfully in neonates with otherwise lethal surfactant B protein deficiency and in children with progressive DIP and NSIP.[100,101] Survival is variable and is complicated by problems with recurrent infections, post-transplantation lymphoid proliferative disease, and bronchiolitis obliterans.[102] The report of the International Society for Heart and Lung Transplantation in 2005 noted that 6% of children less than 1 year of age and 9.6% of those 1 to 10 years of age who received lung transplantation did so as treatment for interstitial pneumonitis and/or pulmonary fibrosis.[103] The 50% survival time for all children with lung transplantation was 4.7 years and a 50% survival time after the first year of 7.5 years.[103] These figures have improved steadily over the last decade and are likely to improve in the future.

Acknowledgment

We wish to thank Dr. Claire Langston for providing the photographs of different histopathologic patterns included in the chapter.

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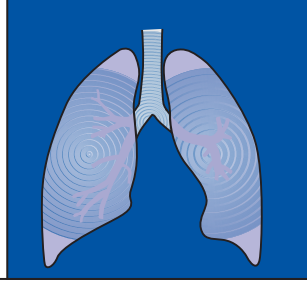

CHAPTER 45 Eosinophilic Lung Diseases and Hypersensitivity Pneumonitis

Ariel Berlinski and John L. Carroll

TEACHING POINTS

- Nonparasitic eosinophilic lung diseases (ELDs) are rare in children.
- Diagnostic criteria include: peripheral eosinophilia and pulmonary infiltrates; eosinophilia on bronchoalveolar lavage (BAL); eosinophilia in lung biopsy (gold standard).
- Development of acute respiratory failure of unknown etiology should prompt early aggressive investigation
- Most ELDs respond well to corticosteroid therapy.

In hypersensitivity pneumonitis (HP)

- High degree of suspicion and thorough environmental exposure history are required to make the diagnosis.
- Pediatric HP is mainly due to exposure to avian and fungal antigens.
- Treatment consists of allergen avoidance and, in some cases, corticosteroids.
- Pediatric HP has an excellent outcome.

EOSINOPHILIC LUNG DISEASES

Eosinophilic lung diseases (ELDs) encompass a wide variety of disorders that feature eosinophilic infiltration of airways, alveoli, or the interstitium of the lung. These different entities can be diagnosed by (1) presence of peripheral blood eosinophilia and the presence of infiltrates on a chest radiograph; or (2) elevated percentage of eosinophils in bronchial lavage fluid; or (3) the presence of eosinophils on lung biopsy.[1,2] Although initially termed "pulmonary infiltrates with eosinophilia," the use of bronchoalveolar lavage (BAL) as a diagnostic tool broadened the spectrum of diseases, and subsequent reports described tissue infiltration with or without peripheral blood eosinophilia.[3] Therefore, a normal eosinophil count in peripheral blood does not exclude the diagnosis of ELD. Moreover, there are cases reported of tissue infiltration with normal radiologic findings.[4] The most common ELDs include simple pulmonary eosinophilia, chronic eosinophilic pneumonia, acute eosinophilic pneumonia, Churg-Strauss syndrome, idiopathic hypereosinophilic syndrome, asthma, allergic bronchopulmonary aspergillosis, bronchocentric granulomatosis, parasitic infections, and drug reactions.[2] Nonparasitic eosinophilic lung diseases are rare in childhood.[1]

Classification

Since its initial description by Löffler and subsequent reports by Crofton and colleagues and Reeder and associates in 1952, several classification schemes have been reported.[3,5,6] The fact that the presence of eosinophils either in blood or in lung tissue is the common denominator between all of these different diseases makes classification problematic. The initial classification by Crofton divided ELD as follows: (1) simple pulmonary eosinophilia; (2) prolonged pulmonary eosinophilia; (3) pulmonary eosinophilia–associated asthma; (4) tropical eosinophilia; and (5) pulmonary eosinophilia with asthma and polyarteritis nodosa.[6] More recently, Cottin and coworkers presented a classification that divided ELD into those of undetermined cause, those of a determined cause (mostly infectious and drug related) and a third group of miscellaneous with possible associated eosinophilia.[7] Alberts presented another classification based on the location of the disease; ELDs were classified as either airways or parenchymal disorders.[8] In Table 45-1 we present a combination of those two recent classifications.

Pathophysiology

To understand the eosinophilic lung diseases, it is necessary to understand the pathophysiological role played by eosinophils in these disorders. Eosinophils are derived from pluripotential $CD34^+$ precursors in the bone marrow. Several cytokines have been shown to be important in this process, including interleukin-3 (IL-3), interleukin-5 (IL-5), and granulocyte-macrophage colony-stimulating factor (GM-CSF). Interleukin-5 is the most specific and is also known as eosinophil-differentiation factor.[9] Once released to the circulation in mature form, eosinophils migrate to the target organs. This process involves the adhesion of the eosinophils to the endothelial cells via the interaction with selectins and integrins. Chemoattractant mediators stimulate diapedesis to the tissues where IL-3, IL-5 and GM-CSF generated by T cells are critical for activation and survival. Eotaxin-1 and eotaxin-2 have been reported as being eosinophil-specific chemoattractant agents. Eosinophils can survive for extended periods of time, depending on the local conditions.[10] Once activated, eosinophils are responsible for the release of proinflammatory cytokines, arachidonic acid–derived mediators, enzymes, and reactive oxygen species. The activation in the

target tissue of the eosinophils results in the release of several proteins including major basic protein, eosinophilic cationic protein, eosinophil-derived neurotoxin, and eosinophil peroxidase. The eosinophilic response in the lungs may act as a double-edged sword; being beneficial during parasitic infestation but detrimental in other clinical situations, such as asthma. The antihelminthic killing properties are due to the release of cytotoxic granular contents. Interleukin-5 produced by Th2 lymphocytes plays a major role in this process.[11] A better understanding of the eosinophil physiology and the roles played by eosinophils in these disorders may allow for development of new therapeutic approaches.[10,12]

Eosinophilia is classified in different degrees of severity according to the absolute count (cells per cubic millimeter) as mild (351 to 1500), moderate (1500 to 5000) and severe (more than 5000).[10] Glucocorticoids act not only by suppressing the transcription of certain genes responsible for the synthesis of inflammatory mediators but also by inhibiting the cytokine dependent survival of the eosinophils.[13,14] Glucocorticoids are very effective in rapidly clearing eosinophils from the bloodstream. This should be kept in mind in the diagnostic process. Other therapeutic options will be discussed with each specific disease.

Table 45-1
Classification of the Eosinophilic Lung Diseases (ELDs)

ELD	Location
ELD of Known Etiology	
Eosinophilic pneumonias of parasitic origin	Parenchyma
Eosinophilic pneumonias of other infectious causes	Parenchyma
Allergic bronchopulmonary aspergillosis and related syndromes	Airways
Drug-, toxin-, radiation-induced eosinophilic pneumonias	Parenchyma
ELD of Unknown Etiology	
Idiopathic simple pulmonary eosinophilia	Parenchyma
Idiopathic chronic eosinophilic pneumonia	Parenchyma
Idiopathic acute eosinophilic pneumonia	Parenchyma
Churg-Strauss syndrome	Parenchyma
Hypereosinophilic syndrome	Parenchyma
Miscellaneous Lung Diseases with Possible Associated Eosinophilia	
Asthma and eosinophilic bronchitis	Airways
Idiopathic interstitial pneumonia	Parenchyma
Langerhans cell granulomatosis	Parenchyma
Lung transplantation	Parenchyma

Modified from Cottin V, Cordier JF: Eosinophilic pneumonias. Allergy 60(7):841-857, 2005; and Alberts WM: Eosinophilic interstitial lung disease. Curr Opin Pulm Med 10(5):419-424, 2004.

Specific Eosinophilic Lung Diseases

DRUG-, TOXIN-, AND RADIATION-INDUCED REACTIONS

Many drugs, including some drugs used to treat pulmonary conditions, can induce ELD. The mechanism is not completely clear. It is speculated that macrophages, after consuming the drugs, then act in their role of antigen-presenting cells. The antigen-receptor is then recognized by the lymphocyte CD4 and the Th2 lymphocyte T cell receptors. This leads to the release of IL-5 by Th2 lymphocytes, resulting in eosinophil production, chemotaxis to the lung, and degranulation.[15]

The following criteria are used to make a diagnosis of drug-associated ELD: (1) absence of other likely causes of lung disease; (2) presence of symptoms compatible with the suspected drug; (3) time course compatible with drug-induced ELD; (4) BAL or tissue findings consistent with drug-induced ELD; and (5) clinical improvement after discontinuation of the drug. Definite, probable, and suspected diagnoses are made when five, four, and three criteria, respectively, are met.[15,16] Bronchoalveolar lavage reveals in most cases a lymphocytic alveolitis associated with the eosinophilia.[17] The website www.pneumotox.com maintained by the Groupe d'Etudes de la Pathologie Pulmonaire Iatrogene is an invaluable resource of information of drug-associated lung disease.[18] Table 45-2 shows a list of drugs that have been reported to produce ELD.

The most common clinical presentation of drug- or toxin-induced ELD is simple pulmonary eosinophilia. Patients present with minimal or subacute symptoms, migrating infiltrates on the chest radiograph, and peripheral blood eosinophilia. In addition to cough and dyspnea, patients may also exhibit fever and/or rash. Discontinuation of exposure to the suspected offending drug or toxin results in resolution of the symptoms. On rare occasions, corticosteroids may be

Table 45-2
Drug-Induced Eosinophilic Lung Disease

More than 100 Cases Reported	Between 20 and 100 Cases Reported	About 10 Cases Reported	
Angiotensin-converting enzyme inhibitors	Acetylsalicylic acid	Beclomethasone	Mesalamine
Amiodarone	Anti-inflammatory drugs (nonsteroidal)	Chloroquine	Methylphenidate
Aurothiopropanosulfonate	Antidepressants	Cotrimoxazole	Para-(4)-aminosalicylic acid
Beta-blockers	Carbamazepine	Dapsone	Penicillins
Blood transfusions	Fenfluramine/dexfenfluramine	Desipramine	Phenylbutazone
Captopril	GM-CSF	Diclofenac	Procarbazine
Iodine, radiographic contrast media	Hydrochlorothiazide	Imipramine	Propranolol
L-tryptophan	Minocycline	Interleukin-2	Simvastatin
Methotrexate	Nilutamide	Isoniazid	Streptomycin
Nitrofurantoin	Penicillamine	Isotretinoin	Trimipramine
Phenytoin	Propylthiouracil		
	Sulfamides-sulfonamides		

Adapted from www.pneumotox.com.

required. The prognosis associated with this type of ELD with eosinophilia is excellent.

Two episodes of historical interest are the "toxic oil syndrome" and "eosinophilia-myalgia syndrome," the latter associated with L-tryptophan.[19,20] Both cases illustrate how easily toxic elements can induce ELD.

New exposure to inhaled tobacco has been associated with the development of ELD,[21] as has illicit drugs such as heroin and cocaine. More recently Schorr and colleagues reported 18 cases of acute eosinophilic pneumonia in U.S. military personnel deployed in or near Iraq. Almost all were exposed to fine airborne sand or dust and all smoked tobacco but almost 80% had recently started smoking.[22] Another case of acute eosinophilic pneumonia was reported in a firefighter who participated in the rescue efforts at the World Trade Center area on September 11, 2001.[23] Radiation therapy has also been associated with the development of ELD.[24]

ALLERGIC BRONCHOPULMONARY ASPERGILLOSIS AND RELATED SYNDROMES

Allergic bronchopulmonary aspergillosis (ABPA) occurs mainly in patients with asthma and cystic fibrosis. The disease is the result of the immune response to the presence of the fungus in the airways. Patients present with worsening of lung function and increased pulmonary symptoms such as wheezing. Laboratory findings include peripheral blood eosinophilia, elevated IgE, precipitating antibodies to *Aspergillus fumigatus*, and elevated specific IgE. Radiologic findings include central bronchiectasis and presence of infiltrates. Pathology findings include dilated airways filled with mucus plugs containing macrophages, eosinophils, Charcot-Leyden crystals, and sometimes hyphae or hyphal fragments (Fig. 45-1). Although *A. fumigatus* is responsible for most of ABPA cases, other fungi have also been associated with the syndrome. These include other species of *Aspergillus (A. niger, A. flavus,*

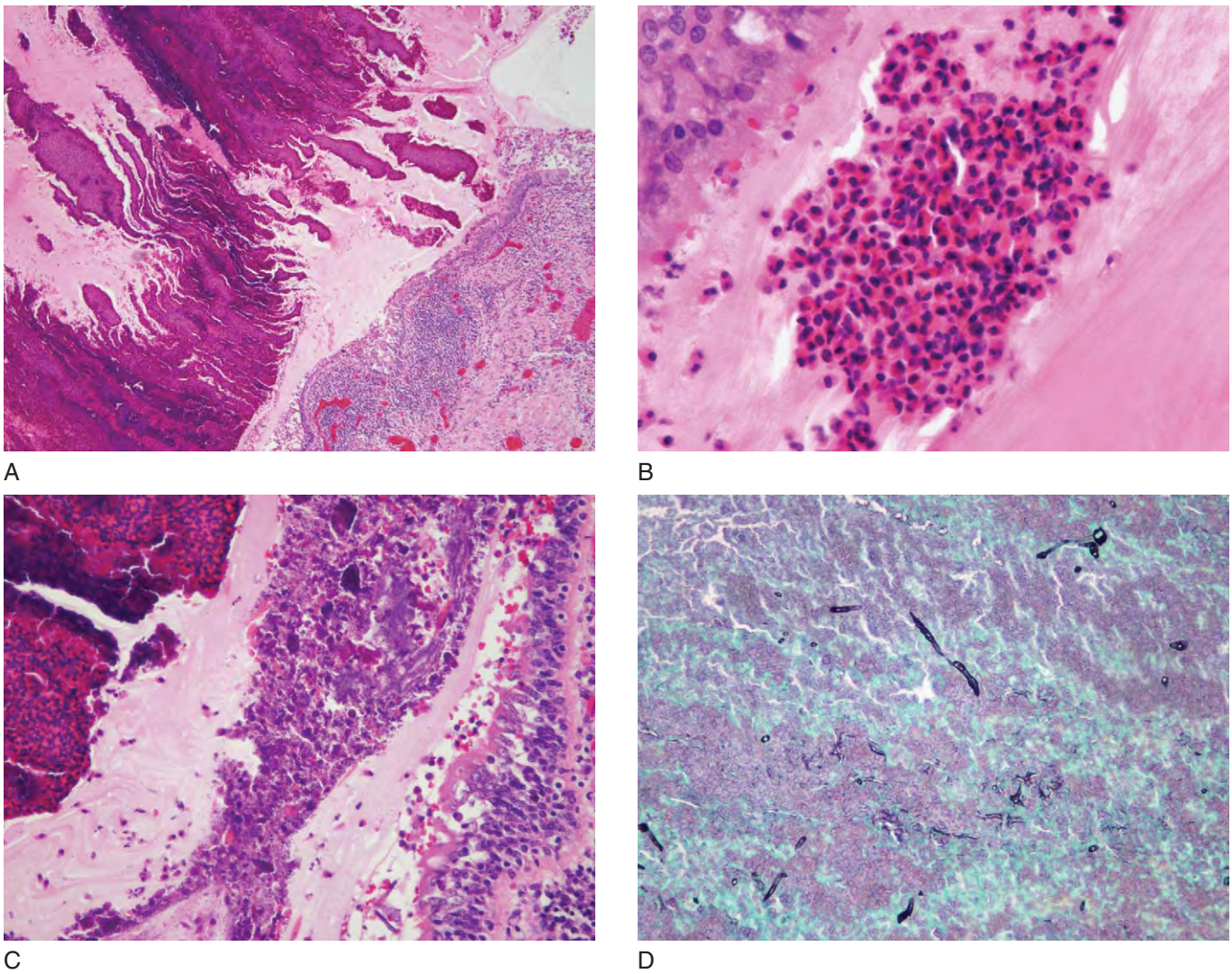

Figure 45-1 Pathology of ABPA: lung biopsy specimens. A, Eosinophilic material within the airways (hematoxylin-eosin stain). **B,** Cluster of eosinophils within mucous material in the airway at a higher power (hematoxylin-eosin stain). **C,** Mucus, cellular debris, and eosinophils within the airway lumen (hematoxylin-eosin stain). **D,** Fungal organisms within cellular debris (GMS stain). (Courtesy of Dr. Claire Langston, Texas Children's Hospital, Houston, Tex.)

A. nidulans, *A. oryzae*, or *A. glaucis)* and other fungi *(Stemphylium lanuginosum*, *Helminthosporium* species, *Candida* species, *Curvularia* species, *Schizophyllum commune*, *Drechslera hawaiiensis*, *Fusarium vasinfectum)*. Current therapy includes long-term corticosteroids and, more recently, itraconazole, which also has been shown to have steroid-sparing properties.[25] The use of itraconazole to treat ABPA in children remains controversial.

Bronchocentric granulomatosis is characterized by focal destructive granulomatous lesions that affect the bronchi and bronchioles.[26] The etiology is most commonly caused by fungi. Furthermore, some authors suggested that bronchocentric granulomatosis is a variant form of ABPA.[27] The clinical presentation is nonspecific and includes fever, cough, chest pain, and malaise. Nearly 50% are patients with asthma. There is no gender preference and the youngest case reported was 9 years of age.[27] Radiologic findings are generally unilateral and are confined to the upper lobes and include two patterns: masses and consolidation.[28] Treatment options include corticosteroids and surgical resection.

PARASITIC INFECTIONS

Many parasites have been identified as responsible for the development of ELD as a result of local action and host response. *Ascaris*, *Strongyloides*, and *Toxocara* frequently cause infection in the United States.[2] However, with the increasing ease of international travel to remote locations, a thorough travel history should be included in the evaluation of ELD.[29] Infection with more than one parasite is not uncommon. Clinical manifestations are nonspecific.

Ascaris lumbricoides infection is the most common helminthic infection in children. There have been reports of cases in the neonatal period. Symptoms are transient and usually include cough, wheezing, and fever; blood eosinophilia may last for a few weeks. The transmission takes place by ingestion of food contaminated with human feces containing parasitic eggs. Treatment is not necessary for asymptomatic patients because of the self-limiting nature of the disease. Symptomatic patients are treated with mebendazole.

Toxocara canis, a universally distributed parasite, is one of the etiologies for visceral larva migrans. The infection occurs after ingestion of eggs released by female worms in the feces of infected dogs. Children attending playgrounds where dogs are allowed and children with pica are at increased risk of infection. Most cases are asymptomatic, but some patients may present with cough, wheezes, or crackles on chest examination. Eosinophils are elevated in both peripheral blood and BAL fluid. The diagnosis is made by enzyme-linked immunosorbent assay.[30] Once the diagnosis is made, ophthalmic evaluation is warranted owing to ocular complications of *Toxocara* infection.[31] Symptomatic treatment is recommended and the use of antiparasitic agents (thiabendazole) for ELD is controversial.

Strongyloides stercoralis is acquired through the skin. The larva migrates to the airway and is then swallowed into the gastrointestinal tract where it matures into an adult worm. One unique characteristic of this parasite is its ability to remain in the host almost indefinitely—sometimes making it difficult to link the travel history with the symptoms. Patients may present with wheezing, bronchitis, and abdominal pain. Immunocompromised patients can develop a severe form characterized by gram-negative sepsis, respiratory failure, and a high mortality rate.[32] Diagnosis is made by serology and treatment is recommended with thiabendazole.

Tropical eosinophilia is caused by two filarial parasites: *Wuchereria bancrofti* and *Brugia malayi*.[33] Humans become infected through the skin by larva deposited by mosquitoes. The mature worm resides in the lymphatics, from which microfilariae are released to the lungs where an intense inflammatory reaction occurs. The interval between infection and development of symptoms may take 6 to 12 months. Patients present with fever, weight loss, malaise, cough, dyspnea, and wheezing. On physical examination crackles and wheezes are frequently heard and lymphadenopathy and hepatomegaly can be found. Diagnosis is made by serology and other laboratory findings, such as eosinophilia in peripheral blood and BAL, as well as very high IgE levels. Tropical eosinophilia is usually treated with the antifilarial antibiotic diethylcarbamazine. Corticosteroids may be required to treat allergic reactions that occur as microfilariae die.

OTHER INFECTIOUS NONPARASITIC CAUSES

Several infectious agents can cause an illness that manifests with ELD. This occurs infrequently and most of the time eosinophilic features are a minor component. Bacterial infections such as tuberculosis and brucellosis, fungal infections such as histoplasmosis and coccidiodomycosis, and viral infections have been reported in the literature to be associated with ELD.[34,35]

SIMPLE PULMONARY EOSINOPHILIA

Simple pulmonary eosinophilia was originally described by Löffler and is characterized by peripheral blood eosinophilia associated with migratory chest infiltrates and minimal symptoms.[5] Eosinophils are also elevated in BAL. The current thought is that most of the patients reported in the original series probably had a parasite-induced ELD. Currently, simple pulmonary eosinophilia is believed to be secondary to parasitic infections or drug reactions. However, in some cases, no etiology is found. Treatment is not necessary and clinical relapse is rare.[36]

IDIOPATHIC ACUTE EOSINOPHILIC PNEUMONIA

This eosinophilic lung disease was first described in 1989.[37] It manifests as an acute illness in a previously healthy individual with the potential development of respiratory failure and the acute lung injury syndrome or acute respiratory distress syndrome. Data from the largest case series reported in the literature show a mean age of 29 years, a slight male predominance, and a 40% smoking rate with most of them being recent smokers.[38-40] However, there have been cases reported of children as young as 10 months of age.[41] It has been suggested that the pathophysiology of this disease is an acute hypersensitivity reaction to an inhaled antigen.[42] The patient's previous activities should be elicited in the history-taking process including indoor renovation work, tank cleaning, smokehouse cleaning, and cave exploration. The clinical presentation includes 1 to 5 days of fever, cough, chest pain, and myalgias. This could develop into progressive respiratory distress and failure. Physical examination reveals tachypnea, tachycardia, and crackles. Chest radiograph shows bilateral infiltrates with both alveolar and interstitial opacities together

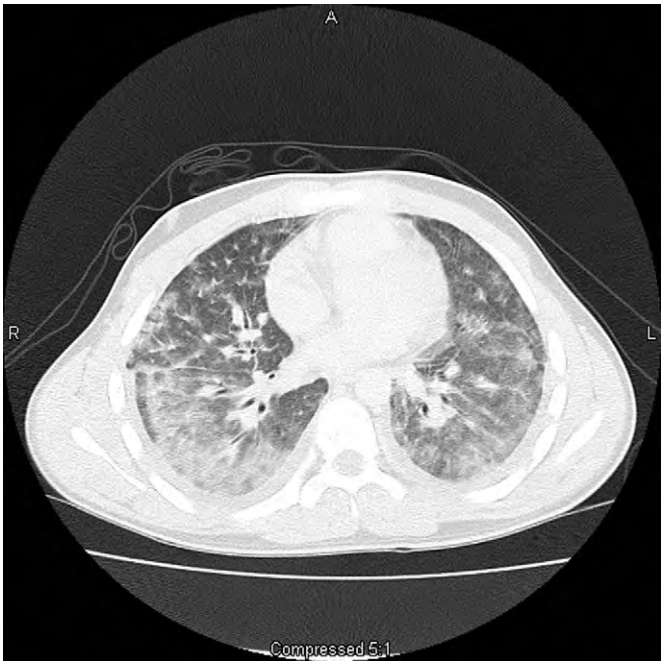

Figure 45-2 CT scan of the chest of patient with acute eosinophilic pneumonia. Note pleural effusion, ground-glass infiltrates, and alveolar opacities.

with interlobular septal thickening and pleural effusion.[43] High resolution computed tomography of the chest reveals ground-glass opacities, bilateral air space consolidation, interlobular septal thickening, nodules, and bilateral pleural effusions[44] (Fig. 45-2). Laboratory testing usually reveals a normal number of eosinophils in the peripheral blood, and a BAL with lymphocytosis, neutrophilia and eosinophilia (greater than 25%) (Fig. 45-3; Box 45-1). Patients may subsequently develop eosinophilia. The histology reveals interstitial edema and fibrin deposition, type II cell detachment from the alveolar walls but with an intact basal lamina.[45] Treatment is with corticosteroids for 2 to 4 weeks. The chest radiograph usually returns to normal after 4 weeks.[40] The disease is not characterized by a relapse, in contrast with chronic eosinophilic pneumonia.

BOX 45-1 Diagnostic Criteria for Acute Eosinophilic Pneumonia

Acute onset of fever and respiratory manifestations
Bilateral diffuse infiltrates on chest radiograph
Oxygen saturation on room air less than 90%
Lung eosinophilia with greater than 25% of eosinophils on BAL or eosinophilic pneumonia lung biopsy and absence of infection or exposure to drug that may cause eosinophilia

Modified from Cottin V, Cordier JF: Eosinophilic pneumonias. Allergy 60(7):841-857, 2005

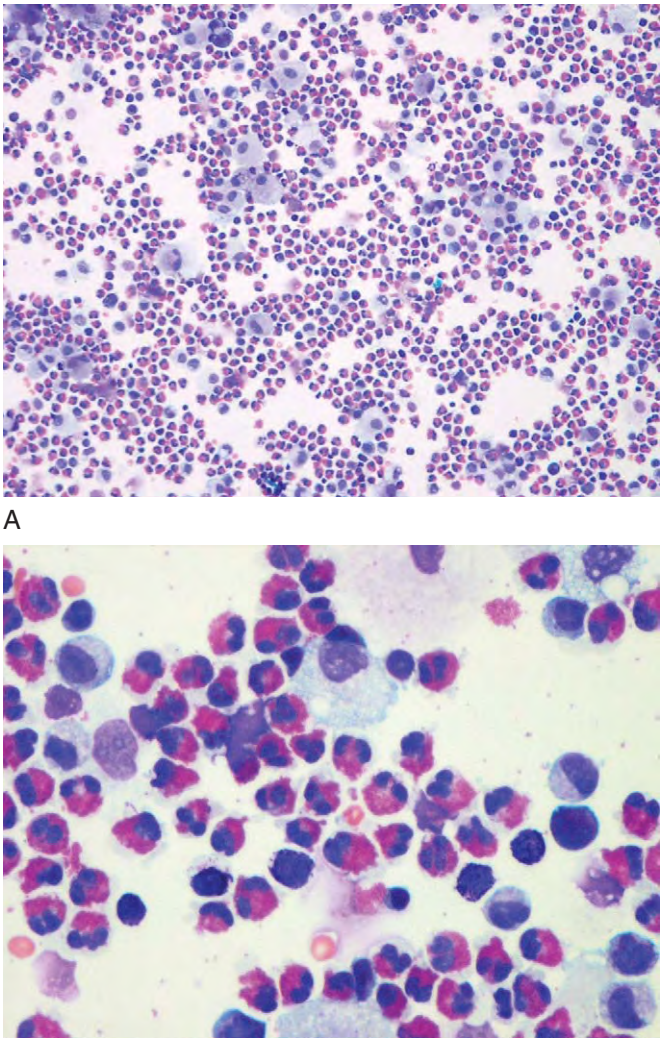

Figure 45-3 Acute eosinophilic pneumonia: BAL specimen (**A**) (Diff Quick stain). Note large amount of eosinophils surrounding alveolar macrophages. **B,** High power view of **A.** (Courtesy of Dr. Dale Ellison, Arkansas Children's Hospital, Little Rock, Ark.)

IDIOPATHIC CHRONIC EOSINOPHILIC PNEUMONIA

Idiopathic chronic eosinophilic pneumonia was first characterized in 1969 by Carrington and colleagues[46] The disease manifests more frequently in women with a 2 : 1 ratio and the mean age at presentation is 45 years. More than 50% have a diagnosis of asthma and more than 90% are nonsmokers.[47,48] However, biopsy-confirmed cases have been reported in 1- and 4-year-old children.[49,50] The clinical course is characterized by progressive onset of respiratory symptoms that include cough, dyspnea, asthenia, and weight loss. Less frequently, chest pain, malaise, and fever are seen. In adults, the mean time between onset of symptoms and diagnosis is 20 weeks. Physical examination reveals wheezes or crackles. Bilateral infiltrates were present in nearly 75% of patients with one half of them restricted to the upper lobes.[51] The classic radiographic pattern is that of a photographic negative of pulmonary edema; unfortunately this is seen in only around 25% of the patients.[48,52] The presence of migratory infiltrates increases the likelihood of making a diagnosis. High resolu-

tion computed tomography of the chest shows bilateral infiltrates mostly in the upper lobes with both peripheral ground-glass and consolidation opacities.[53] Laboratory findings include peripheral blood eosinophilia, elevated C reactive protein and erythrocyte sedimentation rate, and high levels of IgE. Markedly elevated eosinophils, usually greater than 45%, are present in the BAL. Lung biopsy shows eosinophilic infiltration of both alveoli and interstitium. Disruption of the basal lamina is present along with intraluminal fibrosis.[54] The treatment includes prednisone, which results in a dramatic resolution of clinical symptoms and radiologic findings. Patients may require long-term steroid therapy owing to the high rate of relapse during the weaning process or after corticosteroid therapy has been discontinued. Those with a diagnosis of asthma had a lower frequency of relapse than the nonasthmatics.[55] It should be kept in mind that very little is known about this disease in children.

CHURG-STRAUSS SYNDROME

This rare systemic vasculitis was originally reported in 1951 by Churg and Strauss.[56] It is characterized by eosinophilic and granulomatous inflammation of the respiratory system with necrotizing vasculitis affecting small to medium-sized vessels. Churg-Strauss syndrome manifests exclusively in subjects with asthma, usually in their fourth decade, and it has no sex preference.[57] However, children as young as 7 years of age and in infancy have been diagnosed.[58-60] Patients with Churg-Strauss syndrome frequently present with allergic rhinitis, sinusitis, and polyps. The clinical presentation of Churg-Strauss syndrome includes asthenia, weight loss, fever, and myalgias. Dermatologic findings such as purpura and subcutaneous nodules are common. Patients also frequently present with peripheral neuropathy, abdominal pain, and gastroenteritis.[61] Cardiac involvement is often insidious but may lead to severe dysfunction if treatment is not started.

The pathophysiology of the disease remains unclear, although eosinophils have been implicated. Kurosawa and coworkers reported high levels of serum eosinophilic cationic protein and urinary excretion of eosinophil-derived neurotoxin reflecting eosinophil degranulation.[62] Kiene and coworkers reported a Th0 $CD4^+$ cytokine production pattern in T cell lines in Churg-Strauss syndrome. In addition, they reported high production levels of IL-4 and IL-13, as well as a positive correlation between IL-4 production and the eosinophil count.[63] More recently, the National Institutes of Health led a workshop that reviewed the relation between different asthma medications and the development of Churg-Strauss syndrome.[64] They were unable to find conclusive data for any of the studied agents. They speculated that the clinical improvement achieved with any of the medications allowed a decrease in the corticosteroid dose, thereby unmasking the presence of the disease. Peripheral blood and BAL eosinophilia are present. Antineutrophil cytoplasmic antibodies (pANCA) are reported in 50% and 75% of the patients, although its diagnostic value is unclear.[65] Other laboratory findings include elevated IgE and normochromic normocytic anemia. Radiologic findings are characterized by migrating pulmonary infiltrates. Pathologic findings include tissue and vessel infiltration by eosinophils, necrotizing vasculitis, and extravascular granulomas[66] (Fig. 45-4). However, lung biopsy is obtained only on rare occasions because skin lesions provide the pathologic information. The treatment is similar to that of other vasculitides and includes medium- to long-term corticosteroids. If symptoms are not controlled with corticosteroids, cyclophosphamide can be added. Other medications such as methotrexate and azathioprine have been used.

Hypereosinophilic Syndrome

Hypereosinophilic syndrome is a term coined in 1968 to refer to a heterogeneous group of diseases characterized by persistent eosinophilia of unknown origin complicated by end organ damage.[67] The hypereosinophilic syndrome diagnostic criteria are (1) peripheral blood absolute eosinophil count greater than $1500/mm^3$ for at least 6 months; (2) lack of evidence of parasitic or other recognized causes of eosinophilia; and (3) symptoms and signs of organ system involvement.[68]

Katz and colleagues in a recent review reported an age of presentation ranging from $5^1/_2$ months to 16 years, with a mean of 8 years with a slight predominance of males (55%).[69,70] Symptoms included fever, arthralgias, fatigue, rash, and cough. The heart and the lungs were involved in 71% and 55%, respectively.[69] Of note, nearly 20% of the cases were associated with chromosomal abnormalities. Treatment modalities included corticosteroids, vincristine, 6-mercaptopurine, hydroxyurea, and others—with corticosteroids used in 84% of the patients.[69] More recently, two major disease variants have been described in the adult literature; these are termed *lymphocytic hypereosinophilic syndrome* (LHS) and the *myeloproliferative hypereosinophilic syndrome* (MPHS).[71] The MPHS variant is now viewed as a myeloproliferative disorder with overlap with chronic eosinophilic leukemia. In this group, some patients have been characterized by the presence of FIP1-L1-platelet derived growth factor receptor α chain mutation and good response to imatinib mesylate (tyrosine kinase inhibitor).[72] A pediatric case in a 6-year-old boy was recently reported.[73] The LHS variant is seen as a clonal expansion of $CD3^-CD4^+$ T cells associated with hyperproduction of IL-5.[74] The mean survival from diagnosis to death was reported as $10^1/_2$ months with an overall mortality of 60%.[69]

Clinical Approach to Eosinophilic Lung Disease

Most of the time clinicians are asked to see patients with ELD in consultation. We have shown the heterogeneity of the diseases that are included in the designation of ELD. Therefore, a more systematic approach to the evaluation should be taken (Fig. 45-5). If the patient presents with acute respiratory failure, BAL can lead to a diagnosis of idiopathic acute eosinophilic pneumonia. If the patient presents ambulatory, the evaluation starts with a thorough travel history (past and present), a detailed drug history (both prescription, over the counter and illicit) and an environmental (including pets) history. Any preexisting conditions should be noted (e.g., asthma, allergies, cystic fibrosis).

Minimal evaluation includes complete blood count, C-reactive protein, erythrocyte sedimentation rate, serology for *Toxocara* and *Strongyloides*, stool for ova and parasite, imaging studies (chest radiograph and HRCT of the chest). Other tests are performed based on any individual risk assessed by

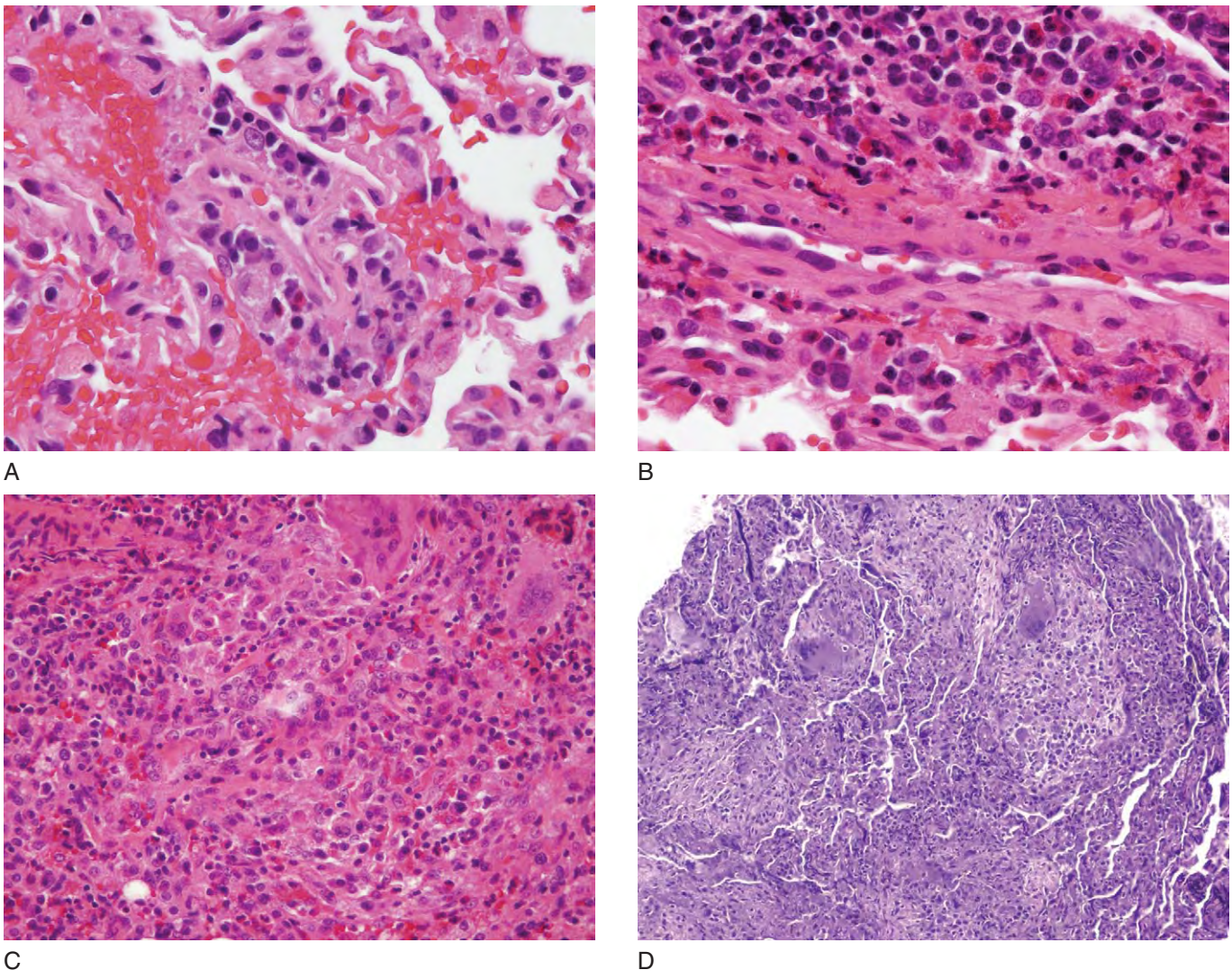

Figure 45-4 Pathology of Churg-Strauss syndrome: lung biopsy specimens. A, Lymphocytic and plasma cell infiltration (hematoxylin-eosin stain). **B,** Lymphocytic, eosinophilic, and plasma cell infiltration (hematoxylin-eosin stain). **C,** Lung biopsy specimen. Note lymphocytic and multinucleated giant cells (hematoxylin-eosin stain). **D,** Poorly formed granuloma without any organisms (acid-fast stain). (Courtesy of Dr. Claire Langston, Texas Children's Hospital, Houston, Tex.)

history. Bronchoscopy with BAL constitutes an invaluable tool in the diagnosis of ELD.

Hypersensitivity Pneumonitis

Hypersensitivity pneumonitis (HP) is an under-recognized immune-mediated lung disease resulting from recurrent inhalation of organic antigens (Table 45-3). The disease has been mainly reported in adults with occupational exposure to antigens, whereas cases reported in children typically involve avian and fungal antigens resulting from residential exposures to pet birds (such as pigeons, parakeets, and cockatiels), and contaminated humidifiers with molds. Several cases have been reported in adults after exposure to hot tubs, indoor swimming pools, and water-damaged buildings.[75] Hypersensitivity pneumonitis, also known as extrinsic allergic alveolitis, was originally described by Ramazzini in 1713 in his book *Diseases of Workers*.[76] That was the first description of what is now called *farmer's lung*. In 1932, Campbell made the first report in modern medicine. Three decades later pigeon breeder's lung was reported in the United Kingdom and the United States.[77,78] The first pediatric case was reported by Stiehm and coworkers in 1967.[79] There has been a case report on an infant as young as 10 weeks old.[80] Since the initial report, 119 cases have been reported in children (Table 45-4).[80-124]

It is estimated that 5% to 15% of exposed persons will develop HP.[125] The development of the disease in exposed subjects is the result of a combination of host susceptibility, antigen characteristics (especially particle size), intensity and length of antigen exposure, host immune response, and modulatory factors.[126-129] The adult literature reports that HP occurs mostly in nonsmokers.[130]

Almost 300 years after the first clinical report, its pathophysiology is not fully understood.[126-128] After a sensitized subject inhales the antigen, immune complexes are formed with precipitating antibodies (IgG) (type III reaction of Gell and Coombs) and the complement cascade is activated. This

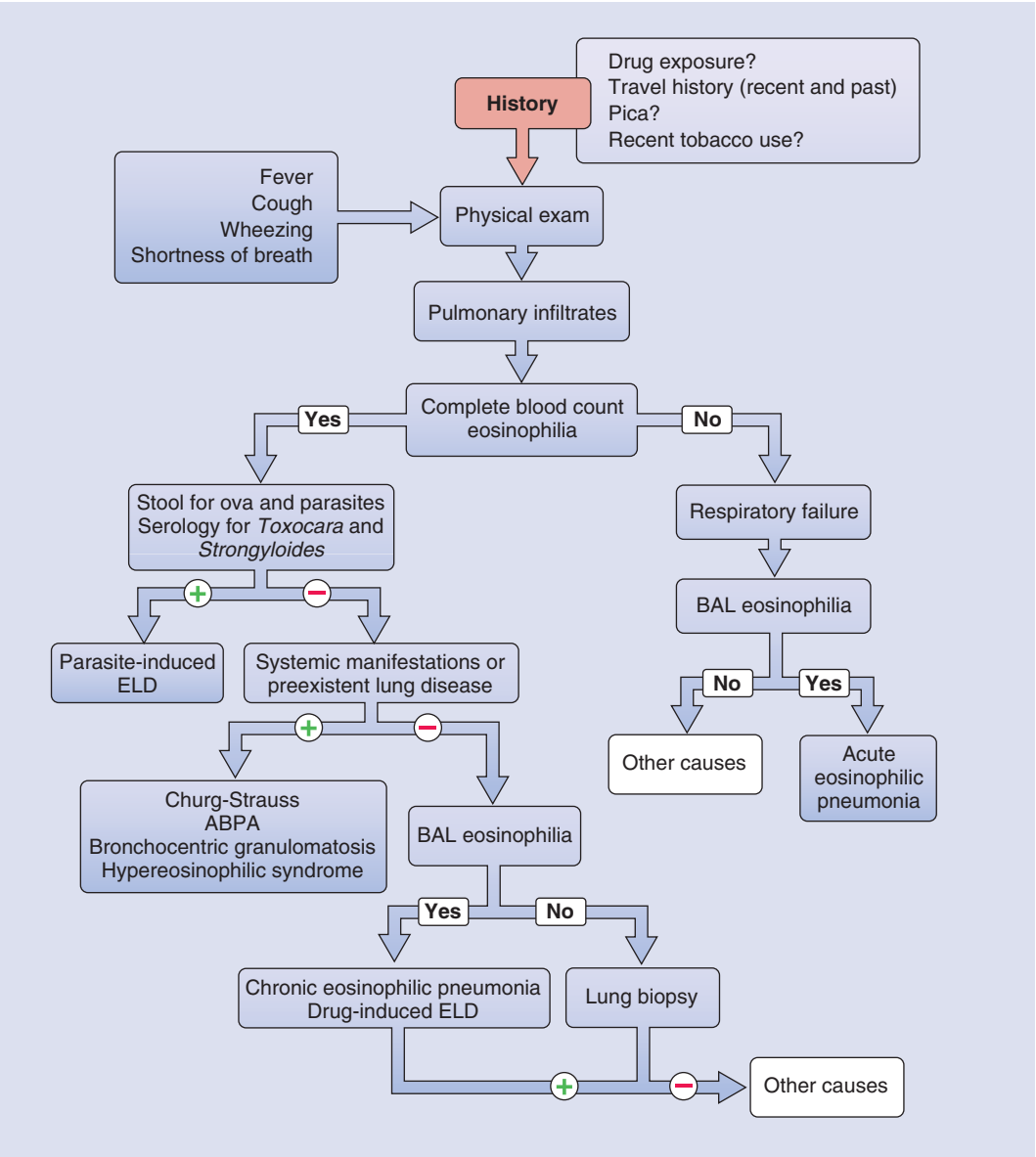

Figure 45-5 Clinical approach to eosinophilic lung disease (ELD). ABPA, allergic bronchopulmonary aspergillosis; BAL, bronchoalveolar lavage. (Modified from Oermann CM, Panesar KS, Langston C, et al: Pulmonary infiltrates with eosinophilia syndromes in children. J Pediatr 136[3]:351-358, 2000.)

leads to a transient neutrophilic alveolitis that is responsible for the acute respiratory symptoms.[131] This event is followed by an influx of activated $CD8^+$ T cells that is followed by an increase of $CD4^+$ T cells.[132] Activated macrophages produce proinflammatory cytokines such as TNF-α, IL-1, and IL-8. The lymphocytic reaction (type IV of Gell and Coombs) is also associated with granulomatous inflammation in the distal airways and alveoli. Although both acute and chronic forms of HP in adults are associated with NK lymphocytosis, the former manifests with $CD4^+$ and the latter with $CD8^+$ cells.[128]

In childhood, the mean age of presentation is approximately 9.7 years and there is a 1.4 : 1 male to female ratio.[79-124,133,134] Seventy-seven percent of reported pediatric cases are caused by exposure to bird antigens (pigeons, doves, parakeets, parrots, and others) and 22% are caused by exposure to molds (*Aspergillus*, *Penicillium*, *Micropolyspora faeni*, *Micromonospora vulgaris*, *Fusarium napiforme*, and others).[79-124]

In a recent study of adults with HP the following were found to be predictors of disease: (1) exposure to a known offending antigen; (2) positive precipitating antibodies to the offending antigen; (3) recurrent episodes of symptoms; inspiratory pulmonary crackles on physical examination; (4) symptoms occurring 4 to 8 hours after exposure; and (6) weight loss.[135] The exposure to a known offending antigen provided an odds ratio of nearly 40. These predictors were validated in 216 patients and retained their accuracy.

Radiologic findings have been found to correlate with pulmonary function in HP. Ground-glass opacification on HRCT correlates with lung restriction and reduction in lung compliance and diffusing capacity.[136-138] Mosaic perfusion patterns and air trapping correlate with increased residual volume.[127,136-138]

Table 45-3
Etiologic Agents in Hypersensitivity Pneumonitis

Antigen	Antigen Source	Typical Disorder
Animal Products		
Avian serum proteins: pigeon, dove, parrot, cockatiel, parakeet	Droppings	Bird-breeder's lung, pigeon breeder's lung, etc.
Duck proteins	Feathers	Duck fever
Turkey proteins	Turkey products	Turkey handler's disease
Chicken proteins	Chicken products	Chicken plucker's disease
Bovine and porcine proteins	Pituitary snuff	Pituitary snuff taker's disease
Rat serum proteins	Rat urine and droppings	Rat lung, laboratory animal worker's lung
Actinomycetes- and Fungus-Laden Vegetable Products		
Thermophilic actinomycetes *(Micromonospora faeni, Thermoactinomyces vulgaris), Aspergillus* species	Moldy hay	Farmer's lung
Thermophilic actinomycetes (*Thermoactinomyces)*	Moldy pressed sugar cane	*Bagassosis sacchari, T. vulgaris*
Thermophilic actinomycetes (*M. faeni, T. vulgaris*)	Moldy compost	Mushroom worker's disease
Penicillium frequentans	Moldy cork	Suberosis
Aspergillus clavatus	Contaminated barley	Malt worker's lung
Cryptostroma corticale	Contaminated maple logs	Maple bark disease
Alternaria species	Contaminated wood pulp	Woodworker's lung
Thermophilic actinomycetes (*Thermoactinomyces, Cephalosporium* species, amebas	Contaminated humidifiers, dehumidifiers, and air conditioners	Humidifier lung *Candida, T. vulgaris, Penicillium* species
Bacillus subtilis	Contaminated wood dust in walls	Familial hypersensitivity pneumonitis
Penicillium casei, Penicillium roqueforti	Cheese casings (mold)	Cheese washer's lung, cheese handler's lung
Rhizopus species, *Mucor* species	Contaminated wood trimmings	Wood trimmer's disease
Saccharomonospora viridis	Dried grasses and leaves	Thatched roof disease
Streptomyces albus	Contaminated fertilizer	*Streptomyces* hypersensitivity pneumonitis
Cephalosporium species	Contaminated basement (sewage)	*Cephalosporium* hypersensitivity
Pullularia species	Sauna water	Sauna taker's disease
B. subtilis enzymes	Detergent	Detergent worker's disease
Mucor stolonifa	Paprika dust	Paprika splitter's disease
Insect Products		
Acarus siro (mite)	Dust	–
Sitophilus granarius (wheat weevil)	Contaminated grain	Miller's lung (wheat weevil disease)
Chemicals		
Altered proteins or hapten protein conjugates	Toluene diisocyanate (TDI)	TDI hypersensitivity pneumonitis
	Trimellitic anhydride (TMA)	TMA hypersensitivity pneumonitis
	Diphenylmethane diisocyanate (MDI)	MDI hypersensitivity pneumonitis
	Heated epoxy resin	Epoxy resin lung
Other Agents		
Coffee dust	?	Coffee worker's lung
Hair dust	Animal proteins	Furrier's lung

Modified from Salvaggio JE: J Allergy Clin Immunol 79:558-571, 1987; and Fink JN: J Allergy Clin Immunol 74:1-10, 1984.

The disease manifests in three clinical forms: acute, subacute, and chronic. However, the reported pediatric literature does not clearly distinguish between these different clinical forms. Acute HP presents 4 to 6 hours after an intense exposure to the antigen. Patients develop a flu-like syndrome with fever, chills, cough, myalgias, and malaise. Acute HP is often initially misdiagnosed as infectious in nature. Physical examination reveals an ill-appearing child with dyspnea and bibasilar crackles. Symptoms usually subside after 24 hours, provided the patient is not re-exposed to the antigen. Laboratory results reveal leukocytosis with neutrophilia, elevated C-reactive protein, and erythrocyte sedimentation rate. The chest radiograph reveals bilateral reticulonodular infiltrates, more evident in the lower lung zones. High resolution CT of the chest shows ground-glass appearance and poorly defined centrilobular nodules.[139] Pulmonary function tests reveal hypoxemia and a restrictive lung disease pattern with increased elastic recoil and decreased diffusing capacity.[140] Radiologic abnormalities were found in 85% (100 out of 118) of reported pediatric cases.[79-124] Treatment of the acute form consists of avoidance of the offending antigen—although corticosteroids may be helpful in severe cases. Radiologic studies and pulmonary function tests should become normal after a few weeks, provided the subject is not re-exposed to the antigen

Subacute HP is the result of repeated low-dose exposures to an antigen, and is even more challenging to diagnose. Systemic (low-grade fevers, arthralgias, myalgias, and fatigue) as well as recurrent respiratory symptoms (exertional dyspnea, cough, sputum production, wheezes, crackles, rhonchi) are present.[141] This presentation is often misdiagnosed as asthma or bronchitis. Micronodular infiltrates and areas of mild fibrosis may be seen on radiographic and HRCT studies. Exertional hypoxemia may be present as well as restrictive changes in pulmonary function testing. Laboratory tests may show an elevated C-reactive protein and erythrocyte sedimentation rate. Lymphocytosis with a normal $CD4^+/CD8^+$ ratio, elevated natural killer cells, and increased expression of human leukocyte antigen-DR were found in BAL of children diagnosed with subacute HP.[119] Moderate abnormalities were also found in biochemical and physical surfactant properties.[142]

Table 45-4
Hypersensitivity Pneumonitis Reported in Children

Patient demographics	Mean age: 9.7 ± 4 years old (n = 103)
	Age range: 0.5 to 17 years old
	Male : female 1.4 : 1 (n = 117)
Etiology (n = 119)	Birds: 77%
	Mold: 22%
	Other: 1%
Signs	Crackles: 71% (n = 78)
	Clubbing: 33% (n = 36)
	Hypoxemia: 84% (n = 67)
Symptoms	Cough: 97% (n = 99)
	Exercise intolerance: 97% (n = 92)
	Weight loss: 89% (n = 64)
	Fever: 74% (n = 68)
Ancillary testing	Abnormal chest radiograph: 85% (n = 118)
	Precipitins: 91% (n = 115)
	Erythrocyte sedimentation rate: 34 mm (n = 53)
	FVC: 52 ± 20% predicted (n = 72)
	FEV_1: 54 ± 20% predicted (n = 44)
Treatment	Antigen avoidance: 99% (n = 111)
	Corticosteroids: 60% (n = 119)
Outcome (n = 114)	Improved: 98%
	Deteriorated: 2%

n, number of reported cases for which information was available.
Data from references 79-124.

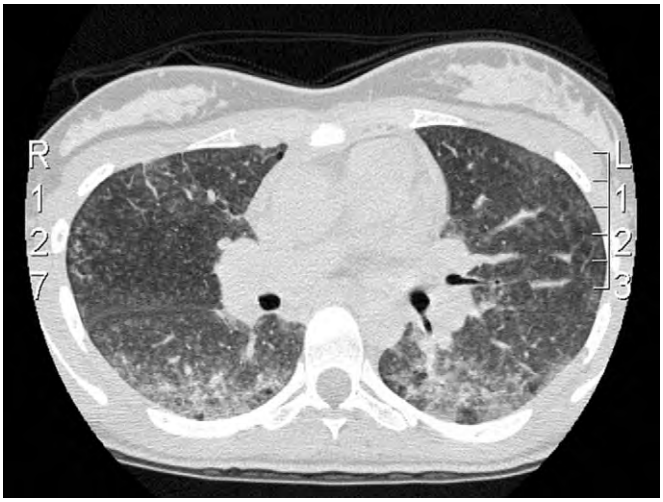

Figure 45-6 CT scan of the chest of patient with hypersensitivity pneumonitis. Note centrilobular nodules, patchy ground-glass infiltrates, and irregular linear opacities. (Courtesy of Dr. Leland Fan, Texas Children's Hospital, Houston, Tex.)

Approximately 5% of adult patients with HP will develop chronic HP,[143] which is characterized by progressive cough, dyspnea on exertion, anorexia, weight loss, and malaise. Physical examination shows crackles and clubbing in 71% and 33% of the affected children, respectively.[133] Chest imaging shows diffuse reticular infiltrates, fibrosis, patchy ground-glass opacities, and centrilobular nodules[144] (Fig. 45-6). Honeycombing is seen in advanced lung disease. Antigen avoidance remains the mainstay of treatment, but 60% of the patients were also treated with corticosteroids.[79-124,134] In patients with chronic HP, even with antigen avoidance and corticosteroid treatment, improvement in pulmonary function may require many months of treatment. The overall prognosis is excellent with only a few cases reporting worsening of clinical status or death.[95]

In summary, lack of standardized antigens, incomplete understanding of the pathophysiology of the disease, and lack of validated diagnostic criteria in the pediatric population make diagnosing HP a difficult task for which a high degree of suspicion and a thorough environmental/exposure history are needed.

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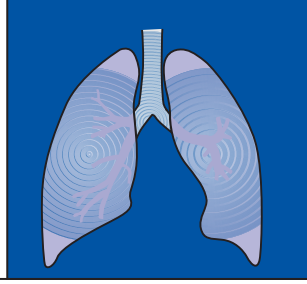

CHAPTER 46 Allergic Bronchopulmonary Aspergillosis

Richard B. Moss

TEACHING POINTS

- Allergic bronchopulmonary aspergillosis (ABPA) exists as one manifestation of a spectrum of *Aspergillus*-induced lung diseases.
- ABPA is an allergic lung disease usually caused by *Aspergillus fumigatus* in immunocompetent individuals.
- ABPA occurs primarily in patients with underlying asthma or cystic fibrosis.
- ABPA is diagnosed by a combination of clinical, physiologic, radiographic, and immunologic criteria, which differ somewhat in patients with underlying asthma or cystic fibrosis.
- ABPA is a chronic relapsing condition in most patients that requires ongoing monitoring and at least episodic treatment.
- ABPA is treated by systemic glucocorticosteroids with use of adjunctive antifungals, primarily itraconazole, in many cases.

ASPERGILLUS IN NATURE AND AS PATHOGEN

The ubiquitous dimorphic fungal genus *Aspergillus* is the only known microbe to cause both invasive life-threatening infection and hypersensitivity respiratory illness in humans.[1] Most *Aspergillus* disease is due to *Aspergillus fumigatus* (Af), but at least 17 of some 175 other species such as *Aspergillus niger*, *A. terreus*, *A. nidulans*, and *A. flavus* have been reported to cause clinical infection or allergic disease.[2-4] Airborne sampling data suggest *Aspergillus* is the most prevalent of airborne fungal spores. Af conidia produce spores of 3 to 5 μm diameter that can penetrate to distal airways, allowing the possibility of inhalational sensitization to spore antigens and/or germination into mycelial growth—if not cleared by local host defense mechanisms.

Aspergillus species grow well at body temperature, and Af can also grow well at much higher temperatures and low oxygen environments, such as those found in compost piles.[5,6] *Aspergillus* spores germinate and grow in the mycelial phase by extension of 7 to 10 μm septate hyphae that branch at an angle of 45 degrees, with Af showing the most rapid growth rates (doubling time of <50 minutes and hyphal extension rate of up to 2 cm/hour). Interestingly, Af growth in vitro is augmented in the presence of hydrocortisone.[7] *Aspergillus* spores are robustly resistant to environmental degradation owing to a dense hydrophobic outer protein layer, the pigment of which confers antiphagocytic protection.[8] Af is usually sensitive to the antifungal agents amphotericin B and itraconazole, but resistance to both has been reported.[9]

ASPERGILLUS PULMONARY DISEASE SPECTRUM

A wide variety of lung disease secondary to *Aspergillus* has been noted—in which the elements of host response seem primarily to drive clinical manifestations—with three main categories of invasive, saprophytic (mycetoma), or allergic disease.[10,11] Box 46-1 lists distinct human pulmonary disease syndromes caused by Af in different host conditions. Host defenses against Af rely primarily on innate mechanisms of immunity such as mucociliary clearance, toll-like receptor bearing monocytes-macrophages, neutrophils, dendritic and natural killer cells, collectins, antimicrobial peptides, chemokines, and cytokines.[12-15] If innate mechanisms are breached, adaptive immunity is invoked leading to antibody and cell-mediated immune responses.[16,17] Immunocompromised hosts are susceptible to saprophytic and invasive forms of aspergillosis, whereas immunocompetent hosts with impaired mucociliary clearance and/or other host risk factors are susceptible to allergic and occasionally saprophytic disease (if there has been previous cavitation). The allergic disease spectrum includes atopic sensitization with development of mold-induced asthma, hypersensitivity pneumonitis, and the complex immunologic hypersensitivity lung disease known as allergic bronchopulmonary aspergillosis. Interestingly, there are numerous case reports of overlap syndromes, suggesting a spectrum of possible disease not only between but also within subjects—for example, development of saprophytic disease (aspergilloma or mycetoma) in patients with preexisting ABPA and vice versa (Fig. 46-1).[10,11,18]

Besides the antiphagocytic spore-coating pigment, *Aspergillus* produces a wide variety of virulence factors.[19] These include a variety of secretory enzymes which may protect it from host defenses and enhance pathogenicity, such as superoxide dismutase, catalase, phospholipase, alkaline protease and elastolytic and collagenolytic metalloproteases.[20] Af proteases in particular induce both respiratory epithelial cell shedding and activation resulting in proinflammatory cytokine secretion (Fig. 46-2)—likely mechanisms allowing penetration of Af antigens into the submucosa where the adaptive immune response may be induced or amplified.[21-23]

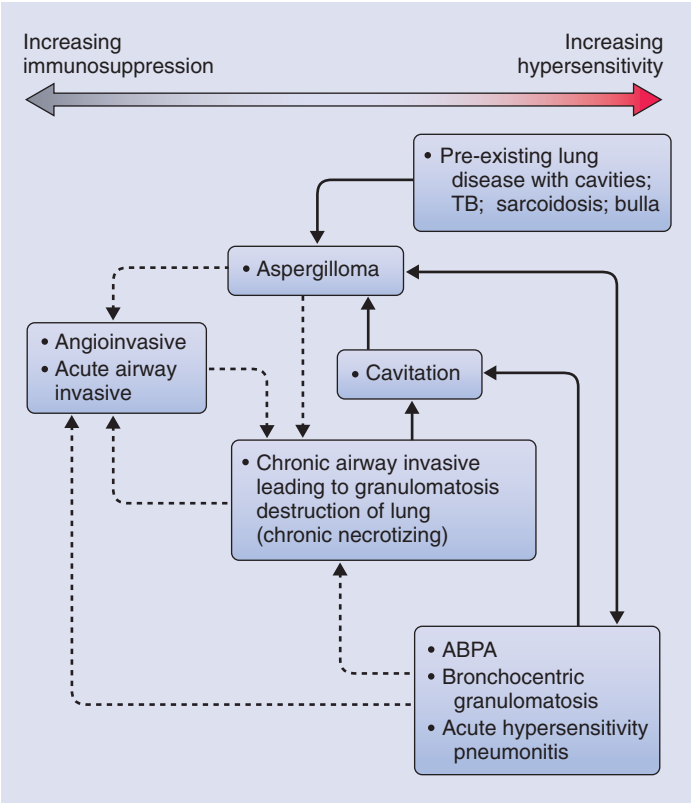

Figure 46-1 Relation of various, potentially coincident, forms of *Aspergillus* lung disease. ABPA, allergic bronchopulmonary aspergillosis. (Redrawn from Buckingham SJ, Hansell DM: Aspergillus in the lung: Diverse and coincident forms. Eur Radiol 13:1786-1800, 2003.)

BOX 46-1 Spectrum of Lung Diseases Caused by *Aspergillus* Species

Saprophytic: structurally damaged host (bronchiectasis, cavities, necrotic tissue)
- Aspergilloma (mycetoma): cavitary colonization and growth, IgG antibodies
- Chronic necrotizing aspergillosis: semi-invasive, intermediate between invasive and saprophytic; chronic disease or mild immunocompromised state

Allergic: immunocompetent host
- Asthma: exposure and IgE antibodies, immediate hypersensitivity
- Allergic bronchopulmonary aspergillosis: endobronchial growth, IgE and IgG antibodies, polyclonal IgE, Th2 cellular response, eosinophilia; asthma, CF, rarely CGD, hyper-IgE syndrome
- Hypersensitivity pneumonitis (allergic alveolitis): parenchymal contact, IgG antibodies, Th1 cellular response
- Bronchocentric granulomatosis
- Eosinophilic pneumonia

Invasive: immunosuppressed host
- Angioinvasive aspergillosis; usually systemic, rare localization in less compromised host
- Acute bronchopneumonia
- Pseudomembranous necrotizing tracheobronchitis: immunosuppressed or chronic lung disease
- Invasive pleural disease

CGD, chronic granulomatous disease

ALLERGIC BRONCHOPULMONARY ASPERGILLOSIS

A form of immunologic hypersensitivity lung disease, allergic bronchopulmonary aspergillosis (ABPA) is induced by Af or occasionally other *Aspergillus* species. Rarely, non-*Aspergillus* fungi have been implicated in allergic bronchopulmonary mycoses but the pathogenetic, pathophysiologic, clinical and radiologic features are similar (Box 46-2). The disease was described by Hinson and colleagues in 1952 in asthmatics as a distinct lung disease syndrome characterized by productive cough, fever, infiltrates, eosinophilia, and growth of Af from sputum.[24] It was later recognized as a complication of cystic fibrosis by Mearns and associates in 1965.[25] Early diagnostic criteria and therapeutic strategies were worked out in patients with asthma in the 1970s and 1980s, with more recent modifications in patients with cystic fibrosis. Pathologically ABPA is characterized by one or more of the following features: mucoid impaction of bronchi, bronchocentric granulomatosis, eosinophilic pneumonia, and exudative or obliterative bronchiolitis (Figs. 46-3 and 46-4).[2] Immunologically, ABPA is characterized by local and circulating IgE and IgG Af antibodies, immediate skin test reactivity to Af, local and peripheral eosinophilia, increased serum IL-2 receptor levels, and raised total serum IgE levels.[26,27] Radiographically, ABPA is characterized by pulmonary infiltrates during the acute phase; chest CT shows segmental and subsegmental varicose or cystic bronchiectasis and mucoid impaction, and small airways may demonstrate centrilobular nodules.[10,18]

Pathogenesis of Allergic Bronchopulmonary Aspergillosis

The earliest phases of ABPA are not understood. Inhaled Af spores may germinate in static mucus plugs or bind to bronchial epithelium. In either case, if normal clearance mechanisms fail, epithelial chemokine and cytokine responses are initiated.[28,29] Af antigens are processed and presented to the adaptive immune system, and this process leads to induction of a Th2-dominated immune response as a key feature leading to clinical ABPA.[30] Resident cell types such as epithelial cells, alveolar macrophages, vascular smooth muscle, and fibroblasts are potential sources of chemokines, which drive recruitment of $CD4^+$ T cells and eosinophils into the airway mucosa and submucosa.[31] Several chemokine signaling systems have been critical in inducing or modifying experimental murine ABPA.[32-34] Recent work in these models strongly suggests that Th2 skewing is due, at least in part, to production of chemokines preferentially evoking a Th2 response, with a prominent role for thymus-activated and thymus-regulated chemokine [TARC/CCL17] and macrophage-derived chemokine [MDC/CCL22] effects mediated through their receptor CCR4.[35] Th2 cytokines such as IL-4,

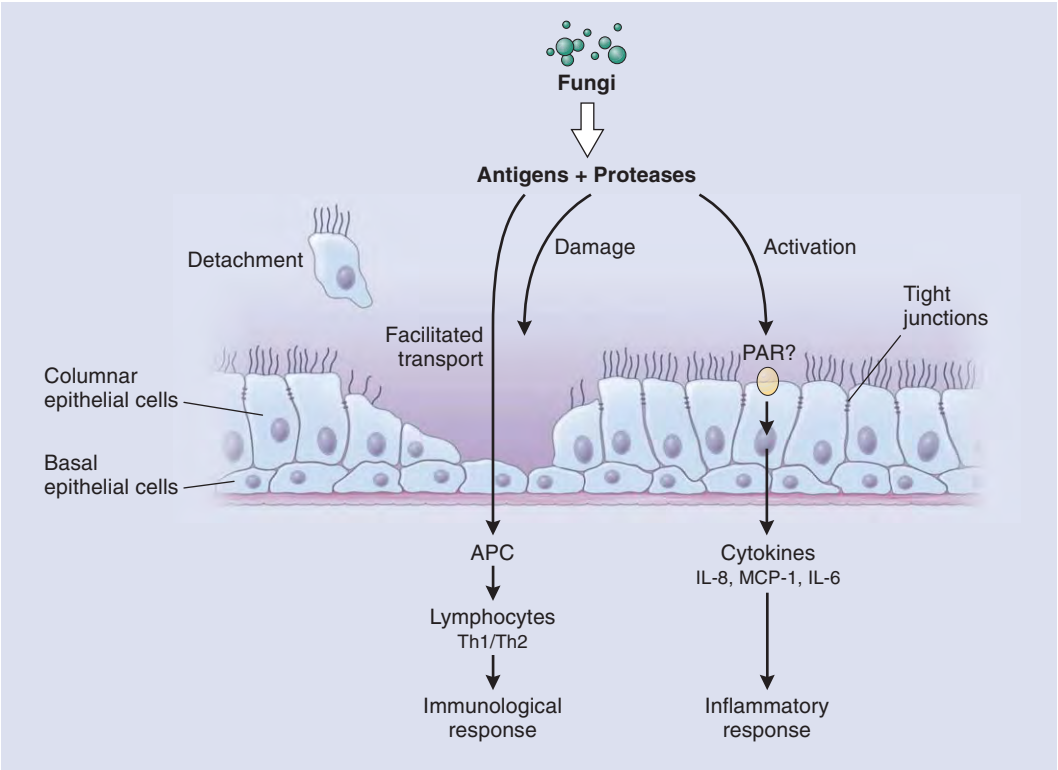

Figure 46-2 Initiation of host response to *Aspergillus* in the lung, showing concomitant epithelial cell damage and cytokine release with immuno-inflammatory consequences. APC, antigen-presenting cells; IL-6, interleukin-6; IL-8, interleukin-8; MCP-1, monocyte chemotactic protein 1; PAR, protease-activated receptor; Th1/Th2, T helper 1 or 2 cells. (Redrawn from Kauffman HF, Chris Tomee JF, van de Riet MA, et al: Protease-dependent activation of epithelial cells by fungal allergens leads to morphologic changes and cytokine production. J Allergy Clin Immunol 105:1185-1193, 2000, with permission from AAAAI.)

BOX 46-2 Reported Causes of Allergic Bronchopulmonary Mycosis Not Due to *Aspergillus fumigatus*

A. niger
A. flavus
A. nidulans
A. orizae
A. glaucus
Scedosporium apiospermum (anamorph of *Pseudallescheria boydii*)
Stemphylium lanuginosum
Helminthosporium species
Candida species
Curvularia species
Schizophyllum commune
Drechslera hawaiiensis
Fusarium vasinfectum

IL-5 and IL-13 play crucial roles in orchestrating the subsequent inflammatory pathology (Fig. 46-5).[30,36,37]

A role for other components of the innate immune response in susceptibility to ABPA has been shown by studies of collectins, innate opsonins important in fungal clearance that include the surfactant proteins A and D and mannose-binding lectin (MBL).[13,14,38] Studies of genetic polymorphisms of surfactant protein A and MBL genes revealed that patients with SP-A2 1649G or 1660G alleles, or the 1011A allele of MBL, are at markedly increased risk for ABPA.[38,39] Similarly, presence of the -1082 GG allele in the IL-10 promoter region is associated with susceptibility to ABPA.[40] This is important because a role for the anti-inflammatory cytokine IL-10 in protection against Af has been shown in experimental murine ABPA; this is in addition to the broader role of IL-10 as an anti-inflammatory cytokine in lung inflammation in both asthma and CF.[41-43] It is likely that further polymorphisms important in the immune response to Af will be found to contribute to ABPA susceptibility or protection.

Serologically ABPA is characterized by a marked local and systemic humoral immune response with highly elevated levels of *Aspergillus*-specific IgE antibodies, potent induction of a polyclonal (nonspecific) IgE response leading to very high serum IgE levels, and augmented IgG and IgA *Aspergillus*-specific antibodies. Predominantly local production of Af-specific IgE and IgA antibodies in the bronchoalveolar lavage fluids and bronchial lymphoid follicles has been demonstrated (Fig. 46-6).[44,45]

At the cellular level, adaptive immune responses have been characterized by in vitro studies of peripheral blood lymphocytes from ABPA patients and controls evaluating their phenotype and cytokine induction profile, which have shown a marked Af-specific $CD4^+$ Th2 response.[46] Af-reactive $CD4^+$ T cell lines from ABPA patients are activated ($CD25^+$, $HLA\text{-}DR^+$) and secrete interleukin-4 [IL-4] but not

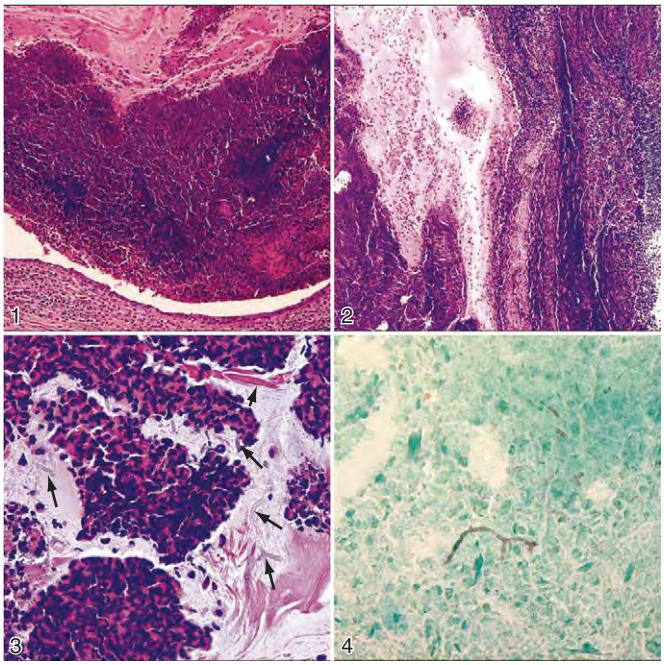

Figure 46-3 Pathology of allergic bronchopulmonary aspergillosis. *Top left,* occlusion of bronchial lumen by inflammatory cells, debris, mucus, and fibrinous material (hematoxylin-eosin, ×100). *Top right,* mucus, inflammatory cells, and debris in bronchial lumen (hematoxylin-eosin, ×100). *Bottom left,* eosinophils, Charcot-Leyden crystals (*arrowhead*), and *Aspergillus* hyphae (*arrows*) in mucus plug (hematoxylin-eosin, ×200). *Bottom right, Aspergillus* hyphae in inflammatory luminal exudates (methenamine silver, ×400). (Reprinted from Zander DS: Allergic bronchopulmonary aspergillosis: An overview. Arch Pathol Lab Med 129:924-928, 2005.)

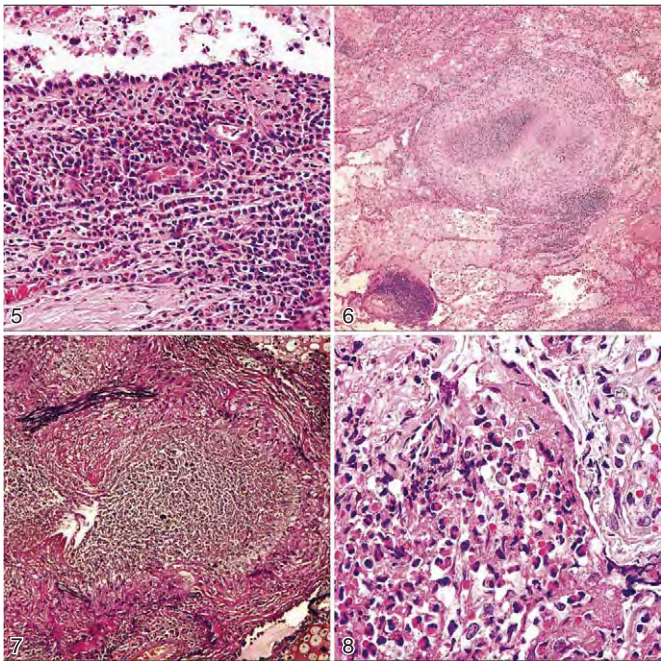

Figure 46-4 Pathology of allergic bronchopulmonary aspergillosis (ABPA). *Top left,* bronchial mucosal infiltrate, predominantly eosinophilic, with some loss of epithelium (hematoxylin-eosin, ×200). *Top right,* bronchocentric granulomatosis (hematoxylin-eosin, ×100). *Bottom left,* granulomatous destruction of elastin fibers (elastic van Gieson, ×200). *Bottom right,* eosinophilic pneumonia in alveolar space (hematoxylin-eosin, ×400). (Reprinted from Zander DS: Allergic bronchopulmonary aspergillosis: An overview. Arch Pathol Lab Med 129:924-928, 2005.)

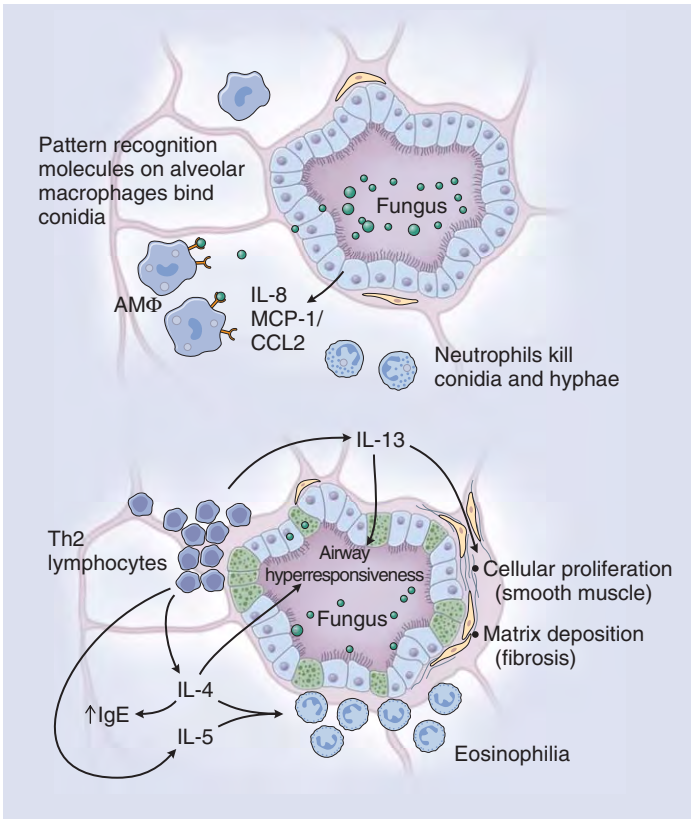

Figure 46-5 Innate immune response to inhaled fungi. *Top,* normal clearance mechanisms by front line phagocytes activated by epithelial response to exposure. *Bottom,* skewed Th2 response with prominent roles of cytokines IL-4 and IL-13 driving B cell response, including IgE production, and IL-5 driving eosinophilia. Remodeling is another feature, partially driven by IL-13. (Redrawn from Schuh JM, Blease K, Kunkel SL, Hogaboam CM: Chemokines and cytokines: Axis and allies in asthma and allergy. Cytokine Growth Factor Rev 14:503-510, 2003, with permission from AAAAI.)

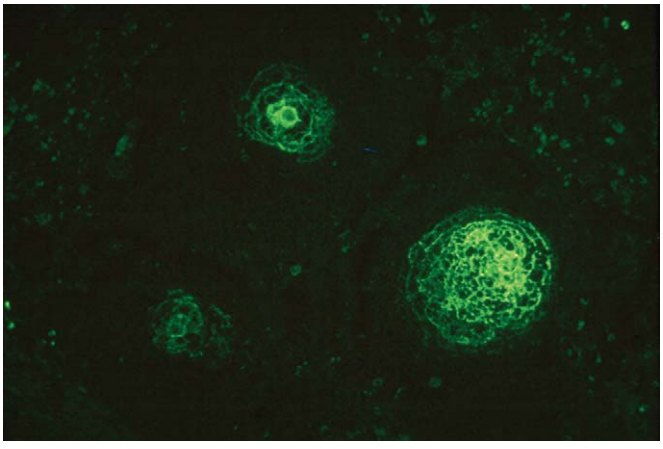

Figure 46-6 Immunofluorescent staining of IgE in germinal center of secondary lymphoid follicles from resected lung tissue of 13-year-old patient with allergic bronchopulmonary aspergillosis (ABPA) (×160). (Reprinted from Slavin RG, Gleich GJ, Hutcheson PS, et al: Localization of IgE to lung germinal lymphoid follicles in a patient with allergic bronchopulmonary aspergillosis. J Allergy Clin Immunol 90:1006-1008, 1992, with permission from AAAAI.)

interferon-γ, a pattern characteristic of the Th2 immune response phenotype, whereas cell lines reactive to other antigens such as tetanus toxoid include Th1 responses.[47] Increased sensitivity to IL-4 may represent an autocrine mechanism contributing to the Th2 skew in ABPA.[37] ABPA patients thereby have an increased frequency of circulating Af-reactive Th2 $CD4^+$ cells. Studies in murine ABPA using a variety of approaches including resistant and susceptible strains, targeted gene knockouts, and treatments with cytokine-specific monoclonal antibodies suggest that although IL-4 production is necessary for the elevated IgE levels, it is not necessary for other crucial features such as bronchial hyperreactivity, inflammation, and remodeling.[36,48] In contrast, $CD4^+$ T cells are necessary and sufficient to cause airway reactivity and inflammation in these models.[49,50]

An immunogenetic feature of ABPA is inheritance of major histocompatibility complex (MHC) alleles, which increase or decrease Th2 responses to Af. ABPA is much more likely in people with MHC alleles DRB1*1503 and 1501, whereas DQ2 is less frequent in ABPA patients than controls and modifies the risk if DR 2/5 alleles are present.[51,52] Thus, both susceptibility and protective alleles for ABPA risk appear to be associated with the MHC, implying pathogenetic roles for certain Af antigenic peptide—genetically restricted MHC interactions involving antigen-presenting cells in the lung. Af allergens associated with sensitization to Af and ABPA have been identified (discussed subsequently), suggesting that certain Af allergens are candidates for MHC-restricted disease induction.[53,54] Supporting this, in one murine model some Af allergens were shown to cause inflammation, airway hyperreactivity, high IgE, eosinophilia and a Th2 immune response, whereas others did not.[55] Af allergens are shown in Table 46-1.

Table 46-1
Allergens of *Aspergillus fumigatus*

Allergen*	kD	Nature of Allergen	Binding of IgE†
Asp f 1	18	Ribotoxin	83‡
Asp f 2	37	Fibrinogen binding (?)	90
Asp f 3	19	Peroxisomal protein	94
Asp f 4	30	—	78
Asp f 5	40	Metalloprotease	93
Asp f 6	26.5	Mn superoxide dismutase	56
Asp f 7	12	—	46
Asp f 8	11	Ribosomal protein-P2	—
Asp f 9	34	—	89
Asp f 10	34	Aspartic protease	28
Asp f 11	24	Peptidyl-prolyl isomerase	—
Asp f 12	47	Heat shock protein-P90	—
Asp f 13	34	Alkaline serine protease	—
Asp f 15	16	—	—
Asp f 16	43	—	70
Asp f 17			
Asp f 18	34	Vacuolar serine protease	—
Asp f 22	46	Enolase	—
Asp f 23	44	L3 ribosomal protein	—

*Allergens of *Aspergillus fumigatus* approved by the International Union of Immunological Society, Allergen Nomenclature Committee, 2004.
†Patients allergic to *A. fumigatus* and their binding to Af allergens.
‡Percentage of sera tested.
Reprinted from Kurup VP: Aspergillus antigens: Which are important? Med Mycol 43: S189-S196, 2005.

Eosinophilia is a prominent feature of ABPA, although recently it has been shown that neutrophils are also involved.[56] Local eosinophilia and extracellular presence of presumptive proinflammatory eosinophil products such as major basic protein are pathologic features of ABPA lesions (Fig. 46-7).[57] Thus, local and systemic eosinophilia accompanies local and systemic augmented IgE secretion as a pathologic feature of ABPA. A role for mast cell and/or basophil activation by Af allergens cross-linking IgE antibodies fixed by high-affinity receptors on the cell surface is suspected from the universal presence of type I immediate hypersensitivity skin test reactions and in vitro basophil histamine release in ABPA patients, but because these phenomena are also seen in many asthmatics and atopics without ABPA, their pathogenic role is unclear. A schematic overview of ABPA pathogenesis is shown in Figure 46-8.

Susceptibility to ABPA appears to be increased by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. This may explain, in part, the higher prevalence of ABPA in CF than in asthma, although many other phenotypic features may also be responsible. There is an increased frequency of CFTR mutations in non-CF asthmatics with ABPA, suggesting a gene-dose effect.[58,59] CF knockout mice have an altered response to Af challenge that strongly resembles human ABPA. CFTR appears to play a role in skewing immune responses to a Th2 phenotype in these CF mouse models.[60,61] It is also possible that *Aspergillus* may be preferentially selected for colonization of lungs in patients with asthma who are heterozygous for CFTR mutations, as well as for CF patients who are, by definition, homozygous for CFTR mutations on both alleles. This potential gene-dose effect may also help explain the higher prevalence of Af colonization and ABPA in CF patients than in asthmatics. Box 46-3 summarizes risk factors for ABPA that emphasize the critical interaction of environmental and host defense elements.

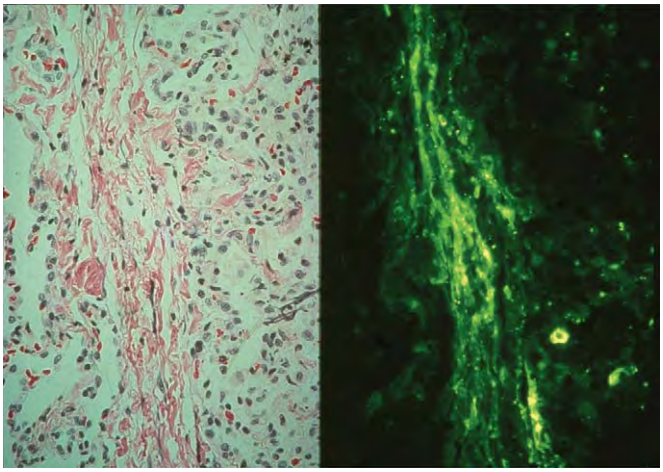

Figure 46-7 Open lung biopsy from 10-year-old patient with allergic bronchopulmonary aspergillosis (ABPA) showing eosinophilic infiltrate (*left*, hematoxylin-eosin) and extensive deposition of extracellular eosinophil major basic protein stained with fluoresceinated anti-MBP antibody (*right*, ×400) in area of interlobular septum. (Reprinted from Slavin RG, Bedrossian CW, Hutcheson PS, et al: A pathologic study of allergic bronchopulmonary aspergillosis. J Allergy Clin Immunol 81:718-725, 1988, with permission from AAAAI.)

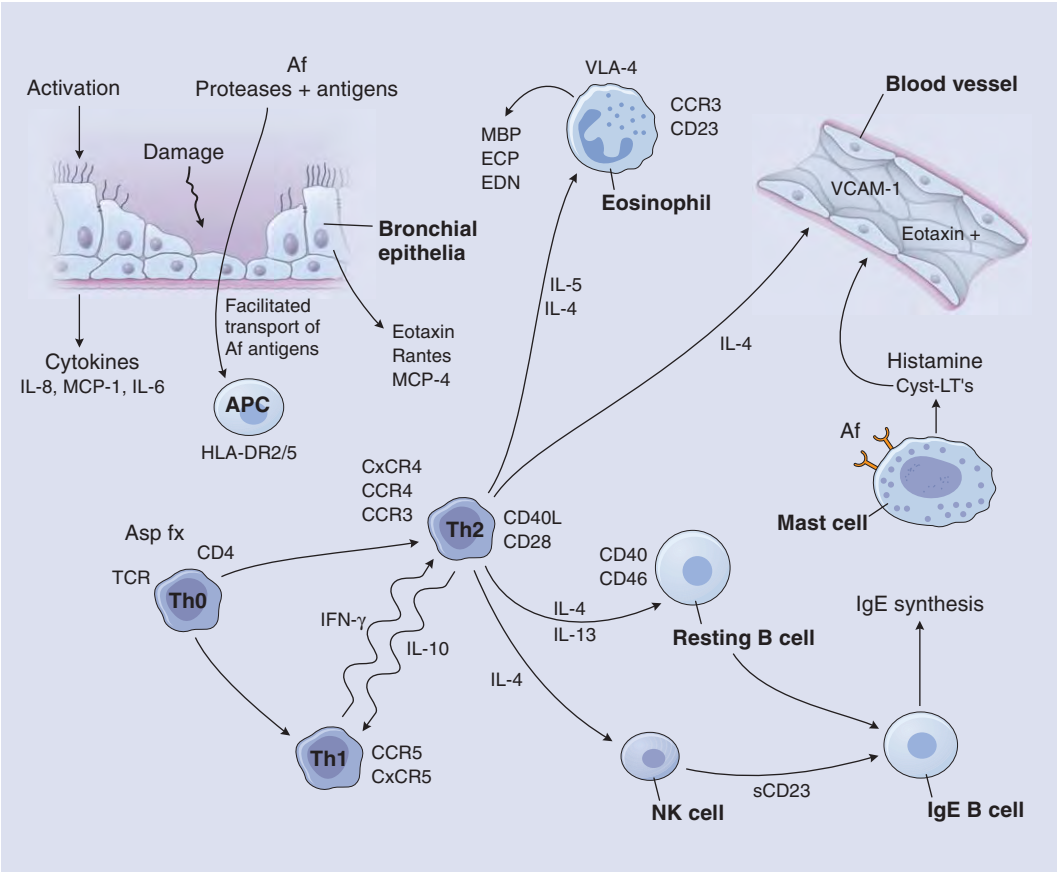

Figure 46-8 Schematic pathogenesis of allergic bronchopulmonary aspergillosis (ABPA) showing breach of epithelium with cytokine release, antigen presentation to T cells, skewed Th2 response with prominent roles for IL-4, IL-5, and IL-13 orchestrating eosinophil and B cell responses.

BOX 46-3 Environmental and Immunologic Risk Factors for Allergic Bronchopulmonary Aspergillosis

Environmental spore exposure (indoor, compost, ambient seasonal)[166,167]
Atopy[90]
CFTR homozygous or heterozygous mutation[58-61]
Surfactant protein polymorphisms (A2 A1660G, G1649C alelles)[38,39]
Mannose-binding lectin polymorphisms (G1011A allele)[39]
IL-10 promoter polymorphism (-1082GG allele)[40]
HLA-DR2 restriction (DRB1*1501 and *1503 alleles)[52]
(HLADQ2 [DQB1*0201 allele] protective)
T cell receptor Vβ chain restriction (Vβ 13)[172]
(Vβ 1 protective)
Increased B cell sensitivity to IL-4[37]
Colonization with *Stenotrophomonas maltophilia* (in CF)[173]

Allergic Bronchopulmonary Aspergillosis in Asthma

ABPA was first recognized in patients with asthma, and diagnostic criteria were developed in this setting.[26,27] Box 46-4 lists the criteria for ABPA in patients with asthma. Immediate cutaneous reactivity to *Aspergillus* species is detectable in 20% to 25% of patients with persistent asthma. In patients with asthma, most studies have reported occurrence of ABPA in 1% to 2% of patients, although recent studies routinely incorporating chest CT to detect central bronchiectasis in asthma patients screened by Af skin testing report prevalences of 5.7% to 8.1%, albeit in mainly adult populations.[62-65]

High-resolution chest CT is very useful in evaluating for ABPA, as bronchiectasis affecting three or more lobes (Fig. 46-9), centrilobular nodules, and mucoid impaction (Fig. 46-10) are findings highly suggestive of allergic bronchopulmonary aspergillosis in asthma.[66] High attenuation mucus plugs are specific for ABPA but insensitive, occurring in only ~25% of ABPA patients with asthma.[67]

Because it is possible to demonstrate serologic changes consistent with ABPA in patients who do not have central bronchiectasis, a partial or prodromal ABPA state termed *ABPA-serologic* [ABPA-S] has been suggested, along with the conventional ABPA with central bronchiectasis.[68] It is unclear how many of the former evolve into the latter if untreated, or over what period of time. Based on clinical, spirometric, serologic, and radiologic findings, ABPA-S patients have a milder type of ABPA.

ABPA onset in childhood was first observed in 1970, and may include acute life-threatening onset, but most cases occur in young adults.[69,70] ABPA can be recognized in five discrete stages, not necessarily phases, which are listed and

BOX 46-4 Diagnosis of Allergic Bronchopulmonary Aspergillosis in Asthma

Classic criteria
- Asthma
- Chest roentgenographic infiltrates—current or in past, may be detectable on CT examination when the chest film is normal
- Immediate cutaneous reactivity to *Aspergillus* species
- Elevated total serum IgE (>417 kU/L or 1000 ng/mL)
- Serum-precipitating antibodies to Af
- Central (proximal—inner 2/3) bronchiectasis on high resolution CT of chest
- Peripheral blood eosinophilia
- Elevated serum IgE-Af and or IgG-Af

Minimum essential criteria
- Asthma
- Immediate cutaneous reactivity to *Aspergillus* species
- Elevated total serum IgE concentration (>417 kU/L or 1000 ng/mL)
- Elevated serum IgE-Af and IgG-Af
- Central bronchiectasis

- Use of oral corticosteroids can reduce the total serum IgE concentration to <1000 ng/mL in some patients with allergic bronchopulmonary aspergillosis (ABPA).
- Confirmatory findings: *Aspergillus* in sputum or bronchoalveolar lavage fluid (BALF), expectoration of brown plugs, dual or late skin test reactivity to *Aspergillus.*

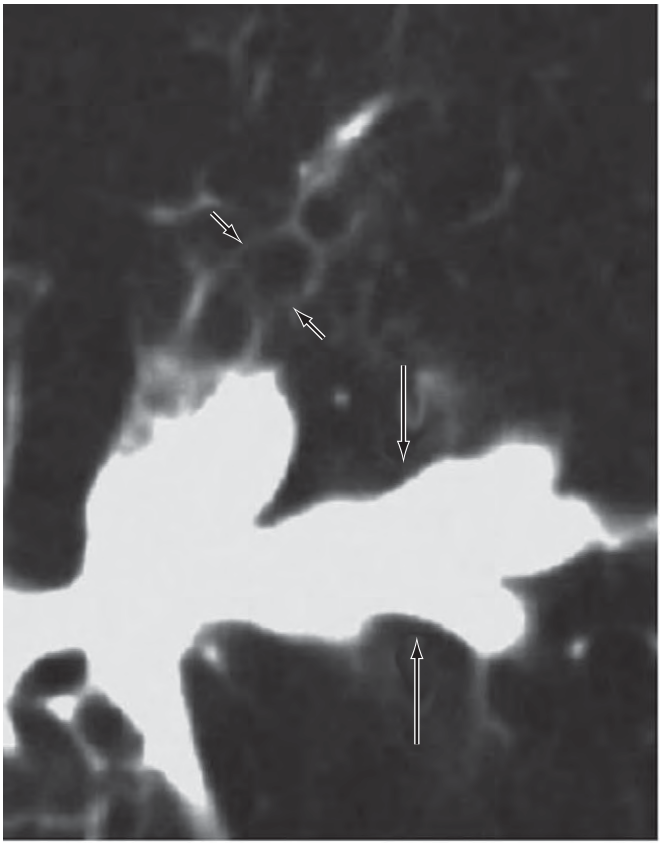

Figure 46-10 High resolution chest CT scan showns detail of patient with allergic bronchopulmonary aspergillosis (ABPA), illustrating varicose bronchiectasis (*short arrows*) and mucoid impaction (*long arrows*) producing "finger-in-glove" appearance. (Reprinted from Greene R: The radiological spectrum of pulmonary aspergillosis. Med Mycol 43:S147-154, 2005.)

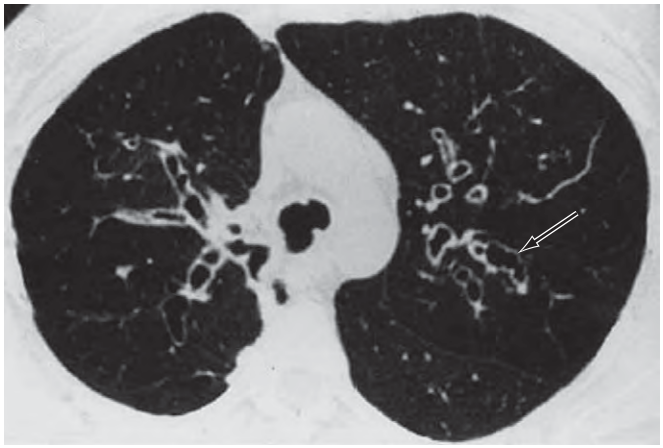

Figure 46-9 High resolution chest CT scan of patient with allergic bronchopulmonary aspergillosis (ABPA) illustrating proximal varicose bronchiectasis (*arrow*). (Reprinted from Buckingham SJ, Hansell DM: Aspergillus in the lung: Diverse and coincident forms. Eur Radiol 13:1786-1800, 2003.)

described in Table 46-2.[71] Treatment varies by stage, in that oral glucocorticosteroids are indicated in acute (stage 1) cases, may be tapered and withdrawn when the patient is in remission (stage 2), and addition of itraconazole is appropriate for patients with relapse (stage 3) or corticosteroid-dependent asthma (stage 4). The effectiveness of itraconazole as a steroid-sparing and anti-inflammatory agent, presumably via reduction in fungal burden, has been convincingly demonstrated. Similar data are not available for other antifungal agents, or for inhaled corticosteroids. It is not clear if any therapy is effective in patients who have end-stage pulmonary fibrosis (stage 5)—but this is rarely, if ever, seen in pediatric cases.[72] Patients with ABPA-S may be classified into stages 1 through 4 but do not have irreversible fibrosis or end-stage respiratory disease. These patients may have recurrent infiltrates and be categorized as stage 3. Fuller treatment recommendations are given in the section on treatment of ABPA in cystic fibrosis.

Allergic Bronchopulmonary Aspergillosis in Cystic Fibrosis

Colonization rates of the airways by Af in patients with CF have been reported to occur over a wide range, likely ascribable to variations in clinical sample acquisition and culturing methods. A large multicenter prospective evaluation in a defined CF patient population (age ≥ 6 years, *Pseudomonas*-positive, moderate lung disease) using a uniform sample acquisition protocol and methodology with centralized microbiology yielded an Af sputum colonization prevalence of about 25%.[73] Af strains differ between CF patients and can persist long term.[74] Both asthmatic and CF patients can develop ABPA with negative sputum cultures, so presence of

Table 46-2
Stages of Allergic Bronchopulmonary Aspergillosis

Stages	Clinical Characteristics	Biology	Radiology
I: Acute	Fever, cough, chest pain, hemoptysis sputum	Elevated total serum IgE levels (± blood eosinophilia)	Pulmonary infiltrate(s) (upper/middle lobes)
II: Remission	Asymptomatic/stable asthma	Normal or elevated total serum IgE levels	No infiltrates (in the absence of systemic corticosteroid therapy for >6 months)
III: Exacerbation	Symptoms mimicking the acute stage or symptomatic	Elevated total serum IgE levels (± blood eosinophilia)	Pulmonary infiltrate(s) (upper/middle lobes)
IV: Corticosteroid-dependent asthma	Persistent severe asthma	Normal or elevated total serum IgE levels	With or without pulmonary infiltrate(s)
V: Fibrosis (end-stage)	Cyanosis, severe dyspnea	Normal or elevated total serum IgE levels	Cavitary lesions, extensive bronchiectasis, fibrosis

Reprinted from Zander DS: Allergic bronchopulmonary aspergillosis: An overview. Arch Pathol Lab Med 129:924-928, 2005.

Af in sputum is not usually a criterion for diagnosis, although it may be supportive (see Box 46-4).[75,76]

In CF, reported ABPA prevalence rates are higher than in asthma, varying from 1% to 16%.[77-98] The USA Cystic Fibrosis Foundation Registry reported a prevalence of 2.2% for patients older than 5 years,[89] similar to the Epidemiologic Study of CF rate of 2% in 14,210 patients.[79] The European Registry of CF (ERCF), found an overall prevalence of 7.8% in 12,447 CF patients from 224 CF centers in nine European countries (range 2.1% in Sweden to 13.6% in Belgium).[97] A national study in 3089 Italian CF patients reported ABPA in 6.2%.[98]

A likely source of the wide range of reported ABPA in CF lies in the difficulty of case ascertainment. The CFF Registry relies on an ABPA diagnosis by the reporting center without stipulating diagnostic criteria. In the ESCF and ERCF Registries, diagnostic criteria were employed, but they varied, and it is not clear whether or how stringently they were applied by the reporting centers.[79,97] In single-center studies, a wide variety of diagnostic criteria have been used. A survey of ABPA diagnostic criteria in 45 U.K. centers found that *Aspergillus*-specific IgE was used only 54% and total serum IgE more than 1000 ng/mL only 45% of the time.[99] In a large single-center study in Italian patients, who were considered to have probable or possible ABPA depending on number of criteria present, 12.2% had probable ABPA and 11.2% had possible ABPA.[100] Notably, up to 10% of acute pulmonary exacerbations in CF may be due to ABPA.[90]

Diagnostic Considerations for Allergic Bronchopulmonary Aspergillosis in Cystic Fibrosis

In CF, diagnosis of ABPA is complicated by features of CF, listed in Box 46-5, that overlap classic diagnostic criteria of ABPA including bronchiectasis, infiltrates, and partially reversible obstructive pulmonary physiology and symptoms.[101] Critical criteria of asthmatic ABPA have been preserved—with the understanding that many CF patients exhibit a variable "asthmatic" component of their CF lung disease in the absence of ABPA (e.g., bronchial hyperreactivity, response to bronchodilators and steroids, wheezing, and response to steroids). Immunologic features of ABPA are also commonly seen in CF patients without ABPA, such as Af-specific immediate skin tests or IgE antibodies, Af-specific IgG or precipitins, and elevations in total IgE. Up to 60% of CF patients may have positive Af skin tests.[80,100-103] Precipitins may be found in up to 25% of CF patients.[92] Total IgE levels may be elevated in up to 25% of CF patients.[82,83,90,92] Most children with CF have serum IgG and IgE antibodies to Af by school age.[104,105] Half of CF patients followed up to 12 years showed loss of previously positive AF-specific IgG and/or IgE antibodies over time.[92] In CF, changes in total serum IgE may be an additional diagnostic variable. A four-fold rise from a stable baseline total IgE to more than 500 IU/mL, or similar large changes in patients with lower IgE, is suggestive of ABPA in CF.[106-108]

BOX 46-5 Similarities between Cystic Fibrosis and Allergic Bronchopulmonary Aspergillosis

Sensitization to *Aspergillus*
- Positive skin test/serum IgE antibody

Episodic obstructive airways disease
Pulmonary infiltrates
Bronchiectasis
Atopy
Humoral immune response to *Aspergillus*
- Serum IgG, IgE, IgA antibodies (ELISA)
- Serum precipitins

Elevated total serum IgE

Chest CT imaging cannot reliably distinguish ABPA from underlying CF. Thin section CT may show infiltrates and/or bronchiectasis not seen on plain radiography.[64,109-112] In general, although bronchiectasis is central in ABPA and more peripheral in CF, some degree of central bronchiectasis is also common in mild CF.[113,114] Although varicose and cystic bronchiectasis is more typical of ABPA than of CF (in which cylindrical bronchiectasis is more common), these forms of bronchiectasis are also seen in up to one third of CF patients.[115] High-attenuation mucus plugs are seen in only a minority of patients with ABPA, whereas mucoid impaction in CF usually lacks this distinctive feature.[67,116]

Because of these difficulties, diagnostic criteria for ABPA in CF patients have been modified as presented in Box 46-6. In addition, because of the high incidence of ABPA and dif-

BOX 46-6 Diagnosis of Allergic Bronchopulmonary Aspergillosis (ABPA) in Cystic Fibrosis

Full Diagnostic Criteria for ABPA in CF

- Acute or subacute clinical deterioration (cough, wheeze, exercise intolerance, exercise-induced asthma, decline in pulmonary function, increased sputum) not attributable to another etiology
- Serum total IgE concentration over 1000 IU/mL (2400 ng/mL), unless patient receiving systemic corticosteroids (if so, retest when off steroids)
- Immediate cutaneous reactivity to *Aspergillus* (prick skin test wheal >3 mm with surrounding erythema, off systemic antihistamines) or in vitro presence of serum IgE antibody to Af
- Precipitating antibodies to Af or serum IgG antibody to Af by an in vitro test
- New or recent abnormalities on chest radiography (infiltrates, mucus plugging) or chest CT (bronchiectasis) that have not cleared with antibiotics and standard physiotherapy

Minimal Diagnostic Criteria

- Acute or subacute clinical deterioration (cough, wheeze, exercise intolerance, exercise-induced asthma, change in pulmonary function, increased sputum) not attributable to another etiology
- Total serum IgE > 500 IU/mL (1200 ng/mL). Note: if ABPA is suspected and total IgE is 200-500 IU/mL, repeat testing in 1 to 3 months recommended. If on steroids, retest when off steroids.
- Immediate cutaneous reactivity to *Aspergillus* (prick skin test wheal >3 mm with surrounding erythema, off systemic antihistamines) or in vitro demonstration of IgE antibody to Af.
- One of the following:
  - Precipitins to Af or in vitro demonstration of IgG antibody against Af
  - New or recent abnormalities on the chest radiograph (infiltrates, mucus plugging) or chest CT (bronchiectasis) that have not cleared with antibiotics and standard physiotherapy

Adapted from Stevens DS, Moss R, Kurup VP, et al: Allergic bronchopulmonary aspergillosis in cystic fibrosis—state of the art. Cystic Fibrosis Foundation Consensus Conference. Clin Infect Dis 37:S225-S264, 2003.

BOX 46-7 Screening for Allergic Bronchopulmonary Aspergillosis in Cystic Fibrosis

- Maintain a high level of suspicion for ABPA after age 6 years.
- Obtain total serum IgE concentration annually. If the total serum IgE is >500 IU/mL, determine immediate cutaneous reactivity to Af or use an in vitro test for IgE antibody against Af. If positive, proceed to Minimal Criteria diagnosis consideration.
- If the total serum IgE concentration is 200-500 IU/mL, repeat if there is increased suspicion for ABPA, such as by a disease exacerbation, and perform further diagnostic tests (immediate skin test reactivity to Af or in vitro test for IgE antibody to Af, precipitins or serum IgG antibody to Af and chest radiography).

Adapted from Stevens DS, Moss R, Kurup VP, et al: Allergic bronchopulmonary aspergillosis in cystic fibrosis—state of the art. Cystic Fibrosis Foundation Consensus Conference. Clin Infect Dis 37:S225-S264, 2003.

ficulty in diagnosis, screening for ABPA in CF patients is recommended (Box 46-7).[75]

The development of methods to identify and produce purified, standardized allergens by recombinant DNA technology is important for both diagnosing and understanding the pathogenesis of ABPA. Af extracts used for skin tests and in vitro antibody assays are antigenically complex, containing dozens of allergens recognized by IgE antibodies in allergic sera.[117] They are not standardized and poorly reproducible. Recombinant DNA technology has allowed for identification and production of many Af allergens (shown in Table 46-1) which may play a role in pathogenesis and diagnostic testing.[118,119] Several show promise for diagnosis of ABPA in patients with CF as well as asthma.[120-127]

Treatment

Treatment of ABPA in CF, outlined in Box 46-8, is essentially the same as in asthma, except that it is complicated by several factors peculiar to CF.[27,75] First, recognition, and therefore prompt treatment, is more difficult because of the diagnostic difficulties and clinical similarities discussed earlier. Second, CF patients are more vulnerable to glucocorticoid toxicity including growth suppression, osteoporosis, and diabetes which are, unlike in asthma patients, common complications of the underlying disease.[128-130] Third, alterations in absorption, distribution and metabolism of drugs, and drug-drug interactions, are common in CF patients. Absorption of enteric-coated prednisolone may be compromised in CF patients, in whom the jejunal pH may be lower than desired.[131] Once absorbed, prednisolone is cleared more rapidly in CF patients, requiring increased dosing or shorter dose intervals.[132]

Itraconazole is an inhibitor of cytochrome P450 3A4. It increases exposure to methylprednisolone and dexamethasone but not prednisolone or endogenous cortisol.[133-139] Concomitant use of itraconazole and inhaled budesonide can result in adrenal suppression and even Cushing syndrome.[140-146]

Oral glucocorticoids are as effective for ABPA in CF as they are in asthma.[75,87,88,90,92,147-153] An attempt should be made to taper corticosteroids in 2 to 3 months. Despite this, in the European Registry of Cystic Fibrosis survey only 56% of CF patients with ABPA received oral corticosteroids (compared to 15% of CF patients without ABPA); inhaled corticosteroids were given to 75% of the CF patients with ABPA compared to 39% of CF patients without ABPA, despite a lack of published information on efficacy of inhaled cortico-

steroids for ABPA.[97] These data suggest that fear of glucocorticoid toxicity may play a significant role in clinician's approach to treatment of ABPA in CF.

Serum IgE levels are a useful way to follow response to therapy and guide dosing.[75,90,106,154] Consideration should be given to initiating oral corticosteroid therapy even in asymptomatic patients if the serum IgE level sharply rises (at least doubles) from a baseline value, even if the absolute level does not reach traditional diagnostic criteria levels of 500 to 1000 IU/mL.[106-108] However, IgE levels alone should not be used to make treatment decisions. Several scenarios to treatment approach are given in Table 46-3.

Reduction of fungal antigenic burden with antifungal agents is a logical addition to the treatment program.[155] This approach has been validated using itraconazole in asthmatic ABPA in several double-blind, placebo-controlled, randomized multicenter studies.[156-159] In CF, uncontrolled studies suggest similar benefits with good tolerance.[90,160] Itraconazole should be used if a patient has a slow or poor response to glucocorticoids, experiences a relapse, is steroid-dependent, or has steroid toxicity (see Box 46-8).[75]

Itraconazole can be given at an adult dose of 200 mg twice daily or a pediatric dose of 5 mg/kg once daily (up to 200 mg). Itraconazole blood levels (target, ≥1 μg/mL) to document adequate absorption (especially if concomitant acid-suppressive therapy), lack of response, or other possible drug interactions. Monitor use or levels of concomitant drugs with potential for drug-drug interaction, especially adrenal suppression with concomitant budesonide. Oral solution has 50% higher bioavailability than capsule.

BOX 46-8 Therapy for Exacerbations of Allergic Bronchopulmonary Aspergillosis

Oral Corticosteroids

Indications	All patients except those with steroid toxicity
Initial	0.5-2.0 mg/kg/day by mouth prednisone equivalent, maximum 60 mg/day, for 1-2 wk
Begin taper	Then 0.5-2 mg/kg/day every other day for 1-2 wk
Taper off	Attempt to taper off in 2-3 mo
Relapse	Increase corticosteroids, add itraconazole; taper corticosteroids when clinical parameters improve

Oral Itraconazole

Indications	Slow/poor response to corticosteroids, relapse, corticosteroid-dependent, or corticosteroid toxicity
Dosing	5 mg/kg/day, maximum dose 400 mg/day by mouth unless itraconazole levels obtained Twice daily dosing required when daily dose exceeds 200 mg.
Duration	3-6 mo
Monitor	LFTs: all cases. Serum itraconazole levels (steady state target ≥1 μg/mL) if concern for

Adjunctive Therapy

- Inhaled corticosteroids, bronchodilators, leukotriene receptor antagonists, omalizumab: no evidence for use in ABPA, may be used for the asthma component of ABPA. Budesonide metabolism (cytochrome P450) inhibition by itraconazole can lead to adrenal insufficiency.
- Uncontrolled reports of agents with possible efficacy: inhaled amphotericin, oral voriconazole, pulse intravenous methylprednisolone
- Environmental manipulation: attempt to search for and lessen mold spore exposure in refractory cases.

Adapted from Stevens DS, Moss R, Kurup VP et al: Allergic bronchopulmonary aspergillosis in cystic fibrosis—state of the art. Cystic Fibrosis Foundation Consensus Conference. Clin Infect Dis 37:S225-S264, 2003.

Table 46-3
Treatment Considerations for Allergic Bronchopulmonary Aspergillosis in Cystic Fibrosis

IgE (IU/mL)	Pulmonary Symptoms and/or Worsening PFT	New Infiltrates CXR/CT	Positive Serology*	Treatment (Rx) Recommendations
>1000 or >2× rise	Yes	Yes	Yes	Rx for ABPA
>1000 or >2× rise	No	No	Yes	No Rx; monitor IgE, CXR, PFT
>1000 or >2× rise	No	Yes	Yes	Rx for CF infection; consider Rx for ABPA if no response
>1000 or >2× rise	Yes	No	Yes	Consider Rx for ABPA, CF infection, and/or asthma
>500 in the past. No change from baseline	Yes	Yes	Yes	Rx for CF infection; consider Rx for ABPA or asthma if no response

*Af-specific IgG, IgE or positive precipitins to Af. Because these test results may not be available quickly, they are not required to initiate any therapy, but should be obtained.
ABPA, allergic bronchopulmonary aspergillosis; CT, chest computed tomography; CF, cystic fibrosis; CXR, chest radiograph; IgE, total serum IgE level; PFT, pulmonary function test; Rx, prescription.
Adapted from Stevens DS, Moss R, Kurup VP, et al: Allergic bronchopulmonary aspergillosis in cystic fibrosis—state of the Art. Cystic Fibrosis Foundation Consensus Conference. Clin Infect Dis 37:S225-S264, 2003.

adequate absorption can be helpful in patients with a poor response. Administration of itraconazole with cola beverage 1 hour before meals or gastric acid suppression will improve absorption. Some patients need higher dosing or switching from capsules to the more bioavailable liquid cyclodestrin suspension (100 mg/5 mL).[161] It may be useful to check sensitivity of Af sputum isolates to azoles and amphotericin B. Itraconazole courses of 3 to 6 months are recommended, with baseline and periodic monitoring of liver function tests.[75]

Therapies for ABPA that have not been adequately evaluated and, therefore, should be considered unproven include use of inhaled corticosteroids, inhaled amphotericin, newer oral azoles (such as voriconazole), pulse methylprednisolone infusions, immunosuppressives (such as low-dose methotrexate and olamizulab).[162-164] Inhaled corticosteroids and other agents useful in asthma for the asthmatic component of ABPA as recommended by current asthma guidelines may be beneficial but should not be sole therapy.[165]

Cases of ABPA have been tied to environmental exposures.[166-168] The role of environmental controls in prophylaxis or treatment of ABPA has not been carefully studied. Measures that may contribute to remission and/or prevent exacerbation include avoidance of outdoor exposures such as turned compost heaps or moldy hay piles, examination and cleaning of humid moldy indoor areas, and use of high-efficiency particulate air (HEPA) filters. Measurement of indoor fungal spore counts may be helpful in identifying occult exposure.[169,170]

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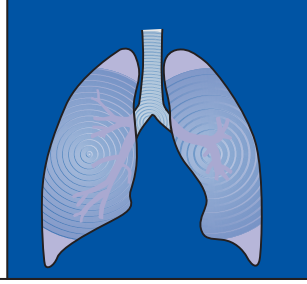


CHAPTER 47 Collagen Vascular Disorders

Jeffrey S. Wagener, Jennifer B. Soep, and Thomas C. Hay

TEACHING POINTS

- Collagen vascular or rheumatic diseases represent autoimmune conditions which can affect the lung.
- Therapy for collagen vascular disease–related lung disorders is focused on controlling the underlying collagen vascular disease.
- Interstitial lung disease and pulmonary vasculitis are the most frequent chronic pulmonary complications of the collagen vascular diseases.
- Inflammatory (non-infectious) pneumonias and pulmonary arterial hypertension can be the manifesting signs of collagen vascular diseases.

Collagen vascular diseases (CVDs) include many conditions that have in common active inflammation and an autoimmune basis (Box 47-1).[1] Within the category of CVDs are primarily vasculitic conditions (Box 47-2) and other systemic inflammatory conditions (including inflammatory bowel disease and Reiter syndrome). All of the CVDs have in common the ability to harm the lung, although the degree and pattern of harm varies greatly. Also, most severe pulmonary complications of CVDs occur primarily in adults, and children are only occasionally affected, suggesting that the CVD is either different in children (as with certain forms of rheumatoid arthritis), or the lung complications have an insidious onset and are not recognized in childhood. There is increasing evidence that pulmonary involvement in CVDs is more frequent in children than previously recognized, indicating the need for increased vigilance in monitoring the respiratory system.

EPIDEMIOLOGY, RISK FACTORS, AND PATHOGENESIS

Pulmonary abnormalities in patients with CVDs can be divided into three groups. First, patients with CVDs are at an increased risk for infection, both because of their primary disease and because of complications secondary to immunosuppressive therapy.[2-4] Opportunistic infections must always be considered first when a CVD patient has respiratory symptoms. Cough, sputum production, and fever are particularly important signs that suggest infection. Although all potential infecting organisms should be considered, particular attention should be paid to cytomegalovirus, *Escherichia coli*, *α-hemolytic streptococci*, *Klebsiella* and *Aerobacter* species, *Legionella pneumophila*, *Candida albicans*, *Aspergillus* species, *Mycobacterium*, and *Pneumocystic carinii*.[3,5,6]

Second, pulmonary complications from pharmacotherapy must be considered. In addition to general immunosuppression, some of the medications used to treat CVDs have selective harmful effects on the lung. Penicillamine can produce hypersensitivity pneumonitis and bronchiolitis obliterans and has been associated with acute pulmonary hemorrhage, alveolar and interstitial fibrosis, and a pulmonary and renal syndrome similar to Goodpasture syndrome.[7-9] Methotrexate can produce an acute pneumonitis as well as pulmonary fibrosis.[10-12] In sensitive individuals, salicylates and nonsteroidal anti-inflammatory drugs produce bronchoconstriction. Biotherapeutics (such as anti-B-lymphocytes and anti–TNF-α) can produce profound immunosuppression and can lead to reactivation of past infections, particularly with mycobacteria.[13,14]

Third, all CVDs have a degree of chronic systemic inflammation that can produce tissue damage either acutely or over time. Lung disease in patients with CVD can involve virtually every part of the respiratory system including the chest wall, diaphragm, pleura and pleural space, interstitium, pulmonary vasculature, alveoli, and airways (Table 47-1).[6]

Chest wall disease is usually related to muscle weakness, as occurs with dermatomyositis, or skeletal rigidity, as occurs with ankylosing spondylitis.[15,16] Muscle weakness may also represent a complication of steroid therapy.[17]

Diaphragm dysfunction and basilar lung atelectasis occur with systemic lupus erythematosus (SLE) in both adults and children.[18-20] This "shrinking lung" syndrome is rarely disabling or progressive if the primary disease is adequately treated.[21] Studies of lung mechanics demonstrate inspiratory and expiratory muscle weakness with decreased transdiaphragmatic pressures.

Pleurisy and pleural effusions are particular problems in patients with SLE but also occur with systemic juvenile rheumatoid arthritis (JRA).[20,22,23] Pleural effusions, although usually bilateral, can be unilateral resulting from a localized intrapleural immunologic reaction (Fig. 47-1). When effusions manifest acutely they should always be evaluated for a possible infectious etiology. Effusions caused by CVD will usually resolve with anti-inflammatory therapy without producing fibrosis or restrictive changes.

Interstitial lung disease (ILD) can begin early in the disease process and complicate any of the CVDs (Fig. 47-2). With disease progression, cytokines, particularly transforming growth factor-β, are released and activate gene expression, resulting in collagen deposition.[24] The result, seen almost exclusively in adults, is extensive fibrosis and honeycomb lung. A different pathologic picture seen in Sjögren syndrome is lymphocytic interstitial pneumonitis (LIP).[25] With LIP there is a dense infiltrate of lymphoplasmacytic cells that are within the alveolar walls and fill the alveolar spaces. The interstitial infiltrates in LIP do not show the heterogeneous cell types seen in the more common interstitial pneumonitis. LIP can have associated amyloid deposition, lymphoid follicles, and giant cells.

Vasculitis occurs in SLE and is the identifying pathologic finding of the various vasculitides. Patchy alveolar hemorrhage and adjacent lung necrosis (Fig. 47-3) develops from immune complex deposition and neutrophil adherence to the endothelium, leading to microangiitis and eventual vessel obstruction and vessel wall disruption.[26] Pulmonary capillaritis also can result in diffuse alveolar hemorrhage, and although this is usually related to a CVD, cases with no obvious systemic disease have been described.[27]

Pulmonary arterial hypertension (PAH) is now recognized to occur with surprising frequency in patients with CVDs. All patients with idiopathic PAH should be evaluated thoroughly because this can be the manifesting symptom of CVD. PAH is most commonly seen in variants of progressive systemic sclerosis (PSS or scleroderma), mixed connective tissue disease, and the CREST syndrome (calcinosis,

BOX 47-1 Pediatric Collagen Vascular or Rheumatic Diseases Affecting the Pulmonary System

Juvenile rheumatoid arthritis
Juvenile ankylosing spondylitis
Systemic lupus erythematosus
Progressive systemic sclerosis (scleroderma)
Dermatomyositis and polymyositis
Mixed connective tissue disease
Sjögren syndrome
Sarcoid
Goodpasture syndrome
Primarily vasculitic conditions
Other inflammatory conditions

BOX 47-2 Pediatric Vasculitic Conditions Affecting the Pulmonary System

Granulomatous vasculitis
  Wegener granulomatosis
  Churg-Strauss syndrome (allergic granulomatosis)
  Lymphomatoid granulomatosis
Leukocytoclastic vasculitis
  Henoch-Schönlein purpura (anaphylactoid purpura)
  Hypersensitivity vasculitis
Polyarteritis
Kawasaki disease
  Polyarteritis nodosa
  Microscopic polyangiitis
Giant cell arteritis
  Takayasu arteritis
Other
  Behçet disease
  Erythema nodosum

Table 47-1
Pulmonary Manifestations of Collagen Vascular Diseases in Childhood

DISEASE	CW	DD	PPE	ILD	LIP	VAS	PAH	AIP	DAH	BO	AW	OTHER
Rheumatic Diseases	+	–	++	±	w/SS	±	+	±	+	–	±	+
Juvenile rheumatoid arthritis	+	++	++	++	w/SS	++	+	+++	++	±	–	
Systemic lupus erythematosus	±	–	+	+++	w/SS	++	+	–	–	+	–	
Progressive systemic sclerosis	++	+	–	+	–	+	+	+	–	–	+	–
Dermatomyositis/polymyositis	++	+	–	–	–	±	+	–	±			
Mixed connective tissue disease	–	±	++	+	–	±	++	±	+	±	–	
Ankylosing spondylitis		++	–	±	+	–	–	–	–	–	–	–
Sjögren syndrome	–	–	+	+	++	–	–	–	–	–		
Vasculitic Diseases												
Wegener granulomatosis	–	–	+	–	–	++	–	–	++	–	+	+
Churg-Strauss syndrome	–	–	–	–	–	++	–	–	–	–	+++	+
Henoch-Schönlein purpura	–	–	–	–	–	+	–	–	+	–	–	
Kawasaki disease	–	–	+	+	–	++	–	–	+	–	–	
Polyarteritis nodosa	±	–	–	–	–	+	–	–	–	–	–	+
Behçet disease	–	–	–	–	–	+	–	–	+	–	–	+
Pulmonary Capillaritis	–	–	–	–	–	++	–	–	–	–	–	–

AIP, acute immunologic pneumonia; AW, airway disease; BO, bronchiolitis obliterans; CW, chest wall disease; DAH, diffuse alveolar hemorrhage; DD, diaphragm dysfunction; LIP, lymphocytic interstitial pneumonitis; OTHER, aspiration, atelectasis, granulomas, thrombosis; PAH, pulmonary arterial hypertension; PPE, pleuritis and/or pleural effusion; VAS, vasculitis; w/SS, with Sjögren syndrome.

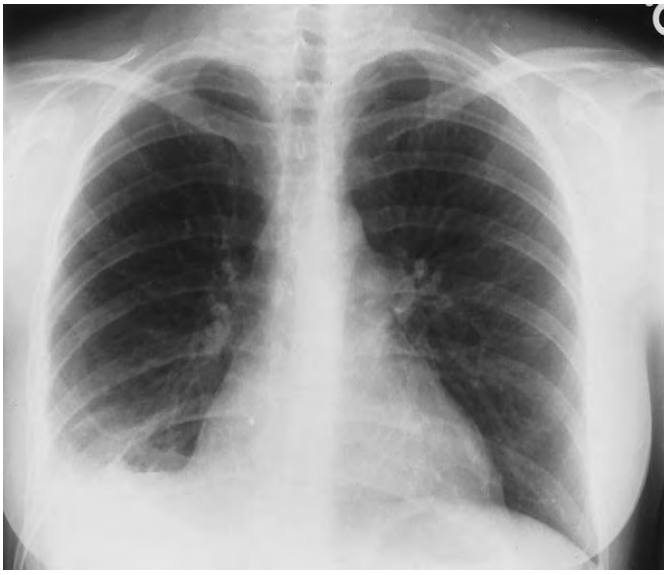


Figure 47-1 Systemic lupus erythematosus patient with right pleural effusion and blunting of the right costophrenic sulcus plus partial right lower lobe atelectasis.

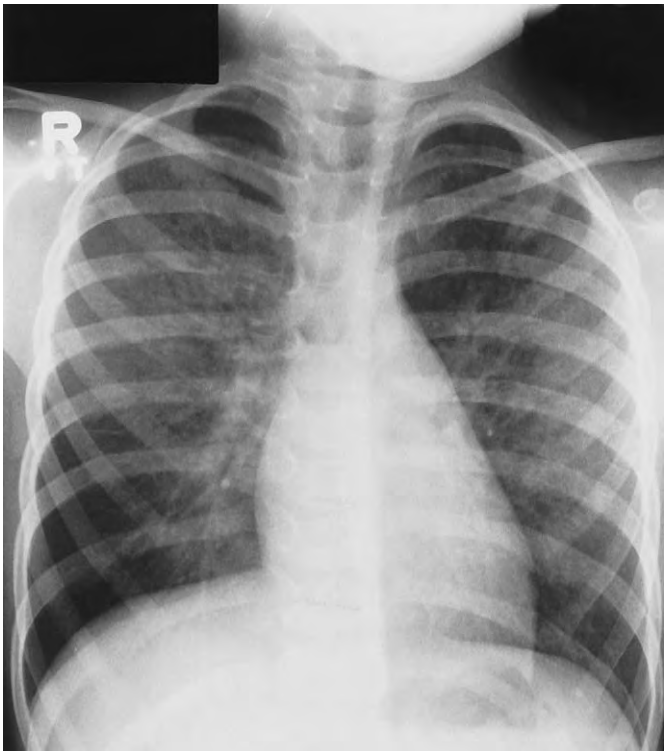


Figure 47-2 Wegener granulomatosis patient with a poorly defined diffuse reticular nodular infiltrate. The initial presentation in the child was thought to be "idiopathic" pulmonary hemosiderosis.

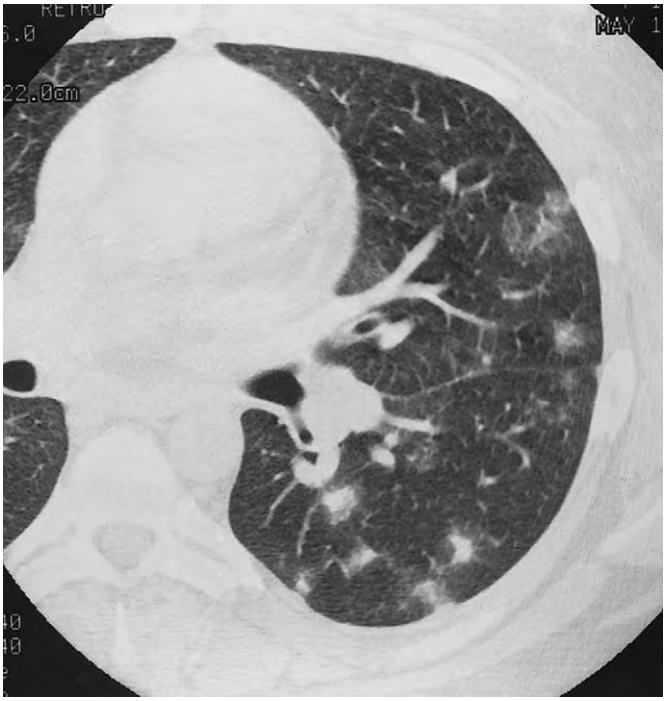


Figure 47-3 Churg-Strauss syndrome patient with a high resolution chest CT scan showing multiple poorly defined, patchy areas of consolidation caused by hemorrhage and vascular exudate.

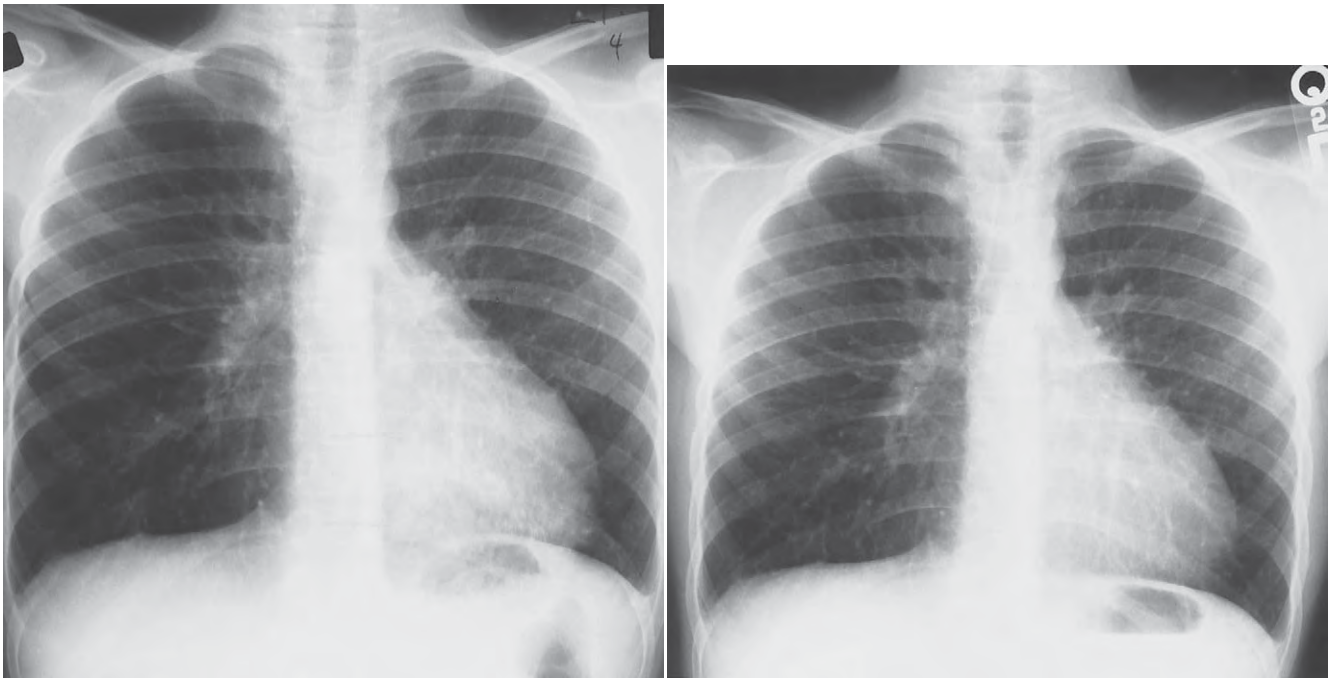
Raynaud phenomenon, esophageal dysfunction, sclerodactyly, and telangiectases).[28] Pulmonary hypertension related to CVD is a primary plexogenic arteriopathy and is characterized by "onion-skin" proliferation of the intima with medial thickening of the arterioles and small muscular arteries of the lung. Inflammation and vessel wall necrosis are not present as in vasculitis. Pulmonary arterial hypertension may also be related to increased pulmonary vasoreactivity and to pulmonary arteriolar thrombosis caused by circulating anticoagulants.[29]

Acute inflammatory (noninfectious) pneumonia is occasionally the presenting problem with CVDs and is most common in SLE (Fig. 47-4).[19,20] Pathologically there is diffuse alveolar damage with mixed interstitial inflammatory cellular deposits, interstitial edema, and fibrin deposition. Red blood cells and hyaline membranes are present in the alveoli.[30]

Diffuse alveolar hemorrhage is seen in SLE and is a possible complication of any of the vasculitic diseases.[31,32] Unlike acute immunologic pneumonia, diffuse alveolar hemorrhage is most likely a complication in an already diagnosed condition and does not usually occur with pleural or pericardial disease. Pathologic findings vary from diffuse microangiitis and capillaritis to hemorrhage without vasculitis. Diagnosis is based on the clinical presentation of an acute infiltrate and a dropping hematocrit. Bronchoscopy and lavage will demonstrate large numbers of red blood cells in the effluent.

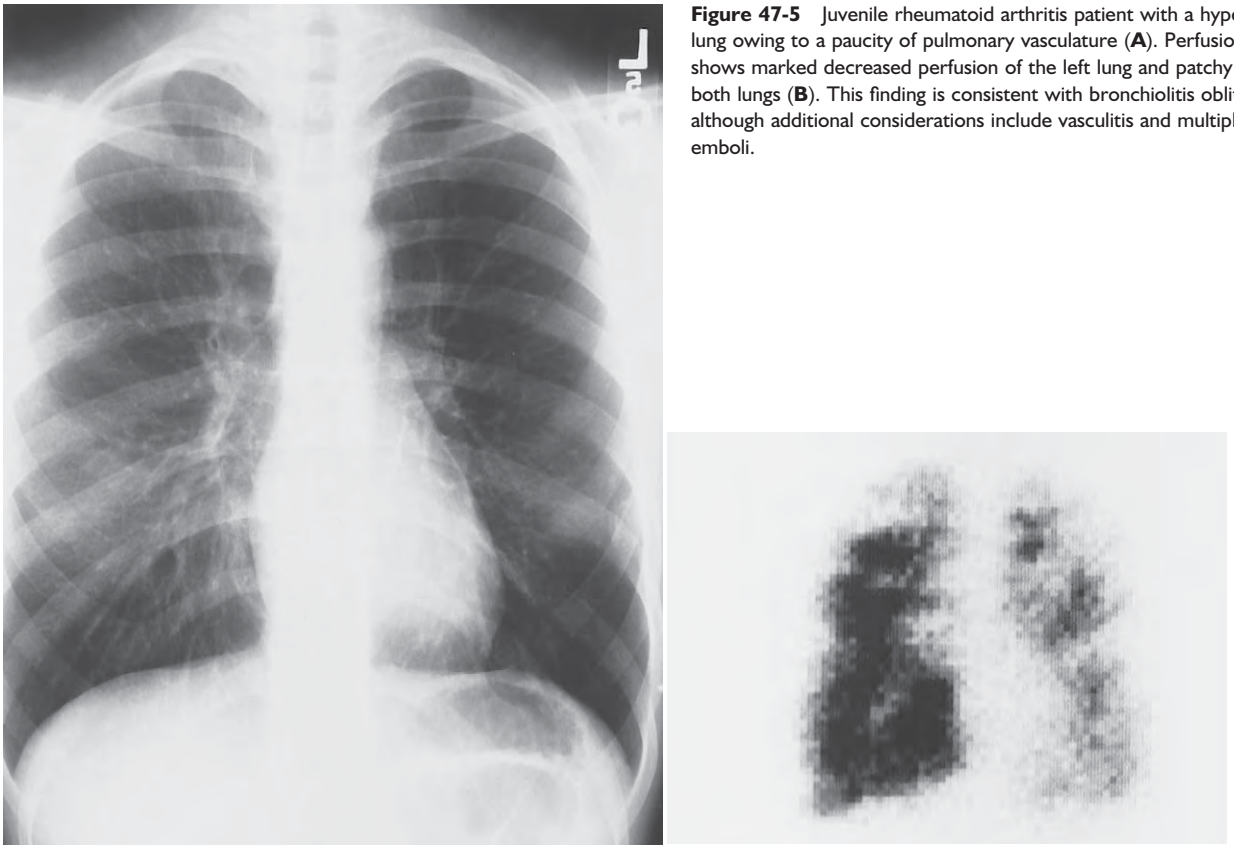
Bronchiolitis obliterans (BO) usually occurs in adults with rheumatoid arthritis but may begin in childhood (Fig. 47-5).[33] BO represents progressive airway obstruction from persistent inflammation and fibrous proliferation of the terminal bronchiolar walls. Eventually there is total obliteration of the airway lumen. Bronchiolitis obliterans with organizing pneumonia (BOOP) is a distinctly different condition that has histologic findings of inflammatory polyps produced by proliferating collagen bundles with acute and chronic inflammatory cells in the terminal respiratory bronchioles. This organizing process extends into the alveolar spaces and produces a clinical picture of restrictive lung disease. The often acute onset of BOOP is distinctly different from that of BO, which is chronic and obstructive.

Airway disease similar to asthma occurs in patients with Churg-Strauss syndrome (allergic granulomatosis).[34] Also,



A B

Figure 47-4 Systemic lupus erythematosus patient with a retrocardiac infiltrate caused by an immunologic pneumonia (**A**). A small pleural effusion is also present. Rapid resolution of pneumonia occurred with steroid therapy (**B**).



A B

Figure 47-5 Juvenile rheumatoid arthritis patient with a hyperlucent left lung owing to a paucity of pulmonary vasculature (**A**). Perfusion scintigraph shows marked decreased perfusion of the left lung and patchy perfusion of both lungs (**B**). This finding is consistent with bronchiolitis obliterans, although additional considerations include vasculitis and multiple pulmonary emboli.

endobronchial obstruction can occur from granulomas in some vasculitic diseases.[35]

CLINICAL FEATURES

Rheumatic Conditions

Juvenile rheumatoid arthritis is the most common CVD in children (see Box 47-1).[1] JRA can manifest with the following three different clinical patterns, all of which have different prognosis and sequelae:

1. Systemic-onset disease occurs most frequently in children younger than age 4 and includes fever, an evanescent macular rash, arthritis, hepatosplenomegaly, leukocytosis, and polyserositis. Pulmonary involvement at the time of presentation is common and includes pleural effusions and an acute inflammatory (noninfectious) pneumonia.[23]
2. Polyarticular JRA (five or more joints involved) resembles the adult disease, although only 10% of children have a positive rheumatoid factor. In contradistinction with the adult disease, symptomatic pulmonary complications are rare. Pulmonary function abnormalities, including a restrictive defect and abnormal diffusing capacity, are more common.[36] Potential complications include recurrent pleurisy with or without pleural effusion, pulmonary nodules, interstitial pneumonitis, and BO (see Fig. 47-5). Pulmonary hypertension is rarely seen in children.
3. Pauciarticular JRA is characterized by chronic arthritis of only a few (four or fewer), usually large joints. Systemic symptoms, except iridocyclitis, are uncommon. Although symptomatic pulmonary complications typically do not occur in children with this form of disease, abnormal carbon monoxide diffusion and small airway obstruction have been described.[36]

Juvenile ankylosing spondylitis (JAS) is an inflammatory joint disease involving the spine and sacroiliac joints. JAS occurs in late childhood and is most common in HLA-B27 positive males. The presentation is similar to that of pauciarticular JRA but the condition progresses to include the spine and sacroiliac joints. Because of limited chest wall motion, patients have restrictive pulmonary function changes with normal lung compliance.[16] Pneumonia may complicate the clinical course due to infections of upper lobe bullae. Clinical pulmonary symptoms are rare in the absence of infection.[6]

Systemic lupus erythematosus is less common than JRA, but is more likely to have pulmonary complications in children as well as adults.[19,37,38] This multisystem inflammatory disease is diagnosed by a constellation of diagnostic criteria. Life-threatening acute immunologic pneumonia can be the initial manifestation of SLE and is difficult to distinguish from an infectious pneumonia (see Fig. 47-4). Pleuritis with or without effusion is relatively common in children with SLE (see Fig. 47-1).[20] Effusions are typically small, but patients often have dyspnea, cough, and fever in addition to pleuritic pain.[22] Pleural fluid usually has a normal glucose and pH, separating this condition from bacterial empyema.[39] High concentrations of antinuclear antibody and double-stranded DNA in the pleural fluid are highly suggestive, but not diagnostic.[40] ILD has been reported in children with SLE from both clinical and autopsy studies.[3,19] Patients may have dyspnea, cough, and chest discomfort, or may have a normal examination and chest radiograph. Pulmonary function tests may show a restrictive pattern with reduced diffusing capacity.[41] Patients with active inflammation can be effectively treated with immunosuppressive therapy and fibrosis is rare in children. Alveolar hemorrhage can produce acute respiratory distress and usually occurs in previously diagnosed SLE patients.[31] Diffusing capacity is typically increased and patients have falling hemoglobin.[42] Diaphragm dysfunction and associated "shrinking lung" have been described in pediatric SLE patients.[19-21] Lower airway obstruction has been described, as has upper airway obstruction caused by laryngeal involvement.[43,44] Finally, the most insidious pulmonary complication of SLE is PAH. Mild PAH is common in adults and is associated with Raynaud phenomenon.[45] Early symptoms include dyspnea with exertion, and echocardiography should be obtained in all symptomatic patients.

Progressive systemic sclerosis, also known as scleroderma, is a rare disease in pediatrics; however, cardiopulmonary complications are common and have been associated with death in childhood.[1] Clinical diagnosis is based on a skin disease that progresses from an edematous phase to an atrophic, taut, immobile dermis in combination with a systemic disease including arthralgia, renal disease, Raynaud phenomenon, and pulmonary fibrosis. Some 50% to 90% of adults with PSS develop ILD, eventually leading to death.[46,47] Radiographic changes include a diffuse reticulonodular interstitial infiltrate (Fig. 47-6) with progression to cystic changes and honeycomb lung.[48] Vasculitis progressing to PAH has also been described in children.[28] Patients with CREST syndrome are at greater risk of developing primary pulmonary vascular disease and should be monitored closely for signs of PAH. Pulmonary function testing, including lung volumes, carbon monoxide diffusing capacity, and the degree of oxygen desaturation with exercise may be particularly helpful in detecting

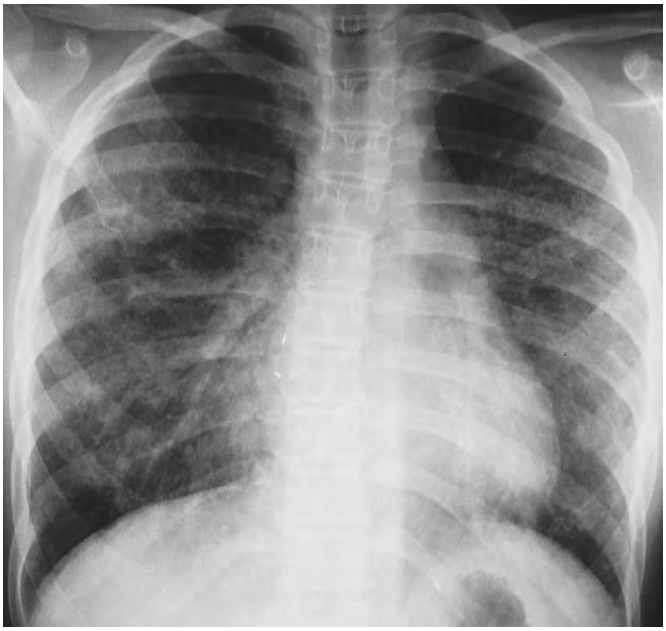


Figure 47-6 Progressive systemic sclerosis patient with a diffuse reticular nodular infiltrate and a spontaneous pneumothorax.

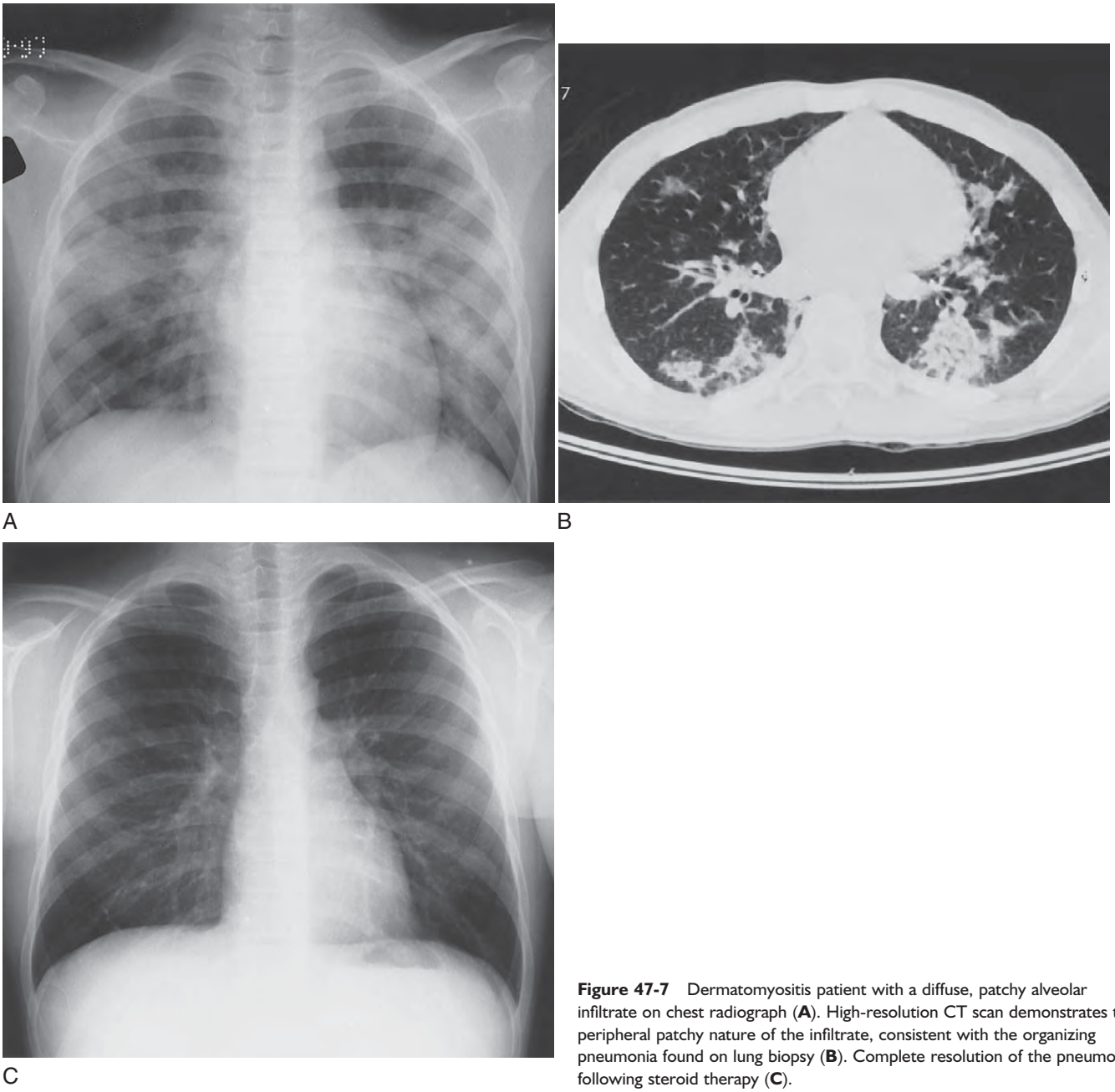


Figure 47-7 Dermatomyositis patient with a diffuse, patchy alveolar infiltrate on chest radiograph (**A**). High-resolution CT scan demonstrates the peripheral patchy nature of the infiltrate, consistent with the organizing pneumonia found on lung biopsy (**B**). Complete resolution of the pneumonia following steroid therapy (**C**).

the early effects of pulmonary restrictive and vascular complications.[49]

Dermatomyositis and polymyositis are characterized by chronic myopathy with vasculitis involving the skin and muscles. Diagnosis is based on the characteristic skin rash, symmetrical proximal muscle weakness, elevated serum levels of muscle enzymes, and if obtained, a myopathic electromyogram and a consistent muscle biopsy. The vasculitis seen in children is pathologically different from that seen in adults and is uniquely responsive to corticosteroid therapy. Respiratory problems can be related to difficulty swallowing due to the weakness of pharyngeal muscles and resulting aspiration.[50] Recurrent atelectasis may be seen on chest radiographs. Patients also may develop progressive respiratory muscle weakness, leading to decreased cough efficiency and eventually ventilatory insufficiency.[15] ILD associated with dermatomyositis, while common in adults, has rarely been reported in children.[51,52] Symptoms include dyspnea, dry cough, and rarely, fever. Longitudinal pulmonary function studies in children suggest that pulmonary disease can manifest in the absence of symptoms.[53] Chest radiographs may show diffuse infiltrates (Fig. 47-7), occasionally complicated with pneumothoraces. There is one reported pediatric case of pulmonary alveolar proteinosis complicating dermatomyositis.[54]

Mixed connective tissue disease is a clinical syndrome with features similar to those of SLE, dermatomyositis, and PSS associated with a circulating antibody specific for the ribonucleoprotein component of extractable nuclear antigen.[55] Pulmonary disease is common in children (Fig. 47-8) and includes pleural effusions, restrictive pulmonary function, and PAH.[56]

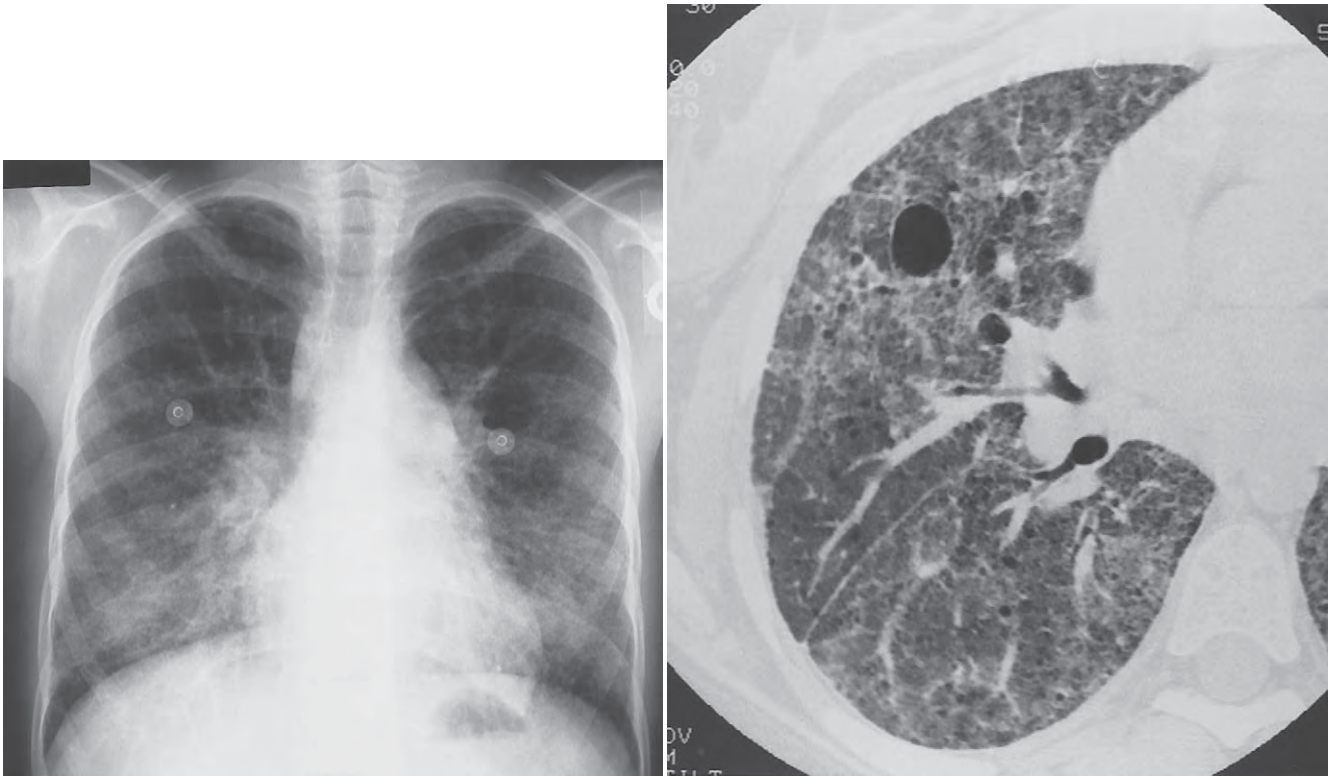


Figure 47-8 Mixed connective tissue disease with a diffuse reticular nodular infiltrate on chest radiograph (**A**). High-resolution CT scan demonstrates diffuse ground-glass opacity with cystic and fibrotic changes (**B**). Bronchiectasis is noted peripherally and is better defined than on plain chest radiography.

Sjögren syndrome is rare in children but can be associated with other CVDs including JRA, SLE, PSS, and dermatomyositis.[57] The classic symptoms of keratoconjunctivitis sicca (dry eyes) and xerostomia (dry mouth) are produced by a lymphocytic inflammation of the exocrine glandular tissue. Pulmonary manifestations occur in about 9% of adults and include pleurisy, atelectasis, pulmonary fibrosis, and LIP.[25,58] Diffuse airway dryness may be responsible for the dry cough and recurrent respiratory infections.[6] The pathologic finding of LIP in a patient with CVD is highly suggestive of Sjögren syndrome.

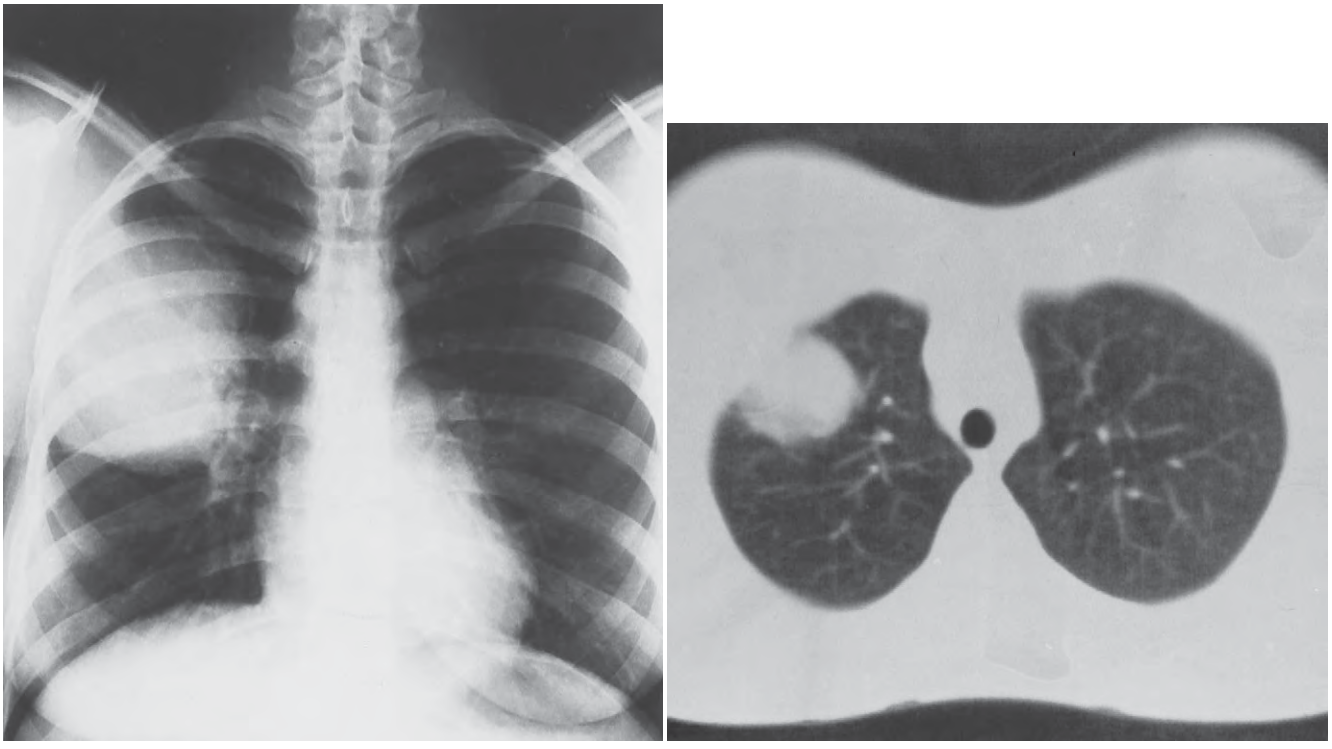
Antiphospholipid syndrome (APS) involves arterial and venous thrombosis and can complicate autoimmune disorders such as SLE and small vessel capillaritis.[59] APS is rare in children but should be considered in patients with complications including pulmonary embolism, primary thrombosis, pulmonary hypertension, and recurrent intra-alveolar hemorrhage. Diagnosis is based on the presence of anticardiolipin antibodies and/or lupus anticoagulant in the serum and is important because therapy includes anti-coagulation in addition to immunosuppression.

Sarcoid is a multisystem granulomatous disease typically developing in young adults and rarely in children.[60] Young children are also more likely to have multi-organ involvement and a poorer prognosis.[61] Respiratory involvement is usually mild and symptoms include cough and exertional dyspnea.[62] Chest radiographs may show hilar adenopathy and occasional parenchymal changes. Pulmonary fibrosis has not been reported in children. Lung function abnormalities are common, including restrictive changes and decreased carbon monoxide–diffusing capacity. Diagnosis requires histologic confirmation, although the serum angiotensin-converting enzyme level correlates well with disease activity.

Goodpasture syndrome is an immune complex disease affecting both the lungs and kidneys.[63] Pulmonary hemorrhage can be the manifesting sign, and diagnosis is based on finding serum antibodies directed to the glomerular basement membrane. Rarely, hemorrhage can be life threatening and require plasmapheresis in addition to immunosuppression.

Primarily Vasculitic Conditions

Wegener granulomatosis (WG) and microscopic polyangiitis are diffuse, small-vessel vasculitic diseases producing necrotizing granulomas, particularly in the respiratory and renal systems. Pediatric patients of all ages can be affected (see Box 47-2). Patients present with cough, fever, chronic rhinosinusitis (particularly in WG), arthralgias, vasculitic rash, hemoptysis, and hematuria or proteinuria.[64,65] Pulmonary disease may predate systemic symptoms and delay diagnosis, particularly in patients diagnosed with "idiopathic" pulmonary hemosiderosis (see Fig. 47-2). Radiographic changes typically include bilateral nodular infiltrates, often with cavitation (Fig. 47-9). Other findings include pleural effusions, pleural thickening, migratory infiltrates, pneumothorax, and endobronchial granulomas producing atelectasis.[35] Diagnosis



A B

Figure 47-9 Wegener granulomatosis patient with a large mass in the right upper lobe extending from the hilum to the pleural surface (**A**). Chest CT scan showing the homogeneous nature of the mass (**B**). Differential considerations include lobar pneumonia, inflammatory pseudotumor, or a chest wall mass. Wegener granulomatosis was diagnosed on biopsy.

is confirmed with the identification of positive antineutrophil cytoplasmic antibodies (cANCA in WG versus pANCA in polyangiitis).[66] Early initiation of vigorous immunosuppressive therapy is important to reduce the major complication of glomerulonephritis and chronic renal failure.[67]

Churg-Strauss syndrome, or allergic angiitis and granulomatosis, is characterized by eosinophilia, fever, vasculitis, and asthma. The most common pulmonary manifestation is asthma, which usually predates the vasculitis. Patchy, nodular lung infiltrates (see Fig. 47-4) can occur with rare cavitation (Fig. 47-10).[34] Histologic findings include eosinophilic pneumonia, necrotizing vasculitis, and granuloma formation.[68]

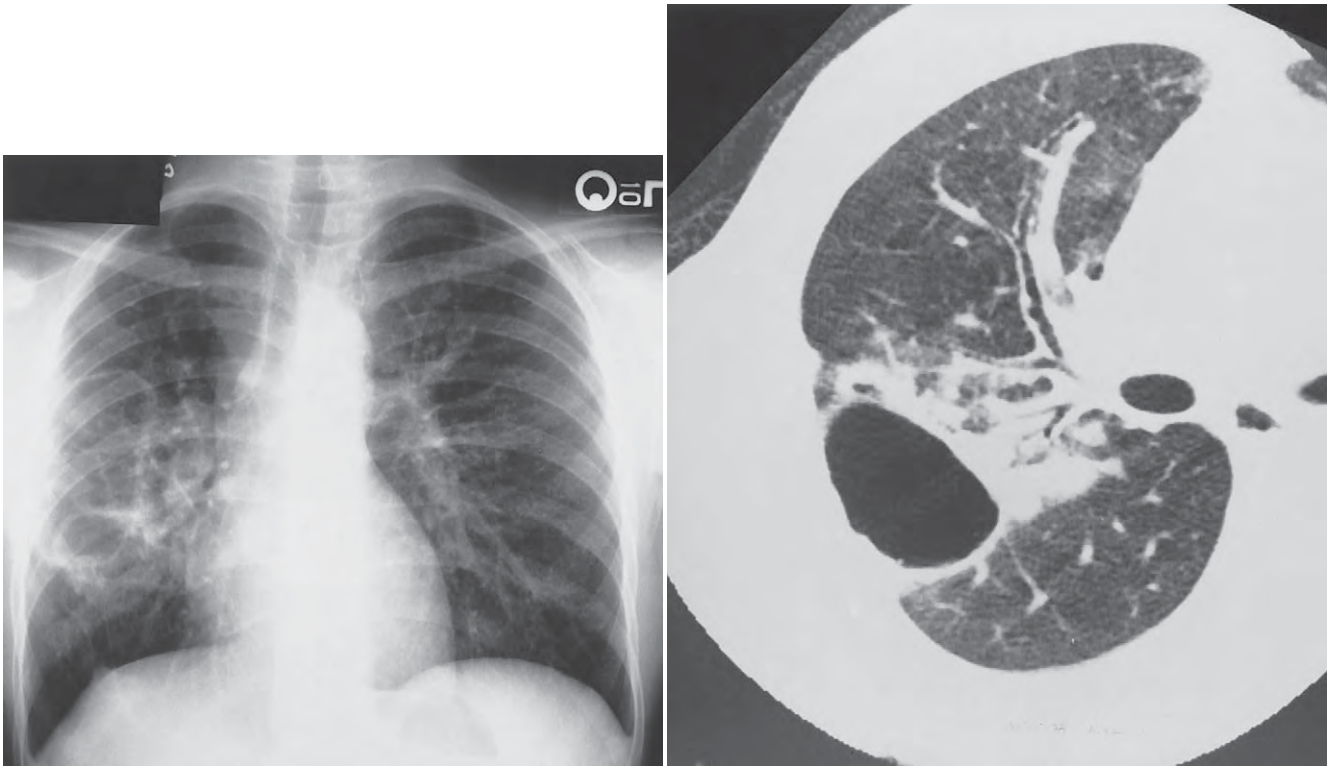
Henoch-Schönlein purpura (HSP), or anaphylactoid purpura, is one of the most common vasculitides in childhood. HSP is most common during the winter and is frequently preceded by an upper respiratory tract infection.[69] Characteristic signs and symptoms include arthritis, arthralgia, abdominal pain, nephritis, and nonthrombocytopenic purpura. Pulmonary complications are rare, but a few cases of fatal alveolar hemorrhage have been reported.[70,71]

Kawasaki disease is a necrotizing arteritis seen most commonly in young children. Patients present with fever, conjunctivitis, lymph node enlargement, rash, strawberry tongue, and erythema of the palms and soles. Cough and respiratory distress are occasionally present and chest radiographic abnormalities include reticulogranular infiltrates, peribronchial cuffing, pleural effusion, atelectasis, and air trapping.[72-74] In addition, cardiac involvement is frequent, with the most serious chronic complication being coronary artery aneurysm. Pulmonary edema secondary to heart failure can occur. Pathologic examination of the lungs often reveals interstitial pneumonia and pulmonary arteritis in fatal cases.

Polyarteritis nodosa is a multi-organ necrotizing vasculitis involving small to medium-sized muscular arteries.[75] Pulmonary complications are uncommon in children but include vasculitis, local thrombosis, and pulmonary edema secondary to cardiac and renal involvement.[76,77] The clinical onset of disease is usually insidious with unexplained fever and weight loss. Abdominal pain, central nervous system disease, arthritis, myalgia, and skin lesions eventually develop in most patients. Vascular thrombosis, necrosis, and aneurysms are seen in the kidneys, heart, and lungs.[75]

Behçet disease is characterized by oral aphthous and genital ulcers in addition to relapsing iritis. Disease onset can be insidious and prolonged. Pulmonary involvement has not been described in children; however, adults can have serious pulmonary complications including pleural effusion, hemorrhage, vasculitis, aneurysms, and emboli.[78]

Pulmonary capillaritis isolated to the lungs and without evidence of a systemic immunologic condition has been described in both children and adults.[27,79,80] Typically these patients present with crackles, cough, dyspnea, and occasionally hemoptysis. Further evaluation detects low oxygen, infil-



A B

Figure 47-10 Churg-Strauss syndrome patient with a large cavitary lesion in the peripheral lung with adjacent pleural thickening and volume loss of the right lung (**A**). Chest CT scan demonstrating bronchiectasis of the right middle lobe in addition to the cavitary lesion (**B**).

trates on chest radiographs, and low hemoglobin. Lung biopsy is needed to distinguish this vasculitis from idiopathic pulmonary hemorrhage. Early intervention with immunosuppression can be lifesaving.

Other Inflammatory Conditions

Reiter syndrome involves a triad of arthritis, conjunctivitis, and urethritis. This inflammatory syndrome occurs most frequently in HLA-B27-positive males, similar to ankylosing spondylitis. Pleuritic chest pain and pleural effusion have been described in acute Reiter syndrome.[81]

Inflammatory bowel disease (IBD) patients develop arthropathies similar to JRA. Other systemic inflammatory manifestations include erythema nodosum, pyoderma gangrenosum, and pulmonary disease.[82] The most common pulmonary complication is ILD, although vasculitis, bronchiectasis (Fig. 47-11), granulomas, pleuritis, and pleural effusion may occur in both adults and children.[83-87] These complications are seen in both ulcerative colitis and regional enteritis (Crohn disease). The ILD appears to improve with improved control of the underlying IBD.[88]

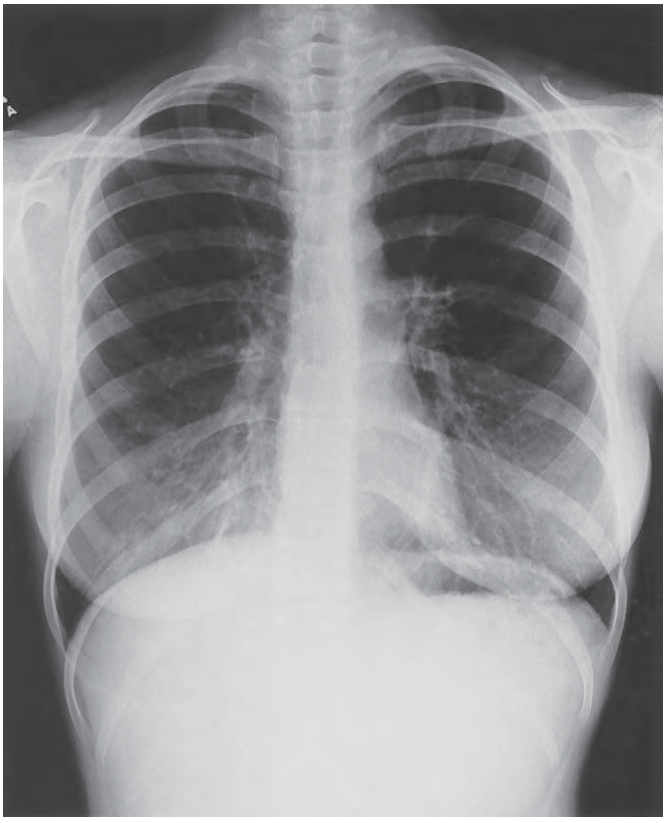
TREATMENT

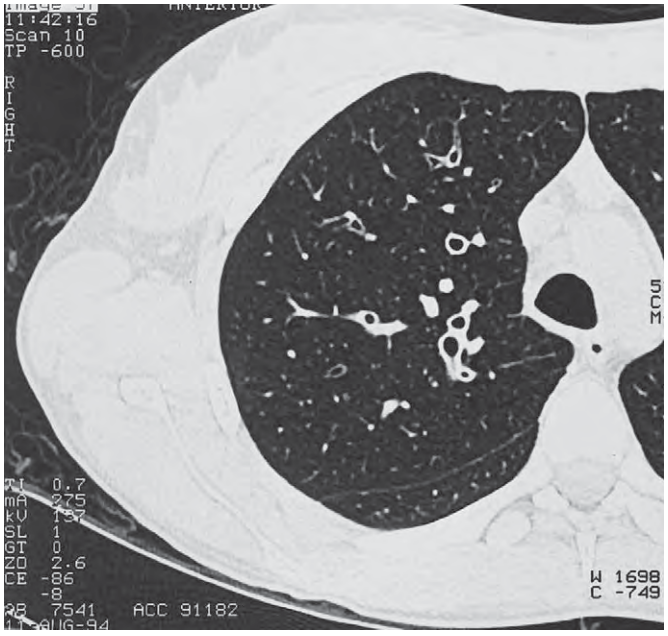
The main challenge in managing pulmonary manifestations of CVDs is determining whether pulmonary symptoms represent a complication of the primary illness, an infectious complication, or a complication related to ongoing therapy. Because of the importance of this separation, invasive diagnostic techniques, such as bronchoscopy and bronchoalveolar lavage (BAL), are frequently necessary. Therapy includes treating infectious complications, reducing the exposure to toxic medications, or adjusting the pharmacologic management of the primary CVD.

BAL is both sensitive and specific for the diagnosis of infectious complications and may be helpful in diagnosing some pulmonary complications of CVDs, particularly alveolar hemorrhage.[89-91] The presence of neutrophils in the BAL fluid of patients with CVD indicates an active alveolitis and may be seen even in patients without clinical or radiographic evidence of pulmonary involvement. Lymphocytosis or eosinophilia may be seen prior to clinically detected ILD.[92]

High resolution computed tomography (HRCT) of the chest is extremely valuable for diagnosis, identifying diffuse or focal peripheral lung disease (Fig. 47-12), determining location for lung biopsy, and monitoring response to therapy in CVD patients with pulmonary complications (see Figs. 47-3, 47-7, and 47-8).[93-95] Combined inspiratory and expiratory HRCT scanning can be used to detect even early BO in CVD patients.[96]

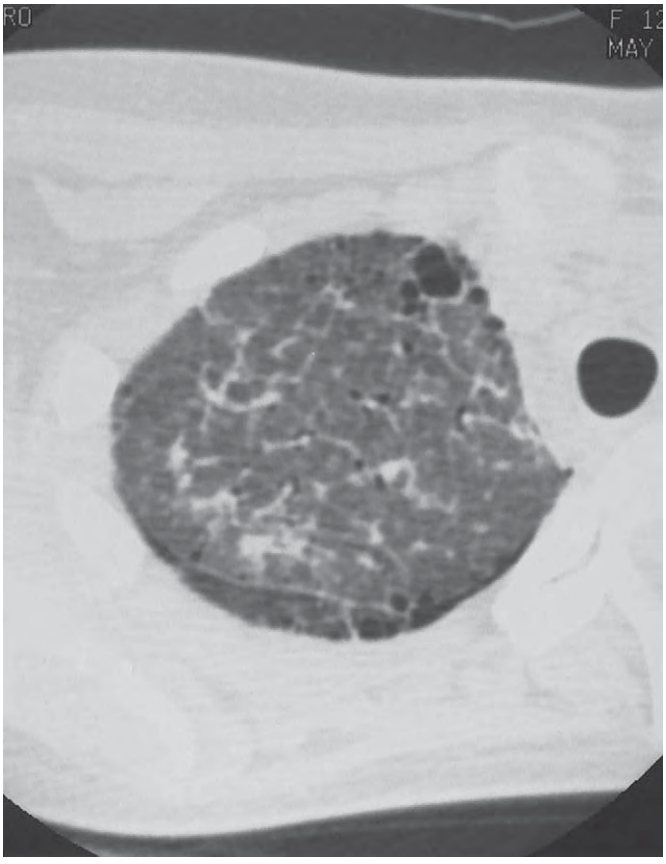
Pulmonary function testing is valuable for explaining respiratory symptoms and can be used to monitor for early ILD.[97,98] Lung volumes and diffusing capacity should be mea-

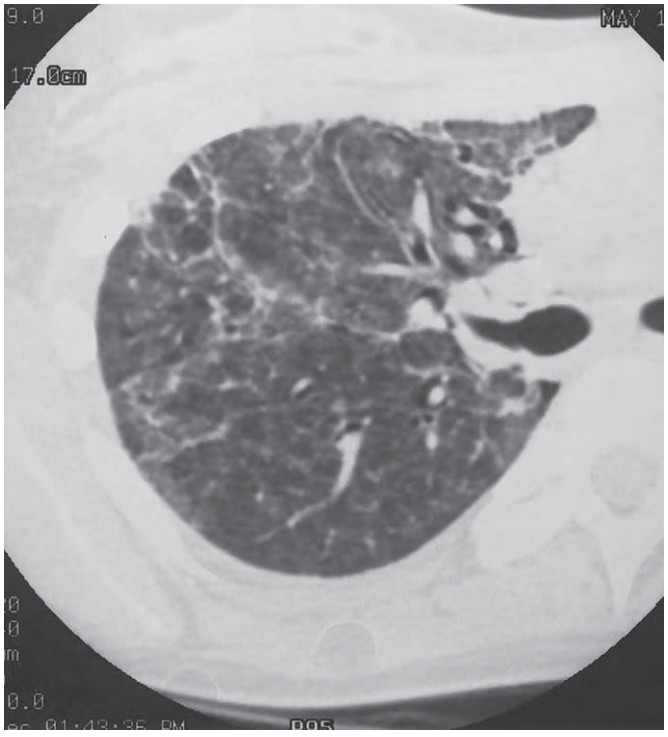




A B

Figure 47-11 Ulcerative colitis patient with diffuse peribronchial thickening suggesting bronchiectasis (**A**). High-resolution CT scan confirms the presence of bronchiectasis and quantitates the extent of disease (**B**). Bronchiectasis typically develops after colectomy.





A B

Figure 47-12 Progressive systemic sclerosis patient with high resolution CT scan showing fibrotic changes with subpleural blebs, septal thickening, and bronchiectasis in the apex (**A**) and mid-lung fields (**B**). Multiple poorly defined nodular densities are seen which were not appreciated on chest radiograph 4 days earlier (see Fig. 47-6).

sured in all patients with CVD and respiratory symptoms. Detecting airway disease and determining reversibility with bronchodilators can be helpful because respiratory symptoms may be related to mild asthma and unrelated to the CVD. Exercise testing, paying close attention to oxygenation, can be an easy and sensitive technique for detecting the earliest signs of ILD in CVD patients.

Echocardiography and estimation of pulmonary artery pressure is valuable in monitoring patients with known diffuse interstitial lung disease, as well as evaluating any patient with exercise limitation. Often echocardiography during exercise is needed to determine the degree of pulmonary vasoreactivity and to diagnose early PAH.[99,100]

PITFALLS AND CONTROVERSIES

Pulmonary complications from CVDs are infrequent in childhood but represent some of the most serious complications in adults. Acute infectious and medication-related complications need to be separated from complications related to the CVD. Chronic pulmonary complications can be insidious, and early detection may be able to reduce long-term disability. Some adult CVD complications may have their origin during childhood, and pulmonary function monitoring should be considered for all patients with CVD who are at risk for developing chronic pulmonary complications. Finally, any CVD patient with exercise limitation should be investigated for PAH as well as possible ILD.

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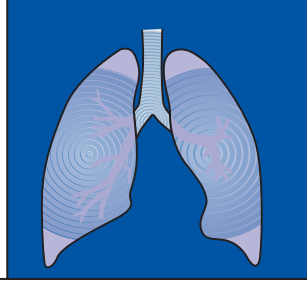

CHAPTER 48 Pulmonary Alveolar Proteinosis

Jeffrey S. Wagener and Robin R. Deterding

TEACHING POINTS

- Alveolar proteinosis can be divided into three distinct patient groups.
- Alveolar lipoproteinaceous material is composed primarily of altered surfactant.
- Granulocyte-macrophage colony stimulating factor (GM-CSF) neutralizing antibody is present in acquired alveolar proteinosis.
- Whole-lung lavage and aerosolized GM-CSF are generally effective therapies in acquired alveolar proteinosis.
- Most patients eventually recover to a state of quiescent disease with minimal to no symptoms.

Pulmonary alveolar proteinosis (PAP) is a rare disease characterized by excess accumulation of proteinaceous and lipid-rich material in the alveolar spaces. Originally described in 26 patients by Rosen and colleagues in 1958,[1] PAP is now recognized to represent three distinct clinical forms with different pathogenic pathways (Box 48-1).[2] More that 90% of reported cases of PAP have historically had no identified etiology and are termed *acquired* or *idiopathic*. Recent descriptions of abnormal granulocyte-macrophage colony-stimulating factor (GM-CSF) activity are leading to a better understanding of the pathogenesis and potential therapy for these patients.[3]

Less common, and also occurring primarily in adults, is secondary PAP. Hematologic malignancies are the most common primary underlying condition leading to secondary PAP; however, other immunologic deficiency states and chronic dust exposure can be precursors to secondary PAP.[4,5] Congenital PAP occurs in patients most commonly with mutations in surfactant protein genes and rarely with an abnormal GM-CSF receptor gene.[6-8] Also very rare mutations of the SLC7A7 gene have recently been described associated with lysinuric protein intolerance and PAP.[9] These congenital forms of PAP are predominantly discussed in the chapter on childhood interstitial lung disease (see Chapter 44).

PATHOGENESIS AND EPIDEMIOLOGY

Surfactant production and clearance mechanisms are tightly controlled processes to maintain alveolar homeostasis. The alveolar macrophage is critical to the clearance of surfactant. GM-CSF is required to stimulate alveolar macrophages to process and reuse surfactant. Disruption of this clearance leads to excess surfactant and abnormal accumulation in the lung.

Understanding of the pathogenesis of acquired PAP has advanced rapidly since two groups of investigators described typical pulmonary pathology in gene knockout mice for GM-CSF.[10,11] GM-CSF replacement by gene overexpression or tracheal or aerosol administration prevented the development of lung disease.[12-15] Additionally, in humans with acquired PAP, reduced GM-CSF activity is associated with a neutralizing autoantibody against GM-CSF that is present in both serum and bronchoalveolar lavage (BAL) fluid.[16-19] Although this antibody does not appear to affect GM-CSF gene expression or the beta-c receptor, there is decreased protein secretion that leads to abnormal macrophage function, reduced surfactant clearance, and abnormal alveolar homeostasis.[20,21] These findings suggest that acquired PAP is a localized pulmonary condition resulting from decreased phospholipid clearance and accumulation of surfactant protein.[22]

Secondary PAP is significantly less common than the acquired disease. Rare cases have been reported in children, usually related to immunodeficiencies and hematologic malignancies, although one case was reported in a child with dermatomyositis.[7,23-26] Other causes of PAP in adults include high exposure to respirable-sized particles of silica, aluminum dust, cement dust, titanium dioxide, and cellulose fiber.[27-31] Immunosuppression related to organ transplantation has rarely been associated with PAP.[32] Although opportunistic infections occur in patients with PAP, they are unlikely to be causative. The most likely pathophysiology for secondary PAP is deficiency in number or function of alveolar macrophages and, thus, decreased clearance of surfactant. Of interest, myeloid leukemias and myelodysplastic syndromes may have alveolar macrophages derived from the malignant clone and following successful chemotherapy and normal hematopoiesis, the PAP may resolve.[5]

Most information on the epidemiology of PAP comes from the adult literature.[2] There is a male predominance and the median reported age of diagnosis is 39 years, although women with PAP tend to be younger than men. Diagnosis is often delayed, with the median time to diagnosis after first onset of symptoms being about 7 months. Most adult patients have a history of smoking tobacco. There is also a slight increased chance that the patient may have an autoimmune disorder such as rheumatoid arthritis, multiple sclerosis, and immunoglobulin-A nephropathy.[2]

BOX 48-1 Clinical Forms of Pulmonary Alveolar Proteinosis

- Acquired or "Idiopathic"
  - GM-CSF neutralizing antibody positive
  - Other
- Secondary
  - Hematologic malignancies
  - Immunodeficiency disorders
  - Dust exposure (silica, aluminum, etc.)
  - Other
- Congenital
  - Surfactant protein B gene mutation
  - Surfactant protein C gene mutation
  - GM-CSF receptor (beta-chain gene mutation)
  - Lysinuric protein intolerance (SLC7A7 gene mutation)
  - Other

CLINICAL FEATURES

Exercise intolerance is the most common initial symptom in older children and adults with PAP.[2,4,33,34] Patients with both acquired and secondary PAP usually have a gradual, progressive onset of dyspnea. This is in contradistinction with congenital PAP, which usually has a rapid onset. A minimally productive cough is occasionally present, as are signs of systemic illness including fatigue, weight loss, and low-grade fever when the diagnosis is delayed. In young children, respiratory symptoms are often insidious in onset and failure to thrive, gastrointestinal symptoms, and bacterial infections are more common. Persistent pneumonia and diffuse infiltrates on chest radiographs may be another sign that eventually leads to the diagnosis. Rarely, concomitant illnesses such as acquired immunodeficiency syndrome, malignancies, or opportunistic infections complicate the diagnosis because chills, weight loss, and hemoptysis can occur either primarily with PAP or with these underlying diseases.

Physical examination may be normal or may have mild findings of tachypnea, diffuse crackles, and occasionally, clubbing.[35] Late in the disease there may be cyanosis. High fevers are rare and should stimulate looking for secondary infectious complications.

Chest radiographic findings include bilateral alveolar filling defects in more than 50% of cases.[36,37] A symmetrical "batwing" appearance is due to the perihilar nature of the infiltrate and the sparing of disease in the costophrenic angles (Fig. 48-1). Heart size is typically normal and there is no pleural space disease. Additionally, the mediastinum is not involved and lymphadenopathy should not be seen. Computed tomography (CT) usually discloses a far more extensive pattern of diffuse involvement in the alveolar spaces (Fig. 48-2).[38,39] Localized disease should raise concern for another diagnosis.

In patients old enough to perform pulmonary function testing, there is a typical restrictive pattern with decreased total lung capacity and decreased forced vital capacity with proportionately decreased airflows.[34,35,38] Diffusing capacity is decreased—this is primarily related to the restrictive pattern, and diffusing capacity corrected for alveolar volume is commonly normal. Blood gases at rest are usually normal, but oxygenation can dramatically worsen with exercise. Exercise-related desaturation is one of the most sensitive measures of disease activity.[40] Longitudinal monitoring of the degree of exercise a patient can perform prior to desaturation is one of the simplest tests for monitoring disease progression. Infant and young child pulmonary functions have not been reported in PAP; however, one would expect similar findings of restrictive lung disease. Young children are more likely to have tachypnea at the time of diagnosis than are adults.

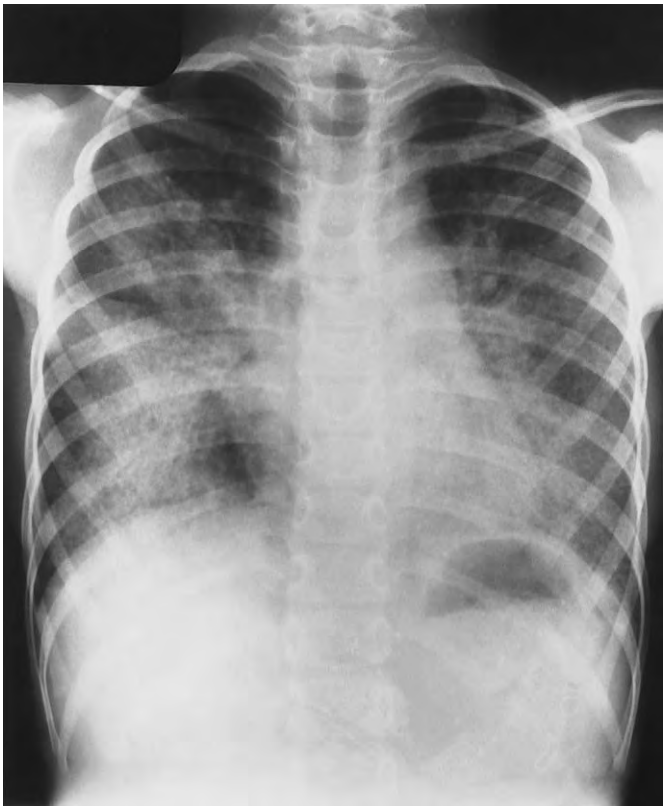

Figure 48-1 Chest radiograph of a 9-year-old child with pulmonary alveolar proteinosis.

DIAGNOSIS

Alveolar proteinosis is diagnosed histologically by the presence of periodic acid–Schiff (PAS)–positive, amorphous, granular material deposited diffusely in the alveolar spaces.[37] This material represents an accumulation of surfactant-derived proteins and lipids. Rarely, there is a mild lymphocytic interstitial infiltrate. Fibrosis is seen only as a late feature in some patients. Electron microscopy demonstrates large amounts of cellular debris without intact cells and numerous laminated phospholipid lamellar bodies.[41] Although open-lung biopsy has been the standard diagnostic technique, better understanding of this lipoproteinaceous alveolar material has led to most PAP cases being diagnosed by BAL.[40] Typically, the effluent is milky and on histology there are foamy-appearing macrophages with diastase-resistant, PAS-positive intracellular inclusions.[37]

Other valuable laboratory tests include looking for neutralizing anti-GM-CSF antibody in either the BAL fluid or serum.

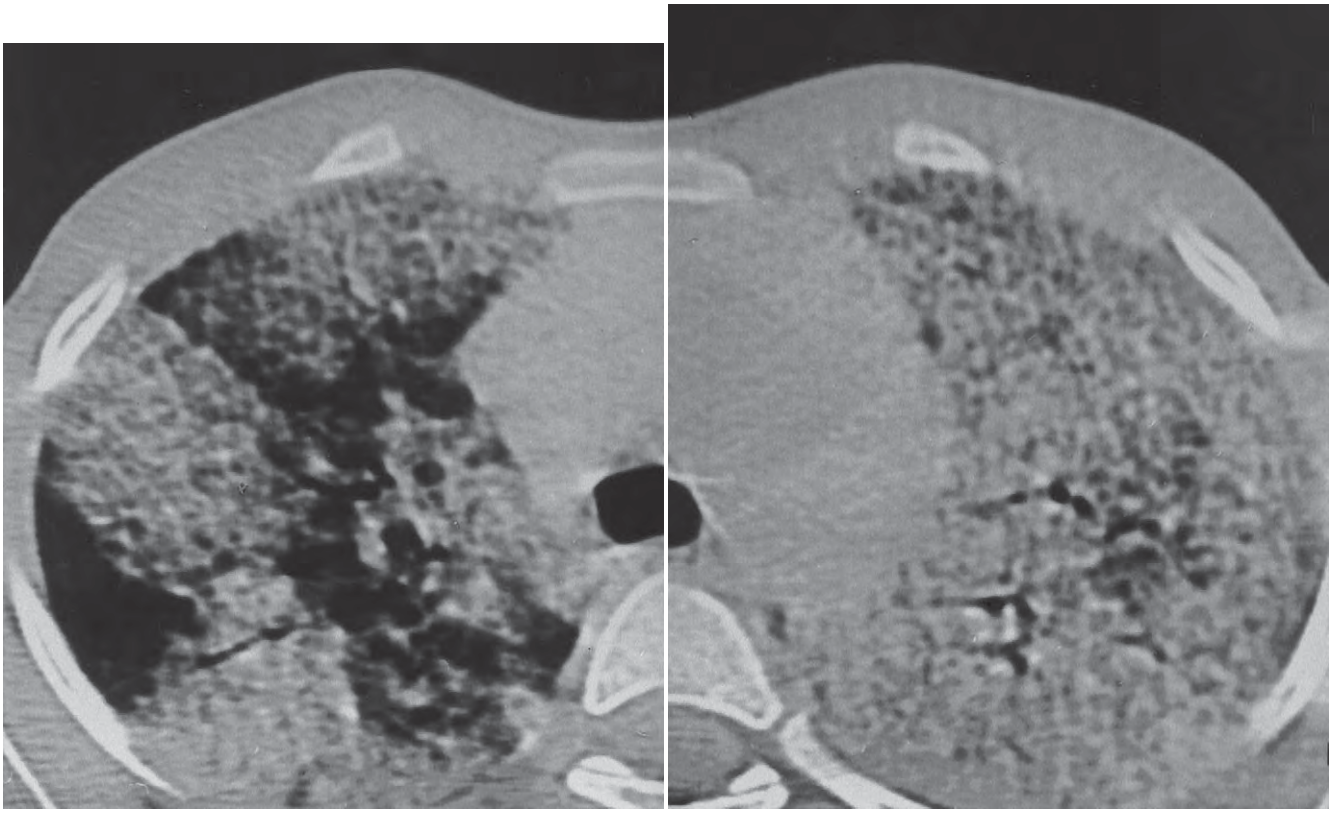

Figure 48-2 Chest computed tomography (CT) scan in the 9-year-old patient with pulmonary alveolar proteinosis whose chest radiograph is shown in Figure 48-1.

Serum anti-GM-CSF antibody is a highly sensitive measure for diagnosing PAP in adults, although it has limited value in monitoring therapy.[42-44] Although antibody has also been identified in children, perhaps due to the rarity of this disease, its value has not been well characterized in children with PAP. Serum LDH correlates well with disease severity and has been suggested as a means to monitor therapy.[45,46] However, LDH is not a sensitive test for diagnosis because most patients will have values in the normal range.

TREATMENT

Numerous therapeutic interventions have been tried unsuccessfully in the past, including systemic steroids and inhaled heparin, acetylcysteine, trypsin, streptokinase, potassium iodide, and surfactant.[2] No therapy was shown to be consistently effective until the introduction of whole lung lavage in 1963.[47,48] More recently the administration of GM-CSF, either systemically or by inhalation, has proved valuable in both adults and children.[22,49-52]

Whole lung lavage in children requires a team including nurses, respiratory therapists, anesthesiologists, and pulmonologists experienced in bronchoscopy and in managing infants and children.[53] The procedure is usually performed under general anesthesia with a double-lumen endotracheal tube inserted with bronchoscopic guidance, ensuring that the tip of the tube is in the main stem bronchus and the balloon, when inflated, is just below the carina and is occluding the main stem bronchus without occluding the upper lobe bronchus. Double lumen endotracheal tubes are generally not available for children who weigh less than 25 kg, and more limited lavage of individual lung segments must be performed. When the patient is appropriately intubated, the lung with the more severe disease, based on chest CT, is lavaged first. The side to be lavaged is deflated and placed dependent with the patient in the lateral recumbent position. Body temperature lavage fluid (normal saline with or without 0.1 U/mL heparin) is instilled, first using 3 to 5 mL/kg to ensure that no fluid leaks into the ventilated side, and then with 12 to 15 mL/kg. The tube through which the fluid is instilled is then clamped and allowed to sit for 1 to 2 minutes before the tube is unclamped and allowed to drain. Chest percussion while the fluid is in the lung may improve the yield of proteinaceous material. Initially, the fluid is milky and yellow to brown in color. The procedure is repeated numerous times until the effluent is clear. Usually only one side is lavaged at a single procedure in children and a repeat procedure is scheduled for the next day if the patient has no complications (Fig. 48-3). Bilateral lavages are routine in adults and can be performed in children if, after 10 minutes of recovery, the lavaged lung is able to maintain adequate ventilation and oxygenation when the remaining lung is degassed. Following the lavage, both lungs are ventilated for 15 to 30 minutes until improved compliance can be documented and oxygenation is adequate with spontaneous ventilation. Frequently, this procedure needs to be repeated several times over years before disease resolution occurs.[54,55] Complications are rare; however, serum electrolytes should be monitored after the

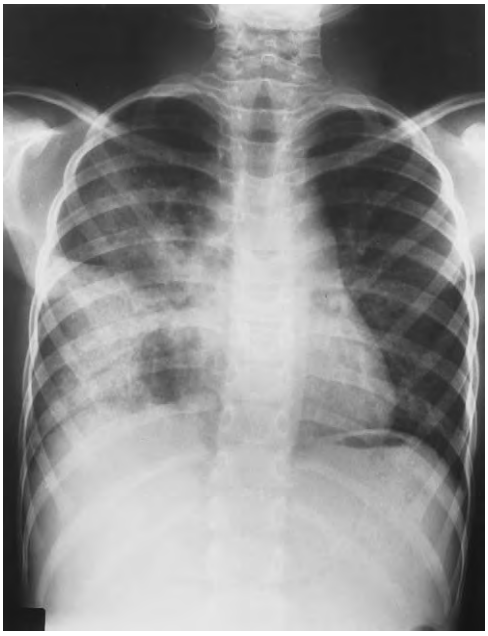

Figure 48-3 Chest radiograph following unilateral (left) lung lavage. Prelavage radiograph is shown in Figure 48-1.

procedure because large amounts of fluid can be absorbed from the lung, thereby producing hyperchloremia and hypokalemia.

GM-CSF has been administered both systemically and by inhalation to patients with PAP.[22,49-52] Although no comparison studies have been performed between whole lung lavage and GM-CSF, initial results suggest that inhaled GM-CSF is at least equally effective for patients with acquired PAP. Wylam and associates[22] report the use of GM-CSF in 12 patients with acquired PAP, two of whom underwent previous whole lung lavage. GM-CSF, 250 μg diluted with normal saline to 2 mL, was administered twice daily with a PARI LC Plus nebulizer (PARI, Starnberg, Germany) for 7 days, every other week. The dose was doubled if no response was documented after 12 weeks of treatment. Eleven patients had improved pulmonary function and only one patient had worsening oxygenation. Most patients reported symptomatic improvement within 4 weeks. Pulmonary function reached peak improvement by 34.5 ± 18.2 weeks. No adverse events were reported. Length of therapy was based on clinical improvement. Five patients relapsed after discontinuing GM-CSF therapy. Four of these patients restarted therapy and all parameters normalized. Several other authors have reported cases or smaller series of patients treated with GM-CSF including one 13-year-old who had not improved after whole lung lavage and was positive for anti-GM-CSF antibody.[49-52,56] Although limited safety data exist in patients with PAP, experience in using GM-CSF to treat malignancies has shown few problems.[57]

CLINICAL COURSE AND PROGNOSIS

Clinical course in acquired PAP can vary from progressive respiratory failure to complete resolution. Reported overall survival is 75% with most deaths due to respiratory failure.[2] The greatest complication risk is pulmonary infection, often from opportunistic organisms (most notably *Nocardia* and *Aspergillus*).[2,3] These infections appear to be related to abnormal macrophage function and often are systemic, suggesting that the effects of PAP are not simply local.[58,59] Infection complications are reduced in patients treated with whole lung lavage, possibly due to improved macrophage function following lavage.[60]

In general, three patterns of disease can be expected: progressive deterioration, stable but with persistent symptoms, and spontaneous improvement.[1] Spontaneous resolution is reported to occur in 8% to 50% of acquired PAP patients.[2] Many of these patients have been treated at least once with whole lung lavage and resolution refers to a lack of symptoms or need for further therapy. Whether the underlying pathophysiology has completely resolved, or is simply in a state of relative quiescence, is not clear because comprehensive evaluations of these patients are rarely reported.[2]

Patients with secondary PAP have a much better prognosis, particularly if the underlying cause (e.g., malignancy) can be effectively treated and macrophage number and function return to normal.[5] Congenital PAP has a generally poor prognosis, particularly if SP-B deficiency is the etiology. One patient with lysinuric protein intolerance had fatal recurrence of PAP following heart-lung transplantation.[9]

PITFALLS AND CONTROVERSIES

While there have been great advances in understanding the underlying pathophysiology of PAP, particularly for acquired disease, choice of therapy still remains challenging owing to lack of well-controlled comparative studies. Acquired disease may resolve spontaneously; however, most patients will require therapy. For patients with GM-CSF antibody, the use of inhaled GM-CSF is a logical choice.[61] However, this therapy may also be effective in patients without antibody and a clinical trial may be indicated in any patient with worsening disease. Whether or not GM-CSF therapy is as effective as whole lung lavage is not clear. Certainly for patients with respiratory distress or disease not improving with GM-CSF, the treatment of choice is whole lung lavage. Additionally, lavage should be considered for patients who have complicating infections. Finally, because of the limited number of patients previously treated, the risk of GM-CSF therapy is not known. Experience from GM-CSF use in malignancies suggests that the risk should be low.[57]

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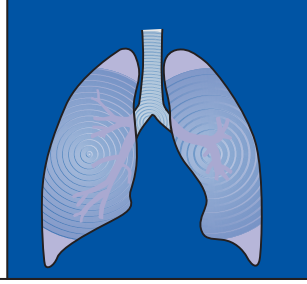

CHAPTER 49 Idiopathic Pulmonary Hemosiderosis

Shahid Ijaz Sheikh and Karen S. McCoy

TEACHING POINTS

- IPH is a rare syndrome. Its etiology may be autoimmune, allergic, or environmental.
- It may manifest acutely with hemoptysis, anemia, cough and dyspnea, and infiltrates on chest radiographs or chronically with pallor, failure to thrive, chronic lung disease—at times with normal physical examination.
- Diagnosis requires careful history and physical examination to confirm pulmonary hemorrhage. If there is clinical suspicion, bronchoscopy with lavage (hemosiderin-laden microphages) is helpful. Other causes of hemoptysis need to be ruled out.
- Pathology consists of thickened alveolar walls, intact erythrocytes in the distal airways, hemosiderin-laden macrophages, and absence of any other disease process or bleeding disorder.
- Treatment consists of systemic glucocorticoids. At times, other immunosuppressive agents including hydroxychloroquine, cyclophosphamide, azathioprine, and methotrexate may also be helpful.
- Prognosis improves with time; rarely it may be fatal.

Idiopathic pulmonary hemosiderosis (IPH) is a rare syndrome characterized by recurrent diffuse alveolar hemorrhage of unknown etiology. It can occur with or without hemoptysis and is associated with pulmonary infiltrates and iron deficiency anemia secondary to deposition of hemosiderin iron in the alveoli. It is more prevalent in children and may have a high mortality. Alveolar hemorrhage can be a life-threatening condition. Following a bleeding episode the hemoglobin's iron is converted into hemosiderin by the alveolar macrophages within 36 to 72 hours,[1,2] hence the term hemosiderosis. The term pulmonary hemosiderosis should be reserved for persistent or recurrent intra-alveolar bleeding because hemosiderin-laden macrophages reside for up to 4 to 8 weeks in the lungs.[1,2] There are numerous causes of alveolar hemorrhage and the diagnosis of IPH is reserved for those cases where other identifiable causes are excluded. Currently, in the presentation of a patient with hemoptysis, pulmonary infiltrates and anemia with no identifiable cause, the diagnosis of IPH is considered[3,4]—especially when vasculitis/capillaritis, granulomas, or immune depositions[5] are ruled out with appropriate studies.

EPIDEMIOLOGY

IPH is a rare disorder with less than 500 reported cases in the literature. Based on published data, an estimated incidence is between 0.24,[6] and 1.23,[7] per million of selected populations. In a biopsy study of interstitial lung diseases in children, lesions of IPH were found in 8% of cases.[8] About 80% of cases occur in children, the majority being diagnosed in the first decade of life.[4,5] Adult onset accounts for the remaining 20% of cases of IPH, but it is unclear how many are previously undiagnosed childhood-onset IPH; diagnosis is before 30 years of age in most patients. Gender distribution is balanced in childhood-onset IPH, but there is a slight male predominance in adult-onset IPH.[5,9] There have been reports of familial clustering in several reports,[10-12] suggesting a possible genetic or environmental contribution to the disease occurrence.

ETIOLOGY

The etiology of IPH remains unclear. Because a few clusters of cases have been identified, the possibility of environmental, familial, or genetic factors cannot be ruled out. Several familial cases have been reported, suggesting either a hereditary cause or a genetic predisposition to the influence of some unidentified environmental agents.[10,13,14] Some of the hypotheses mentioned in the literature are worth reviewing—although proof is lacking for any of them.

Autoimmune Theory

In the initial use of electron microscopy in investigating patients with IPH, many ultrastructural alveolar membrane lesions were noted. Among findings were vacuolization of the alveolar endothelial cells, focal thickening, and scattered ruptures of the alveolar capillary basement membranes,[15-17] although these lesions are not specific to IPH and were not confirmed by all authors.[18,19] An autoimmune etiology was hypothesized by some investigators based on the demonstration of circulating immune complexes,[20] even though the immunohistochemical examination of lung tissue generally has not supported an immunologic pathogenesis.[16,18-20] It is noted that among those with IPH who survive more then 10 years, almost one fourth of them subsequently develop some form of autoimmune disease.[21,22]

Allergic Theory

In 1962, a study published by Heiner and colleagues[23] suggested a possible causal relationship in a few children with IPH who had detectable plasma antibodies (precipitins and immunoglobulin E (IgE)) against cow's milk protein, which led to the hypothesis of a systemic allergic reaction to milk

components.[23-25] Later studies were mixed in respect to this hypothesis.[5,20]

In the original report by Heiner and colleagues[23] seven infants with this correlation were identified after screening more than 2000 patients with symptoms of chronic pulmonary and upper airway diseases. The children apparently improved on a milk-free diet, although a few of them were later able to tolerate reintroduction of milk in the diet. In 1975, Boat and coworkers[24] reported another group of infants ($n = 6$) presenting with a similar clinical picture and high titers of milk protein precipitins. These infants were identified after screening the sera of 160 children with idiopathic chronic lung disease. These six children presented with recurrent pulmonary infiltrates, associated with a mixture of findings including hemosiderin-laden pulmonary macrophages in five, intermittent wheezing in five, eosinophilia in four, anemia in four, and failure to thrive in four. Three out of these six children later went on to develop upper airway obstruction and cor pulmonale. Elimination of cow's milk from the diet, and adenoidectomy when indicated, resulted in improvement in all six patients. In a subsequent study, these investigators were not able to directly correlate milk precipitin levels as a differentiator between four children presenting with pulmonary hemosiderosis compared with other children with chronic lung diseases, gastrointestinal disease, and upper airway disease.[26] In the last 20 years, this hypothesis is questioned by others who were not able to reproduce the association.

Other researchers have identified more than 10 cases with both pulmonary hemosiderosis and celiac disease.[27-29] These patients had complete remission of their pulmonary manifestations after instituting a gluten-free diet.

Environmental Theory

Other authors[11,30] have proposed an association between the occurrence of IPH and exposure to insecticides, but this has never been confirmed. Recently, many studies linking environmental exposure to fungi (especially *Stachybotrys atra* or *S. chartarum*) in water-damaged houses in Cleveland, Ohio, with infantile pulmonary hemosiderosis suggested an infectious or mycotoxigenic pathogenesis.[31-36] Fungal toxin called *trichothecene* is postulated to be responsible by impeding the angiogenesis underneath the alveolar membranes, making the acinar region prone to bleeding. Review by the Center of Disease Control and Prevention questioned the causal relationship between the exposure to molds (e.g., *S. atra* or *S. chartarum*) and the diagnosis of hemosiderosis.[32] Some of the infants in this cohort had other features such as developmental delay, seizures, and hemoglobinuria, suggesting that these infants should be considered as a separate group due to possible confounding factors.

CLINICAL PRESENTATION

Most of the children with IPH presenting with respiratory symptoms are younger than 6 years of age. Although the absence of hemoptysis does not rule out pulmonary hemorrhage, especially in infants and young children, it is a common presentation of IPH. Infants and children usually present with varying severity of recurrent hemoptysis and anemia, which depends on the severity of the alveolar hemorrhage. In severe attacks, hypoxia and dyspnea may be noted. Between attacks the child may be well, apart from the effects of chronic lung disease and residual anemia, if any. Recovery from an episode of bleeding may be surprisingly rapid and complete. In children, failure to thrive and anemia can be the initial findings. In adults the respiratory symptoms can be more pronounced.[37]

The clinical course can be divided into two phases. Acute episodes correspond to intra-alveolar bleeding, with cough, dyspnea, hemoptysis and sometimes respiratory failure; anemia may be present. At times, there may be a normal examination. The chronic phase is characterized by a slow resolution of previous symptoms, with or without treatment; the patient may or may not return completely to baseline, depending on the degree of residual lung damage. The chronic phase manifests with varying respiratory compromise, pallor, emaciation, failure to thrive, hepatosplenomegaly and, sometimes, a normal examination. In those with fibrosis, bilateral crackles and clubbing may be present.

There are no pathognomonic radiologic findings for IPH. Certain radiologic patterns are closely correlated with the clinical phase. During the acute phase (IPH presentation or exacerbations) the chest radiographs show diffuse alveolar-type infiltrates, with the lower lung fields predominantly affected. On the high-resolution computed tomography (CT) scan,[38] this appears as ground-glass opacity mostly in the areas of infiltrate on plain radiograph. During remission, the alveolar infiltrates may resolve or may be replaced by interstitial opacities with a variable degree of fibrosis.[39]

Unless the bleeding is recent, hematologic investigation will usually show microcytic, hypochromic anemia. Reticulocytosis may be present, depending on available iron stores. In older children, sputum examination, although not very sensitive, can demonstrate intra-alveolar bleeding (erythrocytes and hemosiderin-laden macrophages), by hematoxylin-eosin and Prussian blue (Perl) stains. If the patient is not spontaneously producing sputum, inducing it can be dangerous. Bronchoalveolar lavage (BAL) from involved areas has a higher diagnostic yield than the sputum examination.[40-42] The predominant cellular types are the alveolar macrophages, filled with hemosiderin and intact erythrocytes.

In children old enough to perform tests of lung function, the typical picture is of restrictive lung disease with reduced forced vital capacity (FVC), reduced forced expiratory volume in 1 sec (FEV_1), and a normal FEV_1/FVC ratio.[43] Diffusion studies can reveal the single-breath carbon monoxide uptake to be low or normal during the chronic phase or elevated during the acute phase.[44] Varying respiratory insufficiency can be present and should be reflected in the severity of the pulmonary function abnormality, but the insufficiency may be appreciated only with activity. Investigations to exclude other causes of pulmonary hemorrhage, such as the pulmonary-renal syndromes or cardiac disease, will be negative in IPH.

DIAGNOSIS

To establish a diagnosis of IPH, one has to confirm diffuse alveolar hemorrhage and exclude other diseases that can be associated with diffuse alveolar hemorrhage. Pulmonary hem-

orrhage can be confirmed by the clinical picture, which may include cough, hemoptysis, dyspnea, and increased work of breathing. The presentation includes pallor, multiple opacities on chest radiographs and/or high resolution CT scan of the chest. A plain chest radiograph can be very helpful in determining the site of the bleeding, but a normal radiograph does not rule out diffuse pulmonary hemorrhage. A normal chest radiograph also does not prove that bleeding was of extrapulmonary origin. Presence of iron deficiency anemia in cases of recurrent hemorrhage and bronchoalveolar lavage with hemosiderin-laden macrophages on bronchoscopy can be of further help.

When pulmonary hemorrhage is confirmed, the next step is to rule out other diseases which can manifest with pulmonary hemorrhage, which should include a careful history, examination, and appropriate special investigations (Table 49-1). Computed tomography of the chest with contrast may be needed to define cavitary lesions or the very rare pulmonary arteriovenous malformations which can cause hemoptysis. Rare causes of pulmonary hemorrhage, such as hereditary hemorrhagic telangiectasia, may require pulmonary angiography. Bronchoscopy can be very helpful and should include careful inspection of the upper airway and bronchoalveolar lavage (BAL) where appropriate. During active bleeding, the approximate location of the bleeding can also be determined. It may be advisable to do rigid bronchoscopy in cases of severe acute hemorrhage, especially if any attempt to stop bleeding is desired because it can provide better control of the airway both for removal of blood and clots and for any corrective procedure. If there is no active bleeding and no obvious cause (e.g., foreign body) is suspected, BAL should be performed to look for hemosiderin-laden macrophages (HLMs) as an indication of previous pulmonary hemorrhage. Sherman and associates[2] reported that HLMs were not found during the first 2 days after an acute bleed, and were still present 5 days after the bleed, but not at autopsy in one infant 12 days after the bleed. Epstein and colleagues[1] in a mouse model reported that HLMs began to appear on day 3 (2.8% total cell count) after the acute introduction of blood into the lungs, peaked (60%) at day 6, remained high until day 10, and then fell to low levels (10%) by 1 to 2 months. Optimal timing of BAL for IPH diagnosis is from 3 days post bleed or, if complicated by respiratory failure, prior to extubation. Based on these studies, if the plain chest radiograph, bronchoscopy, and bronchoalveolar lavage (performed between 3 to 14 days after the suspected bleed) are all normal, then it is unlikely that there was a true pulmonary hemorrhage. In this instance, it would be advisable to wait to see if there are any further episodes of suspected bleeding, which can be investigated similarly.

Table 49-1
Common Causes and Related Diagnostic Studies of Hemoptysis

Possible Causes of Hemoptysis	Diagnostic Studies
Infection	
Bacterial	
Lung abscess	Chest radiograph
Tuberculosis	Purified protein derivative (PPD)
Bronchiectasis	Chest radiograph, high resolution chest computed tomography (CT) scan
Cystic fibrosis	Sweat chloride >60 mEq/L
Immune deficiency	Abnormal immunoglobulin levels
Fungal	
Histoplasmosis, Coccidioidomycosis, etc.	Positive immunodiffusion and/or complement fixation titers by serology
Vasculitis Syndromes	
Immune-Complex Mediated	C1q binding assay, C3b binding assay Raji cell assay, complement level (CH-50)
Henoch-Schönlein purpura	Purpura/arthritis/abdominal pains
Wegener granulomatosis	Anti-proteinase-3 antibody (cANCA)
Polyarteritis nodosa	Anti-proteinase-3 antibody (cANCA) Anti-myeloperoxidase antibody (pANCA)
Other Immune-Mediated Diseases	
Goodpasture syndrome	Circulating antiglomerular basement membrane antibodies, nephritis
Systemic lupus erythematosus (SLE)	Anti-double stranded DNA, high antinuclear antibodies (ANA), and erythrocyte sedimemtation rate
Allergic bronchopulmonary aspergillosis (ABPA)	*Aspergillus* skin reactivity, *Aspergillus fumigatus*–specific IgG and IgE antibodies in serum
Cardiovascular	
Congenital heart defects/ congestive heart failure	Electrocardiogram and echocardiogram
Congenital Pulmonary Malformations	
Pulmonary sequestrations	Infiltrate on chest radiograph and chest CT scan
Pulmonary Embolism	Abnormal ventilation/perfusion ($\dot{V}/\dot{Q}$) scan
Neoplasms	Abnormal chest radiographs, CT scan, and bronchoscopic examination
Retained Foreign Body	Foreign body seen on bronchoscopy
Hematologic	High prothrombin time (PT) and/or activated partial thromboplastin time (APTT)
Trauma	History of trauma
Idiopathic Pulmonary Hemosiderosis (IPH)	Hemosiderin-laden macrophages in bronchial lavage or sputum/anemia
Hereditary Hemorrhagic Telangiectasia	Pulmonary angiography
Factitious hemoptysis precipitated by patient or caretakers	Careful history and negative work-up

If bleeding into the lungs is confirmed and is not due to a localized lesion in the airway, and the child does not have CF or bronchiectasis from another cause, a cardiology evaluation including echocardiography should also be performed. In the absence of significant cardiac pathology, investigations for possible pulmonary-renal syndromes should begin. This should include ANA, anti-double-stranded DNA, ANCA (both perinuclear and cytoplasmic variants), anti-GBM antibodies, antiphospholipid antibodies, IgG and IgE cow's milk protein antibodies, and rheumatoid factor. Also, patients can be tested for celiac disease with plasma antigliadin and antireticulin antibodies, although a lack of gastrointestinal symptoms makes this diagnosis unlikely. These studies should be performed much earlier if the child is known to have a systemic disease or if there are suggestive findings such as a rash, blood, or cellular casts in the urine. In the absence of systemic disease, it is likely that the cause of the pulmonary hemorrhage is IPH, which is essentially a diagnosis of exclusion. Open lung biopsy is rarely needed.

PATHOLOGY

The diagnosis of IPH can usually be made by clinical presentation and by exclusion of other causes of pulmonary hemorrhage; lung biopsy is rarely, if ever, justified. Occasionally, when it is not possible to exclude all systemic causes, lung biopsy may be necessary. The lung histology in IPH shows many red blood cells in alveoli and the interstitium after recent active bleeding, without any evidence of vasculitis. After a few days, macrophages in both areas contain hemosiderin.

In IPH, the lungs demonstrate the macroscopic finding of the so-called brown induration[3] due to various degrees of fibrosis and infiltration with iron. The diagnosis is strongly supported by features on light microscopy[5,15,16,18,19] which include thickened alveolar walls, intact erythrocytes in the distal airways and alveoli (a reflection of recent/active diffuse pulmonary hemorrhage),[5] multiple hemosiderin-laden macrophages (subacute/chronic or recurrent intrapulmonary bleeding) and the absence of any focal or diffuse smooth muscle cell proliferation, malignancy, infections, vascular malformations, pulmonary infarcts, capillaritis/vasculitis, or granulomatous inflammation. Useful ancillary tests are immunohistochemistry and immunofluorescence to exclude any intrapulmonary immunoglobulin or immune complex deposition. Electron microscopy may be important in those cases where other studies do not specifically rule out an immune deposition, particularly in the alveolar basement membrane, but is not necessary in routine cases. Electron microscopy lacks any evidence of electron dense deposits in the alveolar basement membrane.[16,18,19,45]

TREATMENT

Because this disease is rare, prospective controlled studies and large longitudinal surveys are not possible and most of the concepts regarding management of IPH are developed from observational studies on small numbers of patients, and data collected over years of observation are often incomplete.

Among the available data, the most commonly used medications are systemic glucocorticoids, which have produced clinical improvement in many patients in the acute phase of IPH and have been shown to have an impact on mortality,[5,9,13] although the dose, efficacy, and duration of use in the post-acute phase is not clear. Recommended starting dose is around 1 mg/kg/day of prednisolone for weeks to months, until the new alveolar infiltrates improve, and then taper over the next few months if symptoms do not recur. The majority of the patients with IPH seem to respond favorably to chronic oral corticosteroids, with a decreased number of IPH exacerbations and, possibly, a decline in fibrogenesis.[13,18,46,47] In children and adolescents, long-term treatment with oral corticosteroids can have undesirable side-effects. There is also a risk of a higher rate of recurrence with decreasing dose of chronic corticosteroid therapy, and these patients should be monitored for ophthalmologic changes and effect on bone mineralization. Medic Alert identification for chronic steroids and education regarding stress-steroid prophylaxis are warranted. The role of *Pneumocystis carinii* prophylaxis is unclear. There are insufficient data on the use of inhaled corticosteroids[48,49] in this clinical setting.

Other immunosuppressive agents, including hydroxychloroquine, cyclophosphamide, azathioprine, and methotrexate, have been tried with variable results.[7,15,50-55] Only two cases of single-lung transplantation have been reported.[56,57] Unfortunately, both cases had a clinical course complicated by IPH recurrence in the transplanted lungs—raising questions regarding this therapeutic option in IPH.

PROGNOSIS

Because of the small number of patients and lack of follow-up studies with large patient numbers, it is difficult to assess short- and long-term prognosis. Mortality from IPH is usually from pulmonary causes, including acute respiratory failure secondary to massive alveolar hemorrhage or as a result of chronic respiratory failure and cor pulmonale owing to severe pulmonary fibrosis.[5]

Soergel and coworkers[5] in 1962 reported 68 patients with a mean follow-up of 4 years and in their series 20 patients died, 17 had recurrent exacerbations of pulmonary hemorrhage, 12 had chronic active disease with persisting dyspnea and anemia, and 19 remained asymptomatic.[5] Only 28 (41%) in the study were treated with steroids. In this case series, the average survival after the onset of symptoms was 2.5 years.

Chryssanthopoulos and associates[58] in 1983 reported the outcome of 30 children followed for an average of 5 years. The mean survival was 3 years (range, 3 months to 10.5 years) and the mean mortality rate was 60%. Nearly 87% of the patients received steroids at some point in time.[58] Their results suggested that the severity of the disease at its onset does not determine the survival; females have better survival; and younger age of the patients at the onset of IPH seems to carry a less favorable prognosis.

Kiper and colleagues[46] reported 23 children with IPH in 1999. In their study all patients were treated with prednisolone. On remission, patients were kept on low-dose prednisolone for 2 to 14 years. One patient died, seven were lost to follow-up. Fifteen (65%) were followed for an average of 8 years. Seven had no relapse after discontinuation of oral steroids. In the remaining eight patients, attempts to discon-

tinue prednisolone failed because of worsening symptoms. Two of these 8 patients were subsequently weaned to budesonide by inhalation.

Saeed and coworkers[47] in 1999 reported a 28-year experience at the Children's Hospital of Los Angeles. In their series were 17 children with IPH and the projected 5- year survival in the study was 86%. The mean duration of follow-up was 3.6 years (range 0.7 to 10.2 years). Initial treatment consisted of prednisone only in 14 (76%) patients and hydroxychloroquine in 2 (12%) patients. Thirteen patients (76%) required long-term corticosteroids. Eight patients (47%) required other immunosuppressants (hydroxychloroquine or azathioprine) in addition to prednisone to control hemoptysis. Prolonged immunosuppressive therapy might be responsible for better outcome in their study.

Le Clainche and colleagues[21] in 2000 reported data collected from pediatric and adult hospitals throughout France. Their series was limited to children known to have survived at least 10 years. They reported 15 children with mean follow-up of 17.2 years (range 10 to 36 years). In their series, three (20%) of patients, all females, developed systemic disease (rheumatoid polyarthritis or rheumatoid polyarthritis–like diseases). Five of 13 (38%) children were still on treatment at least 10 years after diagnosis. Twelve patients (80%) had mild or no respiratory symptoms (although many had abnormal pulmonary function testing and chest radiographs and were able to lead a normal life. Because an association has been reported between cow's milk allergy and IPH, many children with IPH are placed on milk-free diets. Unless there is unequivocal evidence of true milk allergy, this may not be necessary. In those who recover from IPH, lung function can recover to within the normal range, especially if no further bleeding occurs. In some studies, good prognosis often referred to survival, whereas functional status of survivors was not clearly described. By reviewing the prognosis and survival data over the last 50 years, it is clear that there is a positive pattern in the outcome of these patients that may be because of prolonged immunosuppression, or secondary to spontaneous remission during an era when general supportive medical care is improving.

CONCLUSION

Hemoptysis in children is rare but, if not managed appropriately, it can be fatal. When more common causes such as infection, cystic fibrosis, airway lesions, and cardiac diseases are excluded; focus should be on pulmonary-renal syndromes or idiopathic pulmonary hemosiderosis (see Table 49-1).

IPH is a rare disease of unknown etiology, manifesting with recurrent episodes of diffuse alveolar hemorrhage (with or without hemoptysis) and sideropenic anemia. It occurs most commonly in children. It manifests classically with cough, tachypnea, and hypoxemia. Most of the time, symptoms are accompanied by hemoptysis. Initial work-up includes a chest radiograph that may reveal alveolar infiltrates and hematologic evaluation that may reveal worsening anemia; both findings are suggestive of intrapulmonary bleeding. Confirmation requires numerous hemosiderin-laden macrophages in the alveoli that can be shown by bronchoscopy and examination of bronchoalveolar lavage. In older children, sputum examination may also yield hemosiderin-laden macrophages. Occasionally lung biopsy is needed to confirm absence of capillaritis/vasculitis, granulomatous inflammation, and deposition of immunoglobulins or immune complexes, but lung biopsy is usually not required.

The etiology of IPH is not clear and there are insufficient data to consider it an autoimmune disease, but glucocorticoids and other immunosuppressive drugs seem to be effective during exacerbations. In many patients, oral corticosteroids are also useful during the remission phase. Over the past few decades, there is a significant improvement in morbidity and mortality from IPH, which in part is due to aggressive management of acute alveolar hemorrhage and long-term use of immunosuppressant therapy.

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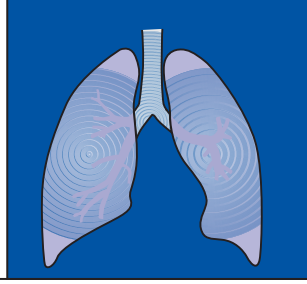

CHAPTER 50 Sarcoidosis

Brigitte Fauroux and Annick Clément

TEACHING POINTS

- Sarcoidosis is a multisytem granulomatous disease of unknown etiology, most commonly affecting young adults; the diagnosis is relatively rare in children.
- Lesions can occur in almost any tissue or organ but the lungs, lymph nodes, eyes, skin, and liver are more commonly involved.
- Clinical symptoms are nonspecific, often minor, and sometimes absent.
- The diagnosis can be supported only by typical histopathologic findings with noncaseating epithelioid-cell granulomas.
- Corticosteroid therapy is the most common treatment and is often effective.
- The prognosis seems to be more severe in younger children and where there is multi-organ involvement.

Sarcoidosis is a multisytem granulomatous disease of unknown etiology, most commonly affecting young adults. The diagnosis is relatively rare in children.[1,2] Divergent prevalence rates and clinical appearances in different races support the existence of predisposing genes, with probably a predominant role of the major histocompatibility complex. Lesions can occur in almost any tissue or organ but the lungs, lymph nodes, eyes, skin, and liver are more commonly involved. Clinical symptoms vary according to the organ involved but they are generally nonspecific and minor. The diagnosis requires typical histopathologic findings with noncaseating epithelioid-cell granulomas. The prognosis seems to be more severe in younger children and with multi-organ involvement. Corticosteroids are the mainstay of therapy and are indicated in case of significant lung or eye lesions, cardiac, neurologic, or multi-organ involvement. Other anti-inflammatory agents occasionally have been used. Spontaneous resolution occurs less often in children than in adults, and despite treatment, a significant number of patients have residual organ system damage or progressive disease.

EPIDEMIOLOGY

The incidence and prevalence of sarcoidosis are influenced by age, race, and geographic localization, although part of this variation can be explained by regional differences in diagnostic awareness and efforts. The two sexes appear to be affected with equal frequency. The disease is encountered most frequently in young adults. The exact prevalence in children is unknown. Cases have been reported in infants as young as 2 and 3 months of age, but the disease is more common in preadolescents and adolescents.[1-3] A National Patient Registry collecting data on patients with sarcoidosis since 1979 in Denmark reported an incidence of 0.29 per 100,000 person-years ≤15 years of age during the period 1979-1994.[2] The incidence was 0.06 in children ≤4 years of age and increased gradually to 1.02 in children aged 14 to 15 years. Thereafter, the incidence continued to increase significantly with age.

Several reports of familial sarcoidosis, human leukocyte antigen (HLA) linkages, and divergent prevalence rates and clinical appearances in different races suggest the existence of genes predisposing for sarcoidosis. Indeed, in a large study on familial aggregation of sarcoidosis, a significant elevated risk of sarcoidosis was observed among first- and second-degree relatives of sarcoidosis patients compared with relatives of matched control subjects. White patients had a markedly higher familial relative risk than African Americans. Genome-wide searches for predisposing genes and a study performed on 225 microsatellite markers tested in 63 families with affected siblings have shown a predominant, although not exclusive, role of the major histocompatibility complex.[4]

ETIOLOGY

The cause of sarcoidosis is unknown (Table 50-1). A combination of environmental and host factors probably cause the characteristic granulomatous response. An infectious, in particular a viral cause, has been evoked in sarcoidosis because high titers of antibodies against lymphotropic viruses (Epstein-Barr virus, human herpesvirus, cytomegalovirus), parainfluenzae, and rubella have been found in some patients. However, a viral cause has not been substantiated by viral cultures or unequivocal tissue analysis. Similar hypotheses have been proposed for mycobacteria, fungi, protozoa, metazoa, spirochetes, and bacteria, but presently no conclusive evidence has been demonstrated. The presence of microorganism-specific antibodies in high titers might reflect generalized B-cell activation in sarcoidosis and does not necessarily indicate a causal relationship. Noncaseating epithelioid granulomas have also been observed in patients with immune disorders, vasculitis, and neoplasms. Exposure to respirable bioaerosols containing endotoxin and microbial contaminants has been shown to cause diseases that are clinically and histologically indistinguishable from sarcoidosis. Most interesting are the case

Table 50-1
Granuloma-Forming Disorders and Potential Etiologies for Sarcoidosis in Childhood

Category	Subcategory	Examples
Infections	Viruses	Epstein-Barr virus, herpes, rubella, measles, cytomegalovirus, coxsackie B, parainfluenza
	Fungi	*Histoplasma* spp, *Aspergillus* spp, *Coccidioides* spp
		Blastomycosis, cryptococcosis
	Protozoa	*Toxoplasma, Leishmania*
	Metazoa	*Schistosoma*
	Spirochetes	*Treponema pallidum*
	Mycobacteria	*Mycobacterium tuberculosis, M. leprae*, nontuberculous mycobacteria
	Bacteria	*Yersinia* spp, *Borrelia* spp, *Brucella* spp
Immune disorders	Idiopathic	Crohn disease, primary biliary cirrhosis, hypogammaglobulinemia, common variable immune deficiency, chronic granulomatous disease, histiocytosis X
Organic dust	Hypersensitivity pneumonitis	Farmer's lung
		Bird fancier's lung
Vasculitis	Idiopathic	Wegener granulomatosis
		Churg-Strauss allergic granulomatosis
		Bronchocentric granulomatosis
		Systemic lupus erythematosus
Neoplasms	Carcinoma, sarcoma	Malignancy-associated granulomas

reports of adult patients who suffered a relapse of sarcoidosis in a transplanted lung despite receiving immunosuppressive therapy. These observations suggest that the etiologic agent could hide within the lung and/or other compartments of the body.

PATHOLOGY AND PATHOGENESIS

The typical histologic findings are those of noncaseating granulomas diffusely scattered within the different tissues (Fig. 50-1). In contrast to granulomas seen in hypersensitivity pneumonitis they are well-formed, compact aggregates. They are usually of varying ages, ranging from highly cellular lesions to collections with diminishing cellularity, some fibrosis, and progressive hyalinization. Two characteristic zones can be seen in a typical, well-developed sarcoid granuloma: (1) a central zone or follicle that is tightly packed with cells, composed primarily of macrophages, multinucleated giant cells (Fig. 50-2), and epithelioid cells; and (2) a peripheral zone consisting of a collar of loosely arranged lymphocytes, monocytes, and fibroblasts. Although many microscopic features may suggest sarcoidosis, the epithelioid granulomas are indistinguishable from those of other idiopathic granulomatous disorders or granulomatous disorders of known origin such as tuberculosis, berylliosis, or hypersensitivity pneumonitis (see Table 50-1).

Studies of bronchoalveolar lavage (BAL) cells have improved the understanding of the immunopathogenesis of sarcoidosis.[5] Activated macrophages and T cells have been identified in different compartments of the sarcoid lung. Classically, the number of alveolar T cells is increased with an increase in CD4+ cells. The T cells of the granulomas exhibit a layer-like distribution, with CD4+ cells expressing an abundance of activation markers predominantly in the inner area and an accumulation of CD8+ cells with smaller numbers of those markers in the outer area. The major source of T cells seems to be a polyclonal nonspecific accumulation accompanied by a clonal expansion. This lymphocyte activation translates into the activation of a cytokine network, which can be summarized as follows.[5] An unknown agent activates resident T cells and macrophages, which subsequently release cytokines (interleukin [IL]-2, IL-12, IL-6, chemokines, and interferon-γ), which prime and activate neighboring cells and are chemotactic for mononuclear cells. The activated cells constitute an alveolitis and the cytokines released (IL-1 and tumor necrosis factor-α) induce and maintain the granulomas, which might contain the unknown "sarcoid agent." Once formed, the granulomas may resolve spontaneously, or if they persist, will become hyalinized and eventually fibrotic, with tissue scarring as the final outcome.

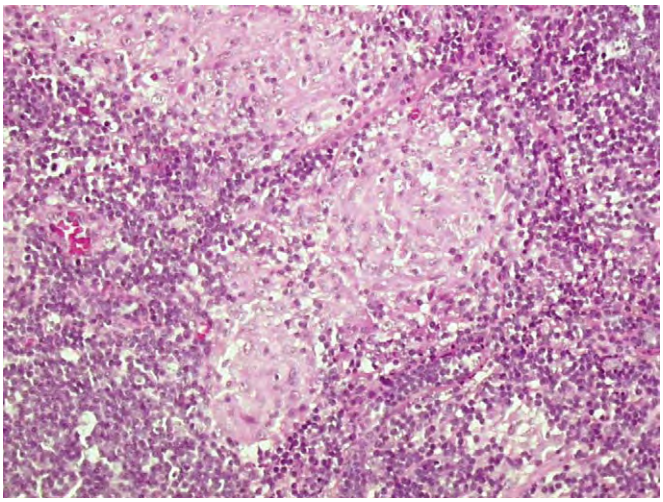

Figure 50-1 Noncaseating epithelioid-cell granulomas in the adenoids of an 11-year-old boy (coloration hematoxylin-eosin-safran [HES] stain, magnification ×25).

CLINICAL FEATURES

Lesions can occur in any tissue or organ. Because symptoms are primarily due to local tissue infiltration and injury by pressure and displacement from sarcoid lesions, the clinical manifestations depend on the organ or system involved (Table 50-2). A nation-wide study in childhood sarcoidosis performed in Denmark showed that common symptoms include

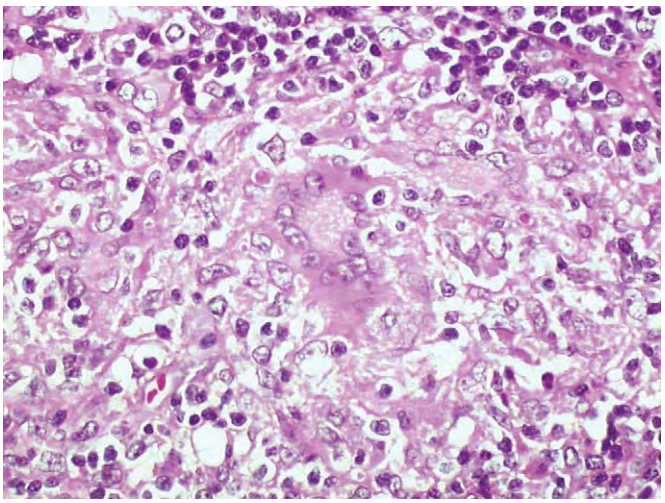

Figure 50-2 Multinucleated giant cell on the adenoid biopsy of an 11-year-old boy (coloration hematoxylin-eosin-safran [HES] stain, magnification ×40).

general malaise, weight loss, fever, lymphadenopathy, skin and ocular manifestations, and central nervous system (CNS) involvement. Clinical manifestations seem to vary according to age. In children younger than 5 years of age, the disease is mainly characterized by involvement of the skin, eyes, and joints; whereas in older children, involvement of the lungs, lymph nodes, and eyes predominate. More than one system is usually involved, and most often, children have at least five or more areas of involvement; this justifies a complete investigation when the diagnosis of sarcoidosis is made.

Whatever the organ involved, general symptoms are common and nonspecific and include weight loss, fatigue, lethargy, anorexia, headache, and, less commonly, prolonged fever. As such, a diagnosis of sarcoidosis must be considered in the case of unexplained, prolonged fever in a child.

Table 50-2
Clinical Manifestations of Sarcoidosis in Children

General symptoms	General malaise, fatigue
	Fever
	Weight loss
	Abdominal discomfort
Lung	Cough
	Chest pain
	Exertional dyspnea
Lymph nodes	Peripheral lymphadenopathy
	Mesenteric lymphadenopathy
	Hilar lymphadenopathy
Eyes	Granulomatous uveitis/iridocyclitis
	Conjunctival granulomas
	Edema of the optic papilla
	Keratitis
	Chorioretinitis
	Glaucoma
Skin	Erythema nodosum
	Papules, plaques, cutaneous and subcutaneous nodules
	Erythroderma, ulcerations, verrucous lesions
	Pustules, ichthyosis
	Calcifications and prurigo
Liver and spleen	Hepatomegaly
	Splenomegaly
Central nervous system	Headache
	Hydrocephalus
	Vertigo
	Seizures
	Nerve palsy
Bones and joint	Pain in extremities
	Arthritis
Heart	Heart block
	Dilated cardiomyopathy
	Ventricular arrhythmias
Other organs	Adenoids and tonsils
	Salivary glands and lacrimal glands
	Muscle granulomas
	Central diabetes insipidus
	Stomach, pancreas, kidney

Lung

The lung and the eyes are the most common organs involved in children. Symptoms referable to the chest are usually mild and often consist of a dry, hacking cough and exertional dyspnea, but most patients are asymptomatic.[6] Physical examination is often normal but findings may include crackles, rhonchi, wheezing, or decreased breath sounds. Bilateral hilar lymph node enlargement, with or without lung changes, is the most common radiographic finding in children. Chest radiograph findings are classified into four stages: stage 0 is a normal chest radiograph; bilateral hilar lymphadenopathy alone is stage I; bilateral hilar lymphadenopathy with pulmonary infiltrates is stage II; parenchymal infiltrates without hilar lymphadenopathy is stage III; and irreversible pulmonary fibrosis is stage IV (see later). In a Danish study including 48 children with sarcoidosis, chest radiographs were normal in 10% of the patients, 71% of the patients had hilar lymphadenopathy (stage I), 8.3% had associated parenchymal involvement (stage II), and only one patient had only parenchymal involvement (stage III).[3] None of the patients had evidence of irreversible pulmonary fibrosis (which some have called stage IV).

Involvement of the lungs is documented on BAL, which shows an increase in the proportion of lymphocytes with an increase in the CD4/CD8 ratio.[7] The presence of an increase in the number of polymorphonuclear neutrophils (PMNs) in BAL fluid has been shown to be associated with a less favorable outcome.[6] This BAL lymphocytosis is not correlated with the activity of the disease, the response to treatment, or the prognosis.[7] Systematic serial BAL is, therefore, not necessary.

Lung function abnormalities are common in children with lung sarcoidosis.[6] Significant decreases in vital capacity (VC), and/or dynamic lung compliance (CLdyn), and/or lung transfer for carbon monoxide (TLCO) are seen but are nonspecific.[6] Resting TLCO has been shown to be the best predictor of arterial desaturation during exercise. Significant lung function abnormalities are an indication for corticosteroid treatment. Improvements in VC and TLCO are generally observed within the first 6 months of treatment, often with no significant further benefit after this period. CLdyn does not seem to improve with treatment and the sole persistence of a decrease in this parameter warrants no specific treatment.[6]

More recently, the value of inflammatory markers in exhaled air has been studied in adult patients with sarcoidosis. Exhaled nitric oxide (NO) concentration is higher in patients with sarcoidosis compared to control subjects. Although this marker allows a nonspecific estimation of the

severity of airway inflammation in various respiratory tract diseases, in sarcoidosis, the concentration of exhaled NO did not relate to the radiographic stage, the activity, or the progression of the disease. Eight-isoprostane, which is thought to be an index of oxidative stress, seems to be interesting. Indeed, the concentration of 8-isoprostane was increased in patients with active sarcoidosis compared to those with nonactive disease and healthy controls, and correlated positively with serum angiotensin-converting enzyme (sACE). But these different inflammatory markers have not been evaluated in pediatric sarcoidosis.

Lymphatics

Similar to mediastinal lymphadenopathy, peripheral lymphadenopathy is common in children. Nineteen (40%) of the 48 children in the Danish study had peripheral lymphadenopathy and this localization contributed to the diagnosis in 15 of them, showing the typical epithelioid cell granulomas without necrosis.[3] The lymph nodes are generally discrete, painless, and freely movable. Involvement of the mesenteric lymph nodes is less common than peripheral and mediastinal lymph nodes.

Eyes

Ocular symptoms are common, with 29% of the children in the Danish study having them.[3] They are a frequent means of diagnosing sarcoidosis in children. Anterior segment disease is the most common, consisting of chronic granulomatous uveitis, acute iritis, and conjunctival granulomas. Posterior segment disease is less common. Sarcoidosis is not a unusual diagnosis in children with noninfected uveitis. Ophthalmologic slit-lamp examination must be performed in every child with documented or suspected sarcoidosis. Indeed, sequelae such as partial or total blindness may occur if treatment is inadequate.

Skin

Skin lesions are common and varied in sarcoidosis including papules, plaques, cutaneous and subcutaneous nodules, erythroderma, ulcerations, verrucous lesions, pustules, ichthyosis, erythema nodosum, calcifications, and prurigo. Nails can be involved but enlargement of lacrimal and salivary glands is more common. Changes in old scars have been observed. Lesions must be biopsied when the diagnosis of sarcoidosis is not firmly established and in situations where another diagnosis, such as connectivitis, must be ruled out. Skin lesions have the main advantage of offering an easy site for biopsy.

Liver and Spleen

Liver and spleen involvement has to be examined systematically with an abdominal ultrasound scan and liver enzyme tests. Indeed, clinical disease is rarely observed but histologic involvement is common, which may justify a liver biopsy when no other organ is easily available for a histologic confirmation.

Neurologic Symptoms

Neurosarcoid is rare and seldom recognized in children. Twenty-nine children have recently been reported in the world literature.[8] Ages were 3 months to 18 years and 48% presented before 13 years of age. Seizures were the most common manifesting symptom (11 of 29, 38%), and 73% of these children were younger than 13-years old at presentation. Twenty-one percent had hypothalamic dysfunction. Five children presented with headache, four with motor signs, and three with papilledema. Twenty-four percent (7 of 29) had mass lesions on imaging. This study shows that neurosarcoid manifests differently in children than in adults. Children are more likely to have seizures, probably because of space-occupying lesions, and less likely to have cranial nerve palsies. Their presentation evolves to an adult pattern as they progress through adolescence. Neurosarcoidosis has an unfavorable prognosis and is an indication for corticosteroid therapy.

Bones and Joint Involvement

Lytic bone lesions are rare in children and are often associated with skin lesions. Acute polyarthritis or chronic arthropathy is seen in 5% to 10% of children.[3] Granulomas are rarely found in joint tissue in transient arthralgia. Differentiation from juvenile rheumatoid arthritis may be difficult in some patients because uveitis can occur in both diseases.

Heart

Involvement of the heart is often underdiagnosed, justifying a systematic electrocardiogram and echocardiography. Cardiac disease, although uncommon, especially in children, has a wide spectrum of clinical manifestations such as heart block, dilated cardiomyopathy, and ventricular arrhythmias. An increased risk of sudden death has been reported in adult patients with sarcoidosis. Lesions of the myocardium have been described and may cause conduction abnormalities. Because the yield of endomyocardial biopsy for definitive diagnosis is low, the diagnosis is often made with a combination of electrocardiography, Holter monitoring, echocardiography, myocardial perfusion imaging and, most recently, magnetic resonance imaging. For symptomatic patients, medical therapy may include a trial of steroids and immunosuppressive therapy. Monoclonal antibodies against tumor necrosis factor may be employed in refractory cases. Heart block warrants a permanent pacemaker, whereas ventricular tachyarrhythmias are typically amiodarone-unresponsive, requiring implantation of a cardioverter-defibrillator.

Involvement of Other Organs

Peripheral neuropathy has been reported.[3] Sarcoidosis may affect the pituitary gland and diabetes has been reported in children. The tonsils are lymph nodes. Systematic histologic examination of enlarged tonsils, especially in older children, is recommended because some enlarged tonsils may be caused by sarcoidosis (see Fig. 50-1).[6] Involvement of the stomach, the pancreas, and the kidney has also been reported.[6]

LABORATORY INVESTIGATIONS

Laboratory changes are not specific and constitute a guide for the diagnosis that should be confirmed by the characteristic histologic features.

Elevation of the erythrocyte sedimentation rate is a common, nonspecific finding during the acute phase of the disease. Hemoglobin values are generally normal; moderate leukopenia, leukocytosis, or eosinophilia can be observed.[3] Hyperproteinemia is due to an absolute, nonspecific increase in serum globulin.

Anergy to tuberculin is classic in sarcoidosis and constitutes a strong element to the diagnosis of the disease, especially in cases of previous positivity. Tuberculin anergy is not influenced by the rate of the tuberculin test positivity in the general population.

Hypercalcemia is observed in approximately 30% of patients but is rarely symptomatic, although some cases of nephrocalcinosis have been reported.[3]

Serum alkaline phosphatase, glutamic-oxaloacetic transaminase, and glutamic-pyruvic transaminase are often elevated, even in the absence of clinical hepatomegaly. Levels are generally moderately elevated and decrease with treatment. Abnormalities of liver function tests can guide the biopsy for histologic diagnosis because in the absence of another organ easily accessible for biopsy, liver biopsy often shows typical sarcoid granulomas when liver function test abnormalities are present.

Serum angiotensin-converting enzyme (sACE) should be measured when a diagnosis of sarcoidosis is being considered. Indeed, although not pathognomonic, an elevation of this enzyme constitutes a strong diagnostic factor. The activity of the sarcoid lesions is associated with an elevation of sACE but also with other enzymes or proteins such as calcitriol and β_2-microglobulin. The source of the increased level of sACE is unknown but it seems to originate from the sarcoid granulomas. The use of sACE in the follow-up of pediatric patients with sarcoidosis has not been clearly established.

The Kveim test is currently abandoned. In this test, sarcoid tissue homogenate was injected intracutaneously, and, if a reaction developed, a biopsy was performed at 24 to 42 days to identify sarcoid granuloma. The lack of sensitivity and specificity, associated with the hazard of the injection of a tissue homogenate of unknown nature, contributed to the abandonment of this test.

HISTOLOGIC DIAGNOSIS

Biopsy of an easily accessible organ, such as a lymph node, a skin lesion, salivary glands, or the liver, should demonstrate the presence of a characteristic epithelioid cell tubercle without necrosis (see Figs. 50-1 and 50-2). These lesions are not pathognomonic and can also be observed in a number of other diseases (see Table 50-1).

TREATMENT

When the diagnosis is confirmed on a histologic examination, the type and number of organs involved should be assessed, together with the severity of the different lesions (Table 50-3). The involvement of some organs, or a severe involvement of a specific organ, requires immediate treatment. The presence of neurosarcoidosis, involvement of the heart, or severe eye or lung function abnormalities are criteria associated with a more severe outcome and justify immediate corticosteroid treatment (Table 50-4). Multiorgan involvement is also associated with a worse prognosis as in adult patients.[9] Young children seem to have a more severe disease than older children. They are less often asymptomatic and multiorgan involvement is frequent (see Table 50-4).[3] The involvement of the CNS and the heart are also pejorative and justify systematic corticosteroid treatment. The presence of PMNs on BAL has also been shown to be associated with a less favorable response to treatment.[6]

Because the cause of sarcoidosis is unknown, no specific therapy is available. Corticosteroids are widely used and are often effective.[9] Methylprednisolone pulses have been able to improve lung function in patients with very severe interstitial lung disease. Inhaled corticosteroids have been used for maintenance treatment in children but in a noncontrolled design and without being able to prevent relapses.

When the decision to initiate corticosteroid therapy has been made, treatment efficacy should be evaluated based on the clinical manifestations and the specific abnormalities of the organs involved. In case of lung disease, chest radiograph and lung function should be monitored regularly, but the systematic use of BAL is not justified in the absence of spe-

Table 50-3
Recommended Tests for Initial Evaluation and Follow-up of Pulmonary Sarcoidosis in a Child

Type of Evaluation	Initial Evaluation	Follow-up
History	Yes	Not applicable
Clinical examination	Yes	Yes
Laboratory Tests		
Peripheral blood counts	Yes	Yes
Calcium	Yes	Yes
Liver enzymes	Yes	Yes
Creatinine, blood urea nitrogen	Yes	Yes
Urine analysis	Yes	Yes
Immunoglobulins	Yes	No
Angiotensin converting enzyme	Yes	Yes
Chest radiograph	Yes	Yes
Lung computed tomography	Yes	No
Bronchoalveolar lavage	Yes	No
Lung function tests with TLCO	Yes	Yes
Ophthalmologic examination	Yes	Yes
Tuberculin skin test	Yes	No
Histologic confirmation	Yes	No

TLCO, lung transfer for carbon monoxide.

Table 50-4
Pejorative Factors in Pediatric Sarcoidosis

Ethnicity	Black ethnicity
Age	Young age
Organ involvement	Multiorgan involvement
	Severe lung disease
	Polymorphonuclear cells on BAL
	Hypercalcemia
	Cardiac sarcoidosis
	Neurosarcoidosis
Response to treatment	Cortico-dependence
	Cortico-resistance

BAL, bronchoalveolar lavage.

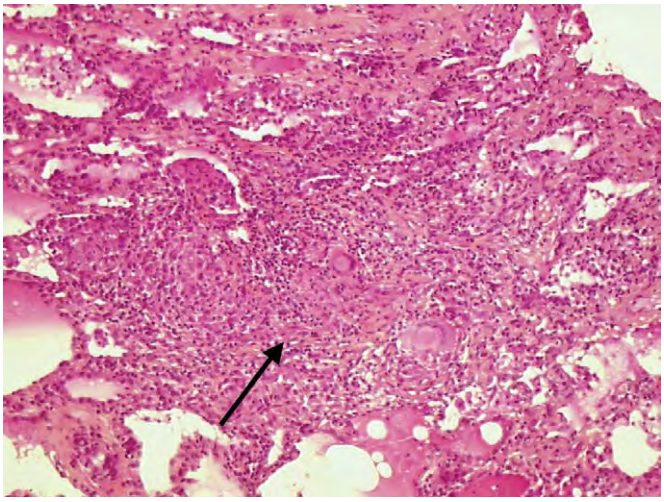

Figure 50-3 Lung biopsy of a 7-year-old boy with severe pulmonary sarcoidosis showing epithelioid granulomas with thickening of the alveolar septa (*arrow*) (coloration hematoxylin-eosin-safran [HES] stain, magnification ×10).

cific reasons (see Table 50-3).[6] Currently, biologic markers of the disease such as sACE cannot be used to guide treatment. A pediatric study has shown that 18 months of corticosteroid treatment may be a reasonable mean duration of treatment for pulmonary sarcoidosis, but the optimal duration for the other organs has not been established.[6] Close monitoring of the potential side effects of corticoid treatment is mandatory. Relapses are common, justifying the prolonged continuation of monitoring after treatment discontinuation. The respiratory disease is usually cured by corticosteroid treatment, but sequelae with fibrotic changes of the lungs may be observed (Fig. 50-3).

For adult patients for whom corticosteroid treatment fails, immunosuppressant drugs such as azathioprine or cyclosporine A have been prescribed, but side effects were severe.[10] Hydroxychloroquine therapy has been used with success in two Australian male children with diffuse sarcoidosis and low-dose methotrexate in seven others. More recently, successful steroid-sparing treatment of severe renal failure secondary to limited renal sarcoidosis was reported in a child treated with mycophenolate mofetil.

As observed in the incidence and presentation of the disease, clinical and genetic factors also influence the prognosis of the disease. A recent large study performed in 215 adults with documented sarcoidosis indicated that the majority of the patients improved or remained stable more than 2 years.[9] African Americans had less improvement in lung function parameters and a more common development of new organ involvement than did whites. Such large follow-up studies are not available in children, but sarcoidosis seems to be more severe in the younger age group. The HLA complex plays a major role in sarcoidosis and some genotypes seem to influence the outcome of the disease. HLA-B*07 independently increased the risk for persistent, as well as for resolving, disease in adults, suggesting an influence on factors common to both forms of sarcoidosis.[11] The allele combination A*03, B*07, DRB1*15 was most strongly associated with persistent disease. Further studies are warranted to evaluate the usefulness of these genetic markers in clinical management.

Some new inflammatory markers have been evaluated recently in sarcoidosis. As such, the soluble IL-2 receptor (sIL2R) appeared to be useful for monitoring respiratory disease severity in adult patients, but its sensitivity and specificity were broad and partially overlapped by sACE. Further studies are warranted, both in adult and pediatric populations.

CONCLUSION

Sarcoidosis is an uncommon disease in children. Diagnosis may be difficult and can be made only by histologic examination of the involved organs. The course of the disease seems to be more severe in younger children; improvement or cure is most often obtained with corticosteroid treatment.

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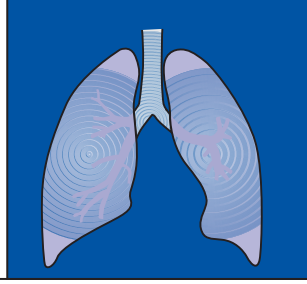


CHAPTER 51 Congenital Immunodeficiency Syndromes

Andrew S. Kemp

TEACHING POINTS

- The clinical presentation of an immunodeficiency disorder depends on the nature of the immune defect.
- Defects in antibody function predispose to lower respiratory tract infection with encapsulated organisms.
- Defects in T cells predispose to viral or *Pneumocystis* infection.
- Defects in phagocytes predispose to infections with bacteria and fungi.
- Unusual associated features may suggest a rare immunodeficiency syndrome.

There are more than 100 primary immunodeficiency disorders. The respiratory system forms a major interface with the external environment and is frequently involved by infection resulting from immunodeficiency. Primary immunodeficiencies are usually congenital and hereditary, although the presentation may be delayed to later childhood or adult life. Table 51-1 shows the relative distribution. This chapter will focus primarily on the impact of these disorders on the respiratory tract.

EPIDEMIOLOGY, RISK FACTORS, AND PATHOGENESIS

The prevalence of some immune deficiencies is shown in Table 51-2. Inherited disorders of antibody function uncommonly manifest in the first 6 months of life owing to transplacental transfer of maternal IgG. In contrast, disorders with T cell defects commonly manifest by 6 months with diarrhea, *Pneumocystis* pneumonia, and failure to thrive. Infants with functional disorders of phagocytes develop infections with *Staphylococcus aureus*, gram-negative enteric bacteria, and fungi—frequently commencing in the first 2 years of life.

Disorders of Antibody Function

Selective IgA deficiency is considered to result from impaired switching from IgM to IgA production.[1] Selective IgA deficiency is defined as a serum IgA level less than 0.05 g/L with normal IgG and IgM levels. The finding of asymptomatic subjects with IgA deficiency indicates that IgA deficiency does not necessarily predispose to significant disease. Because serum IgA levels are low in normal infants, age-related normal ranges are essential for interpretation. Subjects who lack IgA in their serum will also lack it in their secretions. Rarely, absent secretory IgA but normal serum IgA has been found. IgA deficiency may be transient, and children with absent serum IgA have developed IgA in later life. The finding of salivary IgA can indicate subjects with a transient IgA deficiency because salivary IgA levels reach normal adult levels by 6 months of age.[2] The significance of an IgA level below the normal limit but above 0.05 g/L is uncertain. These children should not be classified as having selective IgA deficiency because in at least one half of them, IgA levels will increase into the normal range.[3] Their incidence of respiratory infections may be the same as in normal children.[3] Some cases of IgA deficiency occur in conjunction with abnormalities of the MHC region.[1,4] IgA deficiency has been found in subjects with abnormalities in chromosome 18.[4] Phenytoin, penicillamine, sulfasalazine, and captopril can cause an acquired IgA deficiency.

Approximately one third of subjects with selective IgA deficiency have symptoms of recurrent bronchitis and otitis media.[5,6] More severe lower respiratory tract infections are uncommon and symptoms frequently improve with time. Suppurative disease of the upper or lower respiratory tract may be due to associated IgG2 subclass deficiency.[7] One study of 40 children reported an incidence of pneumonia of 30%,[3] but the presence of an associated IgG subclass deficiency was not determined. Common variable immunodeficiency (CVID) can manifest initially as selective IgA deficiency, with the IgG and IgM levels subsequently declining over a number of years, and should be considered in any patient with IgA deficiency who develops serious bacterial infections such as recurrent pneumonias or meningitis.[1] Immunoglobulin therapy is not indicated for patients with selective IgA deficiency. Anaphylactoid reactions to immunoglobulin can occur due to IgG anti-IgA antibodies that are found in about 25% of subjects.[8] Preparations of intravenous IgG that are low in IgA have been used when immunoglobulin therapy is required in an IgA-deficient subject[9]; however, the risk of anaphylaxis is not completely eliminated.[8,10]

IgG subclass deficiency consists of four subclasses (IgG1 65%, IgG2 25%, IgG3 7%, IgG4 < 5%). Antibody responses against peptides are predominantly IgG1 and IgG3 and against polysaccharides IgG2. The role of IgG4 is unclear, but

Table 51-1
Proportions of Primary Immunodeficiencies (%)

Antibody	65
Combined antibody and T cell	15
Phagocytes	10
T cell	5
Complement	5

is increased in atopic dermatitis and asthma. Only IgG1 and IgG3 cross the placenta. Deficiency may occur in one or more subclasses. IgG subclass deficiency may be multiple or single. Normal individuals may have low or undetectable antibody subclasses.[11] Symptomatic cases have recurrent otitis media, recurrent sinusitis, and suppurative lower respiratory tract disease.[12,13] A history of recurrent bronchitis, particularly if associated with purulent sputum production, recurrent pneumonia, and persisting chest radiographic abnormalities, suggests the possibility of a subclass deficiency. Low IgG subclasses have been found in children with endoscopically proven chronic bronchitis.[14] The most commonly detected deficiencies are IgG2, IgG3, and IgG4; IgG1 deficiency is uncommon. Low levels of IgG1 may predispose infants to acute bronchiolitis.[15] Pre–school-age children are commonly found to have subclass deficiency, which may relate to the difficulties in establishing normal levels and a transient immaturity of the immune system.[16] IgG subclass levels increase with age.[17] In one study of children with sinusitis, one half of the patients were shown to have either low subclasses or poor response to polysaccharide antigens. IgG3 subclass deficiency was the most common abnormality.[18] Deletion of IgG heavy chain genes has occasionally been found in cases of combined IgG2 and IgG4 subclass deficiency.[19]

The significance of isolated IgG4 subclass deficiency is unclear. Confusion has arisen because of the varying sensitivity of the assays. With a sensitive radioimmunoassay, IgG4 deficiency has been detected in individuals with so-called *idiopathic bronchiectasis*, or chronic sinusitis and recurrent otitis media.[12] Individuals with isolated IgG4 deficiency have a normal response to polysaccharide antigens.[20]

The establishment of normal ranges for IgG subclasses throughout childhood has proved difficult and criteria for diagnosis of subclass deficiency are uncertain. Levels are age dependent. Lower levels have been observed in healthy black as compared with white children.[21] The assays have technical difficulties and the reliability of commercial kits has been questioned.[22] Healthy children may have low levels[23] and low levels do not necessarily correlate with defective antibody production.[24] Of more importance than the level is the functional activity, as healthy children with low IgG2 may have normal polysaccharide antibody responses whereas symptomatic children with normal levels can have a defective response.[23] It is important to examine specific antibody responses to polysaccharide antigens; however, the criteria for an adequate response have been difficult to define.[25] Immunization with unconjugated polysaccharides is required.[26] Subjects who fail to respond to unconjugated vaccines may respond to the conjugates.[26,27] Most normal children younger than 2 years have a defective antibody response to unconjugated polysaccharide antigens. The incidence of IgG2 deficiency in more than 500 healthy children was found to be 2% and all were found to have normal responses to polysaccharide antigens and normal in vitro production of IgG2.[23] IgG2 deficiency may also be transient in healthy individuals with resolution over 3 to 4 years. About 20% of the population may appear to be deficient in IgG4 because of the insensitivity of the assay—and to establish a deficiency, radioimmunoassay is required.[28]

Table 51-2
Approximate Prevalence of Immunodeficiency Disorders

Selective IgA deficiency	1 : 500
Common variable immunodeficiency	1 : 10,000
Severe combined immunodeficiency	1 : 12,000
Transient hypogammaglobulinemia of infancy	1 : 16,000
X-linked agammaglobulinemia	1 : 24,000
Chronic granulomatous disease	1 : 125,000

Selective antibody deficiency is a defective response to polysaccharide antigens with normal IgG and subclass levels.[29] This condition manifests with chronic otitis media with discharge, bronchitis, or sinusitis.[25,27] The clinical features are similar to those of children with symptomatic IgG subclass deficiency. The usual age of presentation is in the first 7 years of life. Selective antibody deficiency is diagnosed by demonstrating an impaired response to polysaccharide antigens by immunization with pneumococcal polysaccharide vaccine with normal total IgG and subclass levels.[30] It is important to immunize with unconjugated polysaccharide vaccines.[26]

Regimens for management of **IgG subclass and selective antibody deficiencies** are not well established. Trials comparing regular use of prophylactic broad-spectrum antibiotics and gamma globulin have not been carried out. Some patients will improve with regular broad-spectrum antibiotic use. Immunoglobulin therapy should be instituted only on the basis of a proven defect in antibody responses and significant respiratory tract disease. The dosage of IgG is uncertain but in general the dosages used for hypogammaglobulinemia (400 to 600 mg/kg) monthly have been used. A trial of monthly intravenous immunoglobulin in children with IgG3 subclass deficiency reduced hospitalizations and antibiotic use.[31] If immunoglobulin therapy is instituted, it is important to have a measurable end point such as diminution in episodes of otitis media with drainage, reduction in cough and purulent sputum, or reduction in episodes of documented lower respiratory tract infection. The appropriate duration of immunoglobulin therapy is not clear and the need for immunoglobulin therapy can diminish with age.

In **X-linked agammaglobulinemia (XLA)** pre-B cells in the marrow fail to develop into mature circulating B cells. This is caused by a defect in BTK (Bruton tyrosine kinase) gene on the X chromosome.[32] Tyrosine-kinase is required for normal B cell development. Mutations in immunoglobulin heavy chain genes lead to an autosomal recessive form of early onset hypogammaglobulinemia with clinical features similar to XLA[33]. Most subjects remain healthy for the first 6 to 9 months of life. Nearly all subjects will develop symptoms by 18 months of age, and the diagnosis is usually made within the first 3 years of life.[34,35] As maternally transferred IgG declines, the infant develops recurrent otitis media[35] and

Table 51-3
Incidence of Infections in Patients with X-linked Agammaglobulinemia at Diagnosis and with Chronic Infections

At Diagnosis	
Upper respiratory tract	75%
Lower respiratory tract	65%
Gastrointestinal tract	35%
Skin	28%
Central nervous system	10%
Chronic Infections	
Otitis media	44%
Lower respiratory tract	39%
Sinusitis	39%
Conjunctivitis	19%
Pyoderma	13%
Gastroenteritis	10%

Data from Lederman HM, Winkelstein JA: Medicine 64:145-146, 1985.

upper and lower respiratory tract infections with common respiratory tract organisms, in particular, *Pneumococcus* and *Haemophilus influenzae* b.[34] *Staphylococcus aureus* may also be isolated from the sputum. Some subjects are susceptible to *Mycoplasma pneumoniae* infection, which can manifest as pneumonitis, sinusitis, or arthritis.[36] Most patients suffer infections at more than one anatomic site (Table 51-3). Absent or very small tonsils are a clinical clue. Recurrent pneumonia involving dependent lobes is a common presentation. In contrast to pneumonia in immunocompetent subjects, resolution is often slow and incomplete. There may be persistent collapse of affected lobes. Repeated infection may result in bronchiectasis, pulmonary fibrosis, cor pulmonale, and eventually respiratory failure. Early treatment will minimize complications, and high-dose intravenous gamma globulin reduces chronic lung disease. Death can also occur from severe and widely disseminated enterovirus infections.[34] In contrast to combined defects of antibody and cell-mediated immunity, *Pneumocystis* pneumonia and viral pneumonitis rarely occur in XLA.[34] Mono- or oligoarticular arthritis, which can mimic juvenile rheumatoid arthritis, is a presenting feature in approximately 20% of patients. Septic arthritis caused by *Haemophilus influenzae* b or pneumococcus occurs. Chronic or recurrent conjunctivitis is commonly related to deficiency of secretory antibodies. Transient neutropenia is often associated with acute infections.[34] Pulmonary function tests demonstrate an obstructive pattern with progressive disease. The incidence of pulmonary complications in XLA is less than that in patients with CVID.[37] This may partly relate to the associated T cell defects found in the latter condition. The diagnosis of XLA can be suspected by demonstrating reduced concentrations of IgG, IgA, and IgM, absence of circulating B cells, and no specific antibody response to common antigens, such as tetanus and diphtheria, and confirmed by demonstrating deficient BTK expression on flow cytometry[38] or BTK mutations.[39] The diagnosis can be made in newborn males with a family history by demonstrating absent cord blood B cells. Early diagnosis allows institution of therapy before the development of infection. Approximately 5% of subjects with early onset hypogammaglobulinemia and absent B cells are girls. This autosomal recessive disorder is due to mutation in the immunoglobulin heavy chain gene.[33,39]

Common variable immunodeficiency (CVID) is a heterogeneous group of disorders. Some cases may be caused by a defect in the major histocompatibility complex region on chromosome 6, resulting in arrested B-cell differentiation.[40] Some cases thought to be CVID with low B cells have been found to have BTK mutations, indicating a variant of XLA.[41] In contrast to XLA, there is usually a later onset and the symptoms may be more insidious. More than 95% of patients present after the age of 6 years[42] and presentation is most often in the second or third decades. The spectrum of respiratory infections is similar to that observed in XLA. Episodes of pneumococcal or *Haemophilus influenzae* pneumonia are common.[43] Uncommonly, pneumonia has been associated with *Pseudomonas aeruginosa* or *Pneumocystis carinii*. Another respiratory manifestation is lymphoid interstitial pneumonitis, which presents with cough, dyspnea, weight loss and an interstitial infiltrate—particularly at the lung bases.[44,45] Pulmonary function tests often show a restrictive pattern and lung biopsy may be necessary to make a definitive diagnosis. Some improvement may occur with gamma globulin therapy; however, pneumonitis may progress to pulmonary fibrosis.

Other clinical features are noncaseating granulomas of the lungs, spleen, skin, and liver[46] with hepatosplenomegaly. Diarrhea caused by *Campylobacter jejuni* and *Giardia lamblia* is common.[46] In adults, the incidence of lymphoma is increased. Atypical lymphoid hyperplasia may be confused with malignant lymphoma. CVID is associated with autoimmune hemolytic anemia, and neutropenia[46]; thrombocytopenia may be the initial manifestation.[47] The diagnosis of CVID is made by finding abnormal levels of immunoglobulin with normal or reduced B cells and defective antibody responses to common antigens. There is a variable T cell defect and the T helper (CD4) to T suppressor (CD8) ratio is often decreased.[48] CVID may be complicated by autoimmune hemolytic anemia, thrombocytopenia, or neutropenia, which often requires corticosteroid therapy. The associated T cell defects may worsen with age[42] and predispose to more severe pulmonary disease than is seen in XLA.[37] Despite apparently adequate immunoglobulin replacement, chronic respiratory symptoms are common and progression of lung disease with fibrosis and bronchiectasis has been demonstrated on high resolution computed tomography[49].

Hyper-IgM is the result of a defective ability of B cells to switch from IgM to IgG and IgA due to a defect in CD40 ligand. A T cell surface structure is required for antibody switching.[50,51] The defect leads to abnormalities in T cell function.[52] The disease is usually X-linked, however there are four autosomal recessive forms with a similar phenotype. One recessive form does not have T cell deficiency.[53] Children with hyper-IgM develop suppurative infections of the upper and lower respiratory tract. About one half of them present in the first year of life.[54] In contrast to XLA, *Pneumocystis* pneumonia is a common presentation[55] (Fig. 51-1), except in an autosomal recessive form with normal T cell function.[53] There is often cyclic or persistent neutropenia resulting in oral and upper gastrointestinal tract ulceration. Hemolytic anemia, thrombocytopenia, nephritis, and arthritis are also observed.[55] Bowel infection with *Cryptosporidium*

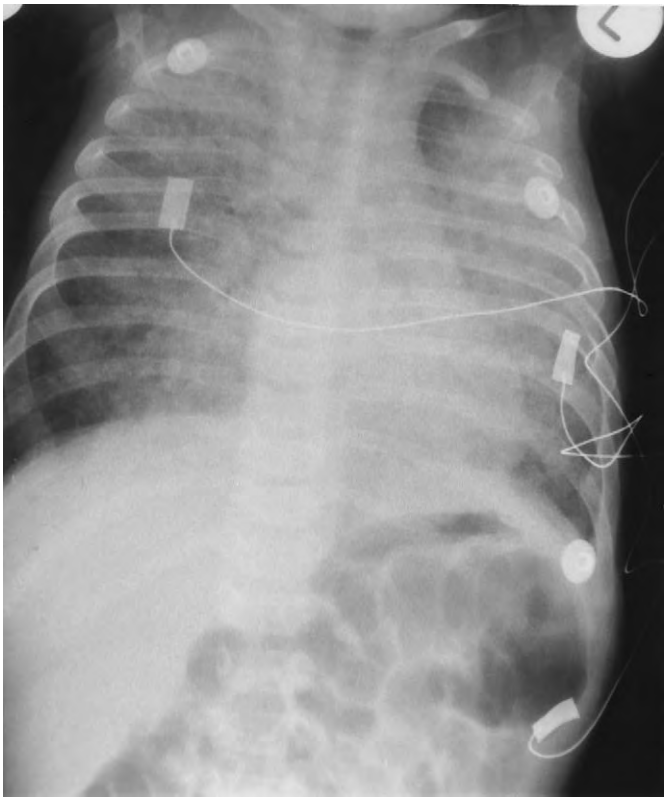


Figure 51-1 *Pneumocystis* pneumonitis in a 6-month-old male infant with immunodeficiency and elevated IgM.

is common and frequently leads to sclerosing cholangitis which may be fatal.[54] The diagnosis of hyper IgM is suggested by low IgA and IgG levels with a normal or elevated IgM. However, only one half of patients have an elevated IgM.[54] B and T cell numbers are usually normal. Primary and secondary antibody responses are diminished and limited to IgM; isoagglutinin titers are low or absent. Definitive diagnosis can be made by demonstration of absent CD40 ligand expression on activated T cells or by identification of mutations in the CD40 ligand gene[53]. Treatment of Hyper-IgM is similar to other forms of agammaglobulinemia with regular intravenous immunoglobulin therapy. Prophylaxis for *Pneumocystis* infection with trimethoprim-sulfamethoxazole should be given. The neutropenia may resolve after immunoglobulin therapy. In severe cases of neutropenia, stimulation with granulocyte macrophage colony-stimulating factor is indicated.

Transient hypogammaglobulinemia of infancy (THI) usually manifests in the second 6 months of life.[56,57] THI may be asymptomatic. Most children do not have serious infections,[56-60] and it is not clear whether children with THI have an increased incidence of infections compared with normal children. The IgG is low but rises into the normal range usually within the first 2 years of life. This disorder is often associated with IgA deficiency, which may persist. The incidence of atopic disease (food hypersensitivity, atopic dermatitis, and asthma) is increased.[57,60] Subjects with THI have a normal antibody response to antigens such as tetanus and diphtheria toxoids.[56] The diagnosis is established in retrospect by demonstrating that the low immunoglobulin levels come up into the normal range.

Immunoglobulin Therapy

For subjects with significant antibody deficiencies (e.g., XLA or CVID) immunoglobulin is usually administered intravenously. The usual dose is 400 to 600 mg/kg every 3 to 4 weeks.[61] This is based on a half-life of IgG in normal individuals of 21 to 28 days. The half-life of infused IgG is variable and dosages may need to be individualized. The aim is to keep the IgG level within the normal range for age or above an arbitrary trough level of around 5 to 6 g/L.[62] Home administration by the subcutaneous route has also been utilized.[63] Meticulous attention should be paid to the episodes of lower respiratory tract suppuration. Prophylactic antibiotics are not generally required but any occurrence of infection, as indicated by purulent sputum, should be treated vigorously with a broad-spectrum antibiotic. High resolution CT may show bronchiectasis or fibrosis not apparent on a chest radiograph.[49] If symptoms do not resolve, a chest radiograph is indicated to determine the extent of infection. Hospital admission for intravenous antibiotic therapy and physiotherapy may be required. The respiratory disease should be monitored by yearly pulmonary function tests. Following the change from intramuscular to high-dose intravenous immunoglobulin therapy, long-term results of high-dose therapy are not fully defined. Acute infections and complications such as pulmonary fibrosis and bronchiectasis appear to be reduced.[46]

With minimization of aggregate formation, serious reactions to intravenous infusions are uncommon. A rare complication of intravenous gamma globulin is non-A, non-B hepatitis which is thought to result from a breakdown in manufacturing process.[64] Subjects on regular immunoglobulin therapy should have liver function tests performed 3 to 4 times a year. Another uncommon complication is aseptic meningitis.[65] In older children, home administration of gamma globulin can be accomplished by the subcutaneous route. The duration of therapy is generally lifelong. With appropriate therapy, subjects may have minimal upper and lower respiratory tract symptoms. Other symptoms such as recurrent conjunctivitis and recurrent diarrhea are not eliminated by intravenous therapy because secretory IgA function is not restored.

Disorders of T Cells

Severe combined immunodeficiency (SCID) results in a deficiency of both B and T cell function. There are at least 10 different molecular defects.[66-68] The most common variant caused by mutations in the gene for the interleukin-2 receptor is X-linked; the others are autosomal recessive.[69] The differing forms are grouped according to the cell surface markers on peripheral blood into T–B+, T–B–, and other forms. The variant due to adenosine deaminase deficiency[70] has profound lymphopenia. SCID is associated with a profound deficiency of both T cell and antibody function. It generally manifests within the first 6 months of life with diarrhea, lower respiratory tract infections, and failure to thrive.[71] More than one half the children present with *Pneumocystis* pneumonia.[68] Early presentation within the first 2 months of life with pneumonitis is particularly likely in patients with ADA deficiency who have the most profound lymphopenia.[70,71] *Pneumocystis* infection may often be insidious with cough and pulmonary infiltrates that progress over

several weeks. In addition to *Pneumocystis* these children often have cytomegalovirus pneumonitis. Oral candidiasis and rashes, in particular a seborrheic dermatitis-like rash, are common. The finding of erythroderma and eosinophilia suggests either the occurrence of the Omenn syndrome variant[71,72] or graft-versus-host disease from maternal lymphocytes.[68] The presence of hepatomegaly and ascites suggests veno-occlusive disease of the liver.[68,73] Recurrent pneumonias can occur with cytomegalovirus, respiratory syncytial virus, *Pneumocystis*, *Candida*, and gram-positive and gram-negative bacteria.[68] Chest radiographs often show a diffuse bilateral disease that is alveolar and/or interstitial in nature (Fig. 51-2) and lung biopsy may show a nonspecific chronic inflammatory infiltrate with lymphoid or histiocytic cells. The lower respiratory tract disease may progress despite antimicrobial therapy and immunoglobulin. B cell proliferative disorders caused by Epstein-Barr virus (EBV) infection with paraproteins, lung infiltrates, and pleural effusions can occur as a complication of the immunodeficiency or following marrow transplantation.[74,75] Histology shows infiltration of immunoblasts in multiple organs. Without marrow transplantation, death in the pre-school years is usual, often from an overwhelming viral infection. SCID should be suspected in any infant who presents with *Pneumocystis* pneumonia. Other clues to the diagnosis are lymphopenia and low levels of immunoglobulins G, A, and M. The number of T cells is markedly reduced, the proliferative response of T cells to mitogens is low or absent, and specific antibody responses are lacking. More definitive diagnosis of the molecular defect should be undertaken where available. Treatment of SCID involves specific antimicrobial therapy and administration of intravenous immunoglobulin. The definitive therapy is bone marrow transplantation. Transplantation from a human leukocyte antigen (HLA)-identical sibling has a more than 90% success rate if performed early in life before the onset of significant infections.[76] In the absence of an HLA-identical donor, a T cell depleted bone marrow transplant from a parent, family relative, or unrelated donor is used. The overall success rate with a non HLA-identical T cell depleted marrow graft is less, with a 35% to 60% long-term survival.[77] Restoration of T cell function without B cell function may occur. Conditioning with intense immunosuppression before transplantation is more likely to result in restoration of B cell function but has a higher risk in the immediate post-transplant period of death from either sepsis or hemorrhage. Lung infection before transplantation is associated with a worse outcome.[77] Prophylactic therapy against *Pneumocystis* should be given. Live virus vaccines should be avoided and, before transplantation, patients should be isolated to prevent life-threatening infections with viruses such as measles, chickenpox, and influenza.

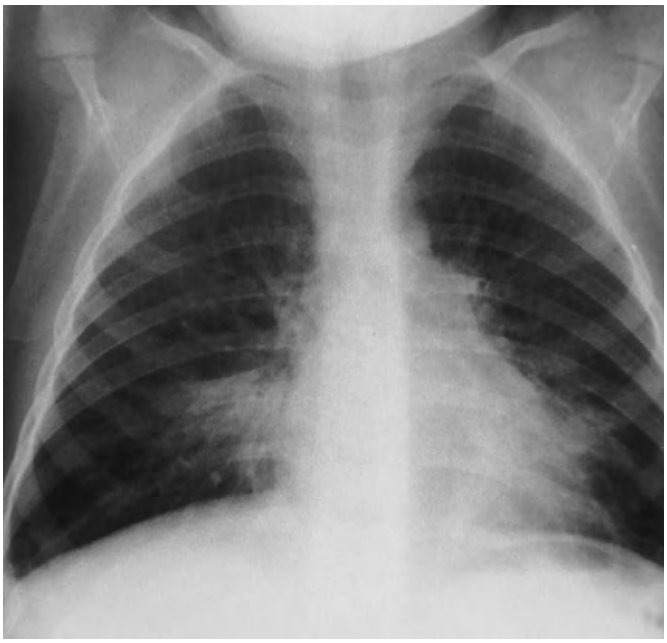


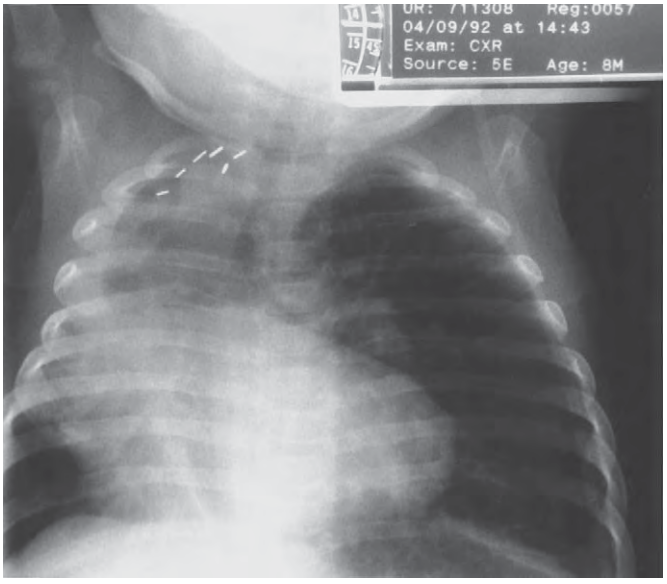
Figure 51-2 Chronic bilateral changes in a 4-year-old male with an X-linked combined immunodeficiency. Lung biopsy showed a nonspecific infiltrate with mononuclear and polymorphonuclear cells.

The **Di George syndrome** consists of a variable degree of thymic and parathyroid hypoplasia and cardiac outflow anomalies, especially truncus arteriosus and interrupted aortic arch.[78,79] The majority of cases result from deletions within chromosome 22q11.[80] Any of the structures derived from the first to the sixth pharyngeal arches and pouches can be affected. Infants usually present because of the cardiac problem. Hypocalcemia may be found and an absent thymus noted at operation. The immunologic defect is variable.[81-83] A 10^9 T helper cell count of less than 500×10^9/L has been associated with a greater incidence of subsequent immunologic problems.[83] Only a minority of cases develop serious infections—in particular viral and *Pneumocystis* pneumonia. Respiratory syncytial virus infections can be severe and there may be prolonged virus excretion. A complicating factor is the occurrence of tracheo- or bronchomalacia (Fig. 51-3) owing to vascular compression and abnormal embryogenesis with defective tracheal ring formation.[84] The natural history of the Di George syndrome is variable and immune function can improve with time. Subjects with T 10^9 cell counts less than 500×10^9/L and abnormal lymphocyte mitogenic responses should be given prophylactic trimethoprim-sulfamethoxazole. If a defective antibody response to common antigens such as tetanus and diphtheria is present, immunoglobulin therapy is indicated. Definitive cure of the immune defect has been difficult. Thymic transplantation has had some success[85] but because of the variability in the natural history, the efficacy is uncertain. Restoration of immunity has been achieved by bone marrow transplantation.[86]

Idiopathic CD4+ T-lymphocytopenia is characterized by a decreased number of CD4+ T-lymphocytes ($<300 \times 10^9$ CD4+ cells/L or <20% of total T cells) on at least two occasions associated with opportunistic infections. The lower respiratory tract is frequently involved with pneumococcal pneumonia, varicella pneumonia, chronic bronchitis, and bronchiectasis.[87]

Disorders of Phagocytes

Chronic granulomatous disease (CGD) is a disorder of oxidative metabolism of phagocytes caused by defects in cytochrome B or cytosolic proteins required for oxidative activity. The phagocytes ingest microorganisms normally—but killing is defective. There are four different genetic causes of CGD.[88]



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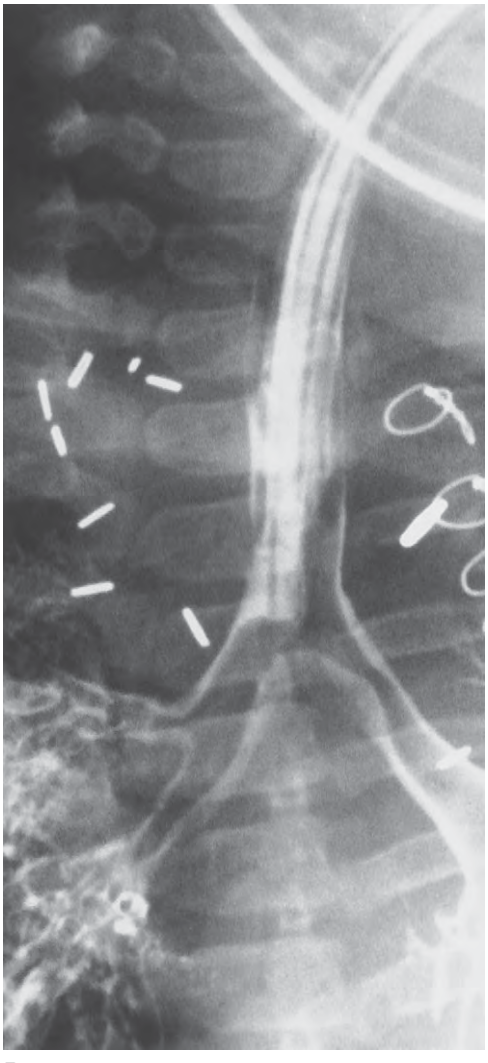


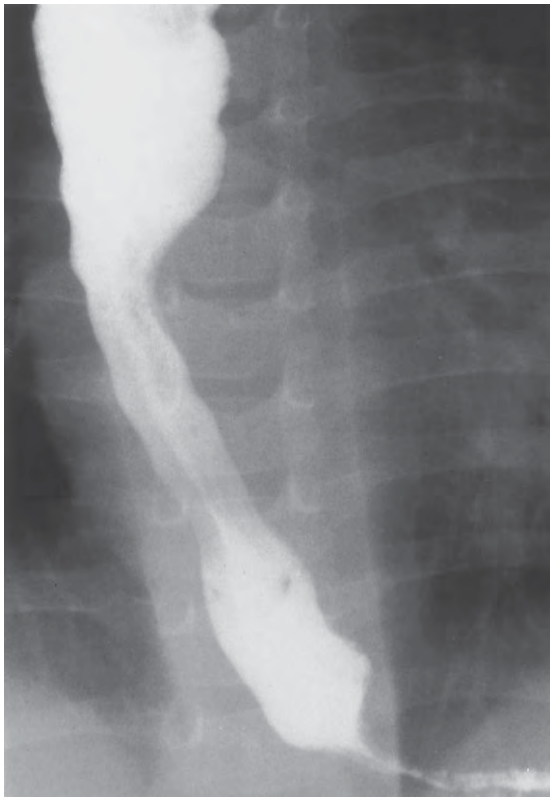
B

Figure 51-3 **A,** Right upper lobe collapse in an 8-month-old male infant with Di George anomaly. **B,** Bronchogram showing malacia in the left main stem bronchus and narrowing at the origin of the right upper lobe bronchus.

Two thirds are X-linked and one third are autosomal recessive. Patients with CGD develop recurrent infections with *Staphylococcus aureus*, *Serratia marcescens*, *Aspergillus*,[89,90] and unusual pathogens such as *Burkholderia cepacia*[91] and *Nocardia*.[92] The lung is the most common site of infection.[93] Infections often begin early in life. Lymphadenitis, cutaneous infections, and obstructive lesions of the genitourinary and gastrointestinal tracts (Fig. 51-4) occur.[94] Pulmonary lesions vary from a patchy bronchopneumonia to consolidation of an entire lobe or lung. Consolidation may be unilateral or bilateral, persist for months, and progress despite antibiotic treatment. An unusual "encapsulated" pneumonia with hilar lymphadenopathy occurs. Lung biopsy shows granulomas but not necessarily pathogenic organisms. Often lobectomy or segmentectomy is required for resolution.[95,96] Osteomyelitis of ribs and vertebral bodies with chest wall invasion is caused by *Aspergillus*.[97] Lung abscesses, empyema, and pleural effusion are uncommon. In a prospective study approximately one third of patients required admission to a hospital for treatment of pulmonary infection over a period of 9 months.[98] Another pulmonary manifestation of CGD is a widespread nodular infiltrate. Histology shows multiple small granulomata. This may be due to disseminated *Aspergillus*. The lesions are often asymptomatic but can progress to pulmonary insufficiency and death. The autosomal recessive disorders may have less severe clinical manifestations than the X-linked form.[99] The diagnosis of CGD is made by demonstrating defects in superoxide production.[100] The NBT slide test is widely available. Measurement by dihydrorhodamine flow cytometry is more quantitative and allows distinction of the autosomal recessive from the X-linked forms.[100]

For treatment of established infection in CGD standard antimicrobial therapies are often required in high dosage for long periods of time. Additional measures include white blood cell transfusions and use of interferon-gamma (INF-γ). Although INF-γ has been shown to be effective when given prophylactically, its role in established infections is less certain. In a controlled trial there was no significant benefit for established lymphadenitis and subcutaneous abscesses.[98] There are reports of resolution or improvement in infection following a combination of INF-γ with antimicrobial therapy.[101,102]

Long-term prophylaxis with trimethoprim/sulfamethoxazole reduced dermatitis and lymphadenitis[103] and may reduce the incidence of pneumonia.[104] Itraconazole is indicated as prophylaxis for *Aspergillus* infection in all cases.[90] Prophylaxis with subcutaneous INF-γ on 3 days per week significantly reduced serious infections.[98] Therapy was given for a mean period of 9 months. Lymphadenitis and episodes of lower respiratory tract infection, including fungal disease, were reduced. Although INF-γ increased the oxidative metabolic activity of phagocytes from some patients with CGD in vivo and in vitro, the mode of action when used prophylactically is uncertain. It is possible that the beneficial effects result from nonspecific activation of the immune system rather than restoration of a phagocyte metabolic defect. The beneficial effects of interferon were more marked in patients younger than 10 years of age and in the X-linked form of the disease.[98] Long-term interferon (years) may reduce serious infections.[105] If there are suitably matched donors, bone



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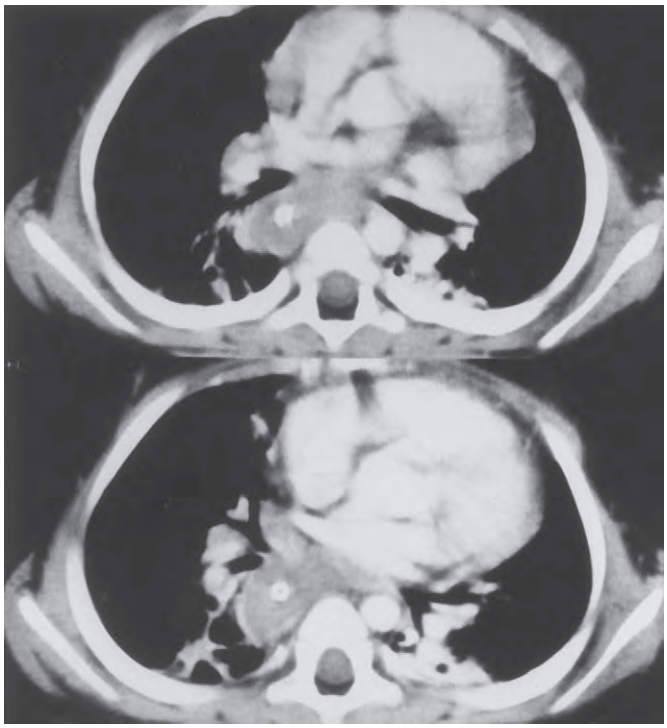

B

Figure 51-4 **A,** Esophageal obstruction caused by an inflammatory granulomatous mass in a 3-year-old male with chronic granulomatous disease. **B,** CT scans showing mass surrounding the esophagus.

marrow transplantation should be considered. The mortality of CGD is about 5% per year for the X-linked and 2% for the autosomal recessive forms.

Cell adhesion molecule deficiency is due to a deficiency of the beta chain subunit of the cell surface adhesion molecules, resulting in defective cellular motility. Moderate and severe phenotypes relate to the degree of expression of the cell adhesion molecules.[106,107] Children with cell adhesion molecule deficiency have delayed separation of the umbilical cord, profound gingivitis, otitis media, and extremely high levels of circulating neutrophils (20 to 60×10^9/L); however, they fail to form pus because of defective neutrophil migration. Viral respiratory tract infections may result in secondary bacterial infections of the trachea and bronchial tree[107]; however, pneumonia is seen in only a minority of subjects. Pyoderma gangrenosum–like skin lesions and delayed wound healing are common. The diagnosis of cell adhesion molecule deficiency is established by functional assays and demonstrating deficiency of cell adhesion molecules on neutrophils with monoclonal antibodies, anti-Mac-1, OKM1, or Leu15.[107] For the severe forms of cell adhesion molecule deficiency, the definitive treatment is bone marrow transplantation because these severe forms are usually fatal within the first 5 years of life.

Table 51-4
Clinical Clues to an Immune Deficiency Disorder in Patients with Severe Respiratory Infections

Disorder	Clinical Clues
Hyper IgE syndrome	Dermatitis, pneumatoceles
Mucocutaneous candidiasis	Persistent oral candidiasis
Wiskott-Aldrich syndrome	Eczema, purpura, thrombocytopenia
Ataxia telangiectasia	Conjunctival telangiectases Depigmented and hyperpigmented cutaneous lesions
Nijmegen breakage syndrome	Microcephaly
TAP deficiency syndrome	Cutaneous necrotizing granulomas
WHIM syndrome	Multiple warts, neutropenia
ICF (immunodeficiency, centromeric instability, and facial anomalies) syndrome	Abnormal facies
Interferon-γ receptor 1 deficiency	Disseminated BCG, disseminated infection with atypical mycobacteria

TAP, transporter associated with antigen presentation; WHIM, warts, hypogammaglobulinemia, infections, and myelokathexis.

Miscellaneous Disorders with Respiratory Tract Involvement

Many of these disorders are rare; however, it is important to be aware of the possibility of immunodeficiency in a child with chronic lower respiratory tract infection. The associated features of the syndromes frequently suggest the diagnosis (Table 51-4).

NATURAL KILLER CELL DEFICIENCY

Children present with severe overwhelming varicella infection, extensive varicella lesions on the skin and mucous membranes,[108,109] and lung involvement (Fig. 51-5). Some patients have a deficiency of circulating B cells although specific antibody function is present.[110] Because only a few cases have been described, the long-term outlook for this disorder is unknown. It is uncertain whether patients have a defective

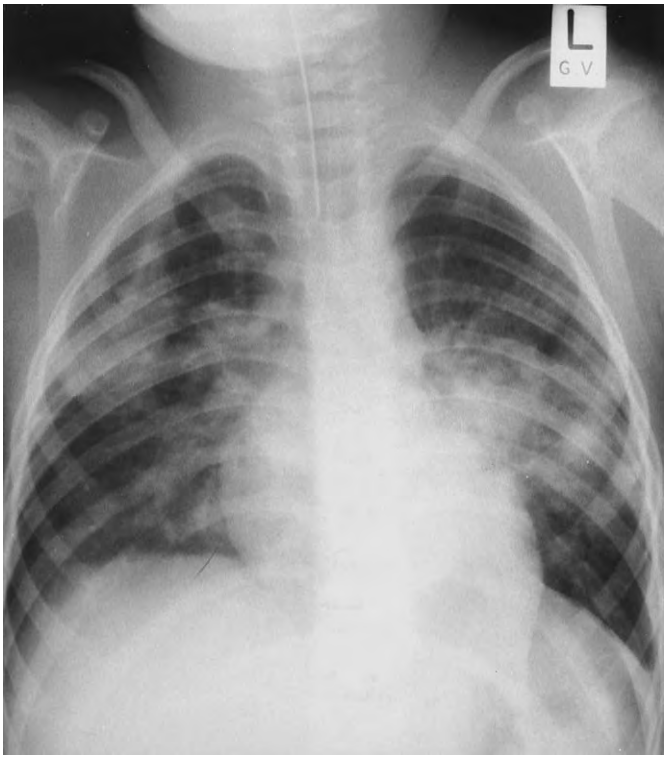

Figure 51-5 Varicella pneumonitis in a 5-year-old male with natural killer cell deficiency and defective α-interferon release. This condition was associated with extensive cutaneous lesions.

immune response to other herpesvirus infections. One patient developed a CMV interstitial pneumonia 4 years after the initial presentation with varicella. Varicella should be treated with intravenous acyclovir.

HYPER IgE SYNDROME

Hyper IgE syndrome was described in 1972.[111] There are autosomal dominant, recessive, and sporadic cases.[112] Hyper IgE manifests in infancy with coarse facies, eczematous dermatitis[113] or a vesicular eruption,[114] peripheral blood eosinophilia, and cutaneous *Candida* infection. The cutaneous changes in infancy are followed by lower respiratory tract infections and marked elevation in serum IgE. Subcutaneous cold abscesses and lower respiratory tract suppurative disease caused by organisms such as *Staphylococcus*, *Haemophilus influenzae*, and *Pseudomonas pyocyanea* often occur. Pneumonia and empyema develop in the first years of life. Pneumatoceles, pulmonary abscesses, bronchopleural fistula, and pneumothorax are common. Pneumatoceles are best demonstrated by CT scan (Fig. 51-6)[115]; they rarely resolve spontaneously, and lobectomy or pneumonectomy may be required.[116] The autosomal recessive form does not develop pneumatoceles.[112]

The immunologic defect is unknown. IgE levels are extremely high (often >10,000 IU/mL).Secretion of the Th1 cytokine INF-γ is reduced.[117] There are variable defects in neutrophil chemotaxis.[118,119] Specific IgE antibodies against *Staphylococcus aureus* and *Candida albicans* are found in the majority of patients. How these contribute to the pathogenesis is unclear.[120] Some subjects have a defective functional antibody response to polysaccharide antigens.[121]

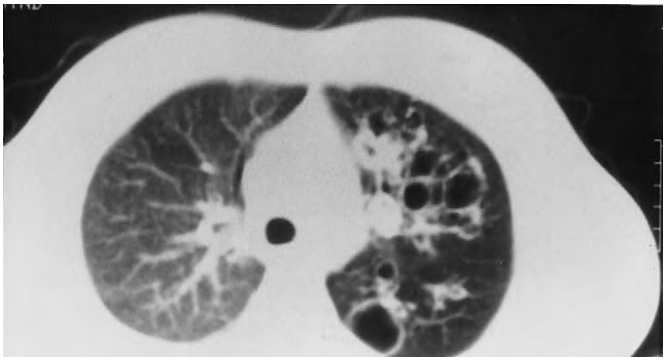

Figure 51-6 Pneumatoceles in a 12-year-old male with hyper IgE syndrome.

Management consists of long-term anti-staphylococcal antibiotic prophylaxis which may act to limit the severity of both the cutaneous involvement and the lung disease.[112] Sputum should be cultured regularly as the detection of *Pseudomonas* may require changes in therapy. The role of immunoglobulin and INF-γ is unclear. Despite regular medical attention, deterioration often occurs and respiratory failure eventually results.

MUCOCUTANEOUS CANDIDIASIS

Mucocutaneous candidiasis is characterized by *Candida* infections of the skin, mucous membrane, and nails. Many, but not all, cases have defects in cell-mediated immunity to *Candida* antigens when measured by delayed hypersensitivity skin tests or in vitro techniques. Some patients have an increased susceptibility to bacterial infections, and develop pneumonia caused by *S. aureus*, *Streptococcus pneumoniae*, or *H. influenzae* b. Fungal or viral pneumonias occur less commonly. A long-term multicenter follow-up study of patients with chronic mucocutaneous candidiasis showed that 14% of these subjects had bronchiectasis and another 40% had either obstructive or restrictive lung disease.[122] Lung disease has been associated with IgG2 and IgG4 subclass deficiency.[123] Patients with chronic mucocutaneous candidiasis and lower respiratory tract disease should have immunoglobulins, immunoglobulin subclasses, and antibody responses to polysaccharides measured. Management is particularly difficult because the use of broad-spectrum antibiotics exacerbates the candidiasis, despite concurrent use of antifungal agents. It is possible that subjects with an ineffective response to polysaccharide antigen would benefit from intravenous gamma globulin.

WISKOTT-ALDRICH SYNDROME

This is an X-linked disorder. Infants usually present with refractory atopic dermatitis and thrombocytopenic purpura. A defective antibody response to polysaccharide antigens is universal.[124,125] After the first year of life, otitis media and pneumonia are common. There is a variable T cell defect and infections with *Pneumocystis*[126] and herpesviruses can occur in later life. The syndrome is associated with a high serum

IgA and low or normal IgG and IgM. There is a variable reduction in T cell number and function. The diagnosis can be established by sizing the platelets, which are small.[127] More definitive diagnosis can be made by demonstrating reduced lymphocyte Wiskott-Aldrich syndrome protein.

Treatment consists of intravenous gammaglobulin when significant antibody defects have been demonstrated. Hemorrhage is a major threat and splenectomy can reduce the risk,[128] but this increases the risk of serious infection with encapsulated organisms. Definitive treatment is by bone marrow or cord blood stem cell transplantation. In the absence of a matched sibling donor, the success of bone marrow transplantation is considerably reduced and rejection of the graft is common.[128]

ATAXIA TELANGIECTASIA

Ataxia telangiectasia is an autosomal recessive disorder with neurologic, endocrinologic, immunologic, and cutaneous abnormalities. The gene for the disorder has been localized to chromosome 11. Most patients present with ataxia in infancy or early childhood. Subsequently, telangiectasia of the skin and conjunctivae and hyperpigmented and depigmented cutaneous patches develop. Approximately one half of the patients develop significant sinopulmonary infections—in particular recurrent sinusitis and lower respiratory tract suppurative disease,[129,130] which may progress to bronchiectasis. IgA deficiency is found in approximately 50% of cases and is usually associated with an IgG2 subclass deficiency.[131] IgE is often absent. Defects in T cell function and number are variable. The most common serologic abnormality is a raised α-fetoprotein, which is present in virtually all cases.[132] The defects in DNA repair lead to an increased incidence of chromosome breaks in cytogenetic studies. More severe respiratory tract disease appears to be associated with more severe neurologic abnormalities and aspiration may worsen the lung disease. Pneumonia is a major cause of death. Intravenous immunoglobulin and antibiotics are indicated if a significant antibody defect is demonstrated. There is a high incidence of malignancy of the lymphoreticular system.

NIJMEGEN BREAKAGE SYNDROME

The Nijmegen breakage syndrome is an autosomal recessive disorder with defects in DNA repair and similar immunologic, cytogenetic, and cellular abnormalities to ataxia telangiectasia; however, α-fetoprotein levels are normal. The affected children have microcephaly, abnormal facies, and suffer from recurrent lower respiratory tract infections.[133]

ICF (IMMUNODEFICIENCY, CENTROMERIC INSTABILITY, AND FACIAL ANOMALIES) SYNDROME

This is a rare autosomal recessive disease caused by abnormality in methylation of DNA. The facial anomalies include epicanthic folds, telecanthus, a flat nasal bridge, macroglossia and mild micrognathia. Subjects have recurrent and prolonged lower respiratory infections, which are a frequent cause of death.[134] Reduced IgA and IgG levels and poor antibody responses are common. There is instability of the chromosome centromeres in chromosomes 1, 9, and 16 resulting in abnormal multibranched configurations.

TAP DEFICIENCY SYNDROME

This syndrome results from deficiency of the transporter associated with antigen presentation (TAP), which is involved in a failure of the assembly of HLA class I molecules on the cell surface.[135] There is normal expression of class II molecules. Sinusitis and otitis media commence within the first 6 years of life and bronchitis and bacterial pneumonia leading to bronchiectasis typically occur in the second decade. Severe viral infections are absent. Lung infection with *Escherichia coli* and *Pseudomonas aeruginosa* occur in the chronic stage of the disease. Progressive lung damage leads to respiratory failure and death. Most patients also develop necrotizing granulomatous skin lesions, typically located on the extremities and on the midface. The cutaneous lesions usually develop after 15 years of age. Diagnosis can be made by demonstrating absence of class I and presence of class II HLA molecules on blood lymphocytes.

WHIM SYNDROME

The acronym WHIM refers to warts, hypogammaglobulinemia, infections, and myelokathexis (kathexis = retention). This syndrome is caused by mutations in chemokine receptor gene CXCR4.[136] Neutropenia in combination with reduced antibody and T cell function leads to recurrent bacterial infections. Respiratory tract involvement includes pneumonia, sinusitis, recurrent suppurative bronchitis, and abscesses. Multiple warts involve the skin and genital mucosa.[137]

HYPOHIDROTIC ECTODERMAL DYSPLASIA WITH IMMUNE DEFICIENCY

This X-linked recessive disorder is caused by mutations in the NEMO gene. Ectodermal abnormalities include sparse hair, delayed tooth eruption, conical teeth, and abnormal sweat glands. Immune deficiency results in failure to thrive, recurrent gastrointestinal tract infection with intractable diarrhea, and lower respiratory tract infections leading to bronchiectasis. Antibody levels may be reduced and there is a poor response to polysaccharide antigens.[138] Death has occurred from disseminated mycobacteria infections.

INF-γ RECEPTOR 1 DEFICIENCY

INF-γ–mediated immunity is a genetically controlled trait that determines the outcome of mycobacterial infection. INF-γ receptor 1 deficiency is caused by mutations in the receptor gene and is characterized by severe infections with environmental mycobacteria and bacille Calmette-Guérin (BCG) disease.[139] There are two forms: a recessive complete disease and a dominant partial deficiency. Subjects with the complete deficiency develop disseminated mycobacterial disease with hepatosplenomegaly, lymphadenopathy, and involvement of bones and lungs with onset in the first decade of life and disseminated BCG disease following BCG vaccination. Disseminated salmonellosis has also been observed. Multifocal mycobacterial osteomyelitis without other organ involvement is seen only in the dominant partial deficiency and manifestation is often delayed until the second decade. The diagnosis can be suspected by demonstrating a reduction of in vitro TNF-α production by peripheral blood mononuclear cells in response to interferon-γ.[139] Defects in IL-12 production have a similar phenotype.

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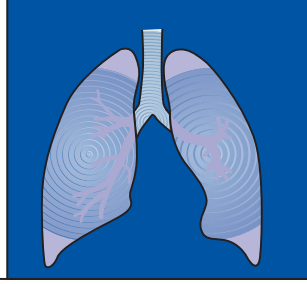

CHAPTER 52

Cor Pulmonale and Pulmonary Complications of Cardiac Disease

Steven H. Abman

TEACHING POINTS

- Recent advances in vascular biology have demonstrated the important roles of nitric oxide (NO), prostacyclin (PGI_2), and endothelin (ET) in the pathogenesis of pulmonary hypertension in children.
- Manipulation of these three pathways has led to novel therapies including inhaled NO, sildenafil, prostacyclin analogs, and endothilin receptor antagonists, which have improved the outcomes of children with pulmonary hypertension.

Abnormalities of the pulmonary circulation contribute significantly to morbidity and mortality in many cardiac and pulmonary diseases of childhood. Structure and function of the pulmonary circulation can be altered by *primary* aberrations of lung growth or development (such as lung hypoplasia, pulmonary hemangiomatosis, arteriovenous fistula, anomalous pulmonary venous return, pulmonary veno-occlusive disease, and others), or *secondary* to injury associated with acute respiratory failure, chronic lung disease after premature birth, chronic hypoventilation, and congenital heart disease. Although the impact of pulmonary hypertension on the clinical course of children with congenital heart disease, persistent pulmonary hypertension of the newborn (PPHN), and idiopathic (or "primary") pulmonary arterial hypertension (iPAH) is most clearly appreciated, the contribution of pulmonary hypertension to the course and ultimate outcome of children with lung disease is often overlooked or underestimated. Pulmonary hypertension is too often a "silent" contributor to morbidity and mortality of many chronic lung disorders in pediatrics, including bronchopulmonary dysplasia (BPD), cystic fibrosis (CF), sickle cell disease (SCD), and various interstitial lung diseases.[1-10] For example, 42% of pediatric patients with interstitial lung disease have evidence of pulmonary hypertension early in their clinical course.[8] Progressive pulmonary hypertension and cor pulmonale, beginning in the pediatric age range, is a common cause and highly predictive of premature death in chronic diseases, such as sickle cell anemia.[7,10,11] In general, clinical strategies that anticipate the development of pulmonary hypertension may allow earlier recognition, more aggressive therapy, and slow the development of pulmonary hypertension in many chronic lung diseases.

Although disease mechanisms and the clinical management of pulmonary hypertension in pediatric patients are often similar to adults with pulmonary hypertension, many aspects of pulmonary vascular disease in children are unique. In contrast to pulmonary vascular disease in adults, pediatric pulmonary hypertension is intrinsically linked to issues of lung growth and development, including many prenatal, perinatal, and later postnatal events. First, the development of pulmonary hypertension in the neonate and young infant reflects the interplay between the normal transition of the pulmonary circulation from fetal to postnatal life. Second, the timing of pulmonary vascular injury is an important determinant of the subsequent response of the developing lung to such adverse stimuli as hypoxia, hypertension, high flow, inflammation, and others. Third, just as the proliferative response of the pulmonary vasculature may be more pronounced in the young lung, the developing lung may also have more potential for recovery over time after removal of an adverse stimulus.[12]

However, the impact of pulmonary hypertension on long-term outcome differs between various pediatric cardiac and respiratory disorders. For example, pulmonary hypertension in infants with BPD is often present early but frequently resolves with therapy over time[1,13,14]; in contrast, pulmonary hypertension develops late in patients with CF and accompanies the steady decline in lung function.[5,6] Thus, in young children and infants with chronic lung disease, changes in the pulmonary circulation and the right side of the heart represent an interplay between normal developmental changes and superimposed cardiovascular and pulmonary stresses (Fig. 52-1).

The purpose of this chapter is to provide a brief overview of the structure and function of the normal pulmonary circulation, and to characterize the clinical pathophysiology, evaluation, and treatment of pulmonary hypertension and cor pulmonale associated with lung diseases in children. Pulmonary hypertension caused by congenital heart disease, vascular rings and slings, vascular anomalies (such as those associated with pulmonary sequestration or lung agenesis), and IPAH are discussed in other chapters.

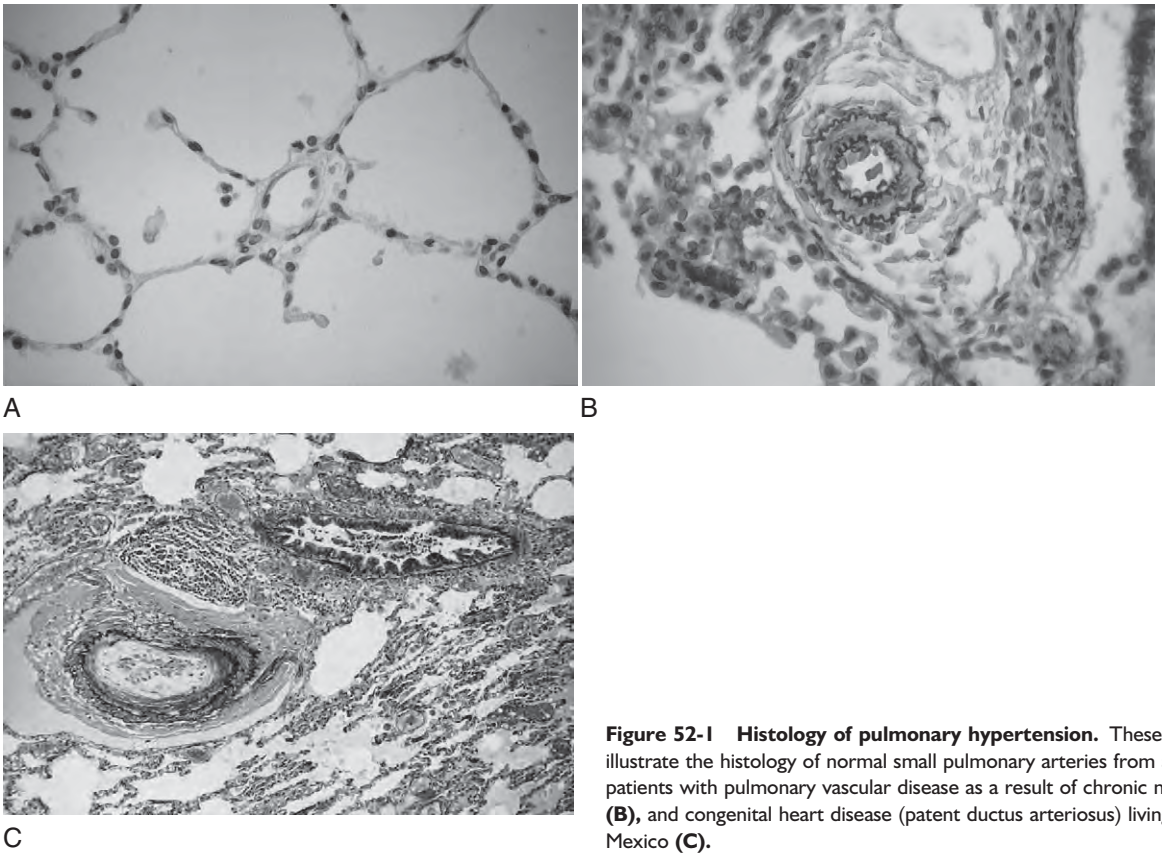

Figure 52-1 Histology of pulmonary hypertension. These photomicrographs illustrate the histology of normal small pulmonary arteries from a control patient **(A),** patients with pulmonary vascular disease as a result of chronic neonatal lung disease **(B),** and congenital heart disease (patent ductus arteriosus) living at high altitude in Mexico **(C).**

DEFINITIONS OF COR PULMONALE AND PULMONARY HYPERTENSION

Cor pulmonale is synonymous with *pulmonary heart disease*, and represents the adaptive response of the right ventricle to increased afterload caused by pulmonary hypertension.[15] Historically, cor pulmonale has been defined as "*hypertrophy* of the right ventricle resulting from diseases affecting the function and/or structure of the lung except where the pulmonary alterations are the result of diseases that primarily affect the left side of the heart or of congenital heart disease."[16] Right ventricular (RV) hypertrophy occurs in response to chronic increases in RV afterload. Although the term *cor pulmonale* has often been reserved for patients with overt signs of RV failure, such signs are generally present very late in the clinical course of pulmonary heart disease. Furthermore, clinical signs of overt right-sided heart failure can easily be masked by signs of severe chronic respiratory disease. A more clinically useful definition of cor pulmonale is the involvement of the right ventricle (either hypertrophy, dilation, or failure), as detected by clinical signs, chest radiograph, electrocardiogram (ECG), echocardiogram, cardiac catheterization, or autopsy, which is caused by altered pulmonary structure and function, provided that the changes are not the result of diseases primarily involving the left or right side of the heart. This is a more expansive definition because signs of advanced right-sided heart failure need not be present. The definition of pulmonary hypertension depends on age and altitude of residence. When directly measured by pulmonary artery catheterization, a mean pulmonary artery pressure (PAP) greater than 25 mm Hg is considered abnormal beyond early childhood. During the early neonatal period, mean PAP gradually falls from systemic levels immediately at birth to adult values by 3 to 6 months. Functionally, PAP is often considered to be clinically significant at a ratio or proportion of mean systemic arterial pressure greater than 50% systemic arterial pressure. ECG and echocardiogram criteria for pulmonary hypertension are discussed in the following section.

CLINICAL SETTINGS ASSOCIATED WITH PULMONARY HYPERTENSION

Pulmonary hypertension can occur as part of an acute or chronic cardiorespiratory process (Box 52-1). For example, high-altitude pulmonary edema (HAPE) or acute hypoxemic respiratory failure in a previously healthy child can cause moderate elevations of PAP as well as increased vascular permeability and altered vasoreactivity. The severity of pulmonary hypertension in response to acute respiratory disease depends in part on age, the presence of underlying cardiac or respiratory disease, genetic makeup, and other factors. For example, neonates with acute respiratory failure often have striking elevations in PAP, which may cause right-to-left shunting across the patent ductus arteriosus or foramen ovale, causing more marked hypoxemia. More commonly, pulmonary hypertension and cor pulmonale are recognized in association with chronic lung, neuromuscular, or cardiac diseases. Disorders commonly associated with chronic hypoxia can be divided into those associated with intrinsic lung disease or those with hypoventilation caused by neurologic or muscular impairment. Although chronic hypoxia contributes to the

BOX 52-1 Diseases Associated with Pulmonary Hypertension in Pediatrics: From the Revised World Health Organization Classification of Pulmonary Hypertension

Group I. Pulmonary Arterial Hypertension

Idiopathic (formerly known as "primary")
Familial
Persistent pulmonary hypertension of the newborn (PPHN)
Related conditions:
- Congenital heart disease (with systemic to pulmonary shunts)
- Portal hypertension
- Collagen vascular disease (esp. scleroderma)
- Drugs and toxins
- HIV infections
- Hemoglobinopathies (esp. sickle cell disease)
- Miscellaneous conditions: thyroid disease, Gaucher disease, glycogen storage disease, hereditary hemorrhagic telangiectasia, myeloproliferative disorders, splenectomy, others

Associated with significant venous or capillary involvement
- Pulmonary veno-occlusive disease
- Pulmonary hemangiomatosis, lymphangiectasia

Group II. Pulmonary Venous Hypertension

Left-sided atrial or ventricular heart disease
Left-sided valvular heart disease

Group III. Pulmonary Hypertension Associated with Chronic Lung Disease or Hypoxemia

Developmental abnormalities: alveolar capillary dysplasia, lung hypoplasia, congenital diaphragmatic hernia
Chronic lung diseases: Bronchopulmonary dysplasia, cystic fibrosis, interstitial lung disease
Sleep disordered breathing, obstructive sleep apnea, chronic upper airway obstruction
Chronic hypoventilation
- Neuromuscular disease, abnormal chest wall, or diaphragm function
- Central hypoventilation syndromes

Chronic high altitude exposure

Group IV. Pulmonary Hypertension due to Chronic Thrombotic and Embolic Disease

Pulmonary embolism (tumor, parasites, foreign material)
Thromboembolic obstruction of proximal, distal pulmonary arteries

Group V. Miscellaneous

Sarcoidosis, pulmonary Langerhans' cell histiocytosis, lymphangiomatosis, compression of vessels (adenopathy, tumor, fibrosing mediastinitis)

development and progression of pulmonary hypertension, pulmonary hypertension often occurs in settings where chronic inflammation and other stimuli are important etiologic factors as well (discussed later). The severity of pulmonary hypertension and degree of RV hypertrophy are likely related to the timing of injury (e.g., interruption of the normal decline in right ventricular predominance during early infancy), duration of pulmonary hypertension, and the presence or absence of left-sided congenital heart disease. Pulmonary venous obstruction, due to veno-occlusive disease or abnormal pulmonary venous return, can masquerade as interstitial lung disease.[8] Pulmonary hypertension is associated with high mortality in many chronic lung diseases, including BPD, CF, and interstitial lung disease—but in some settings, it is unclear whether RV hypertrophy serves as an important marker of advanced disease or an actual cause of death with advanced lung disease. Similarly, cor pulmonale is present in more than 70% of patients dying with CF,[5] but whether aggressive treatment of pulmonary hypertension will alter outcome is unknown.

DEVELOPMENTAL PHYSIOLOGY OF THE PULMONARY CIRCULATION

Insight into pulmonary hypertension in infants and young children begins with an understanding of normal growth and development of the perinatal lung, mechanisms that contribute to the normal postnatal adaptation of the pulmonary circulation after birth and during infancy, and unique responses of the developing lung circulation to injury.

Fetal Pulmonary Circulation

Development of the pulmonary circulation in utero is characterized by early growth of large central arteries with the subsequent development of the microcirculation later in gestation.[17] By the 16th week of gestation, all bronchial airway generations have formed along with their accompanying conducting pulmonary arteries. During the third trimester, pulmonary vascular surface area increases about 10-fold with the concomitant development of the distal airway, alveolar ducts, and saccules. Multiple mechanisms coordinate precise temporal and spatial signaling between vascular and alveolar growth, including critical roles for vascular endothelial growth factor (VEGF), nitric oxide (NO), and others.[18] Both angiogenic and vasculogenic mechanisms have been implicated in lung vascular growth during development, but the relative contributions of each during each phase of lung development are controversial. Importantly, disruption of vascular growth during fetal and early postnatal life can markedly impair lung structure and cause lung hypoplasia.[19]

In addition to increases in pulmonary artery number, changes in pulmonary vascular structure also occur with development. In the normal fetus, small pulmonary arteries associated with the respiratory bronchioles, alveolar ducts, and saccules have minimal smooth muscle (Fig. 52-2).[20] As the pulmonary circulation develops, pulmonary arteries acquire a muscle coat, which has a thickness roughly proportionate to vessel size. At birth, few intra-acinar arteries are muscularized, and vascular smooth muscle cells differentiate in distal arteries with normal postnatal growth. Larger arter-

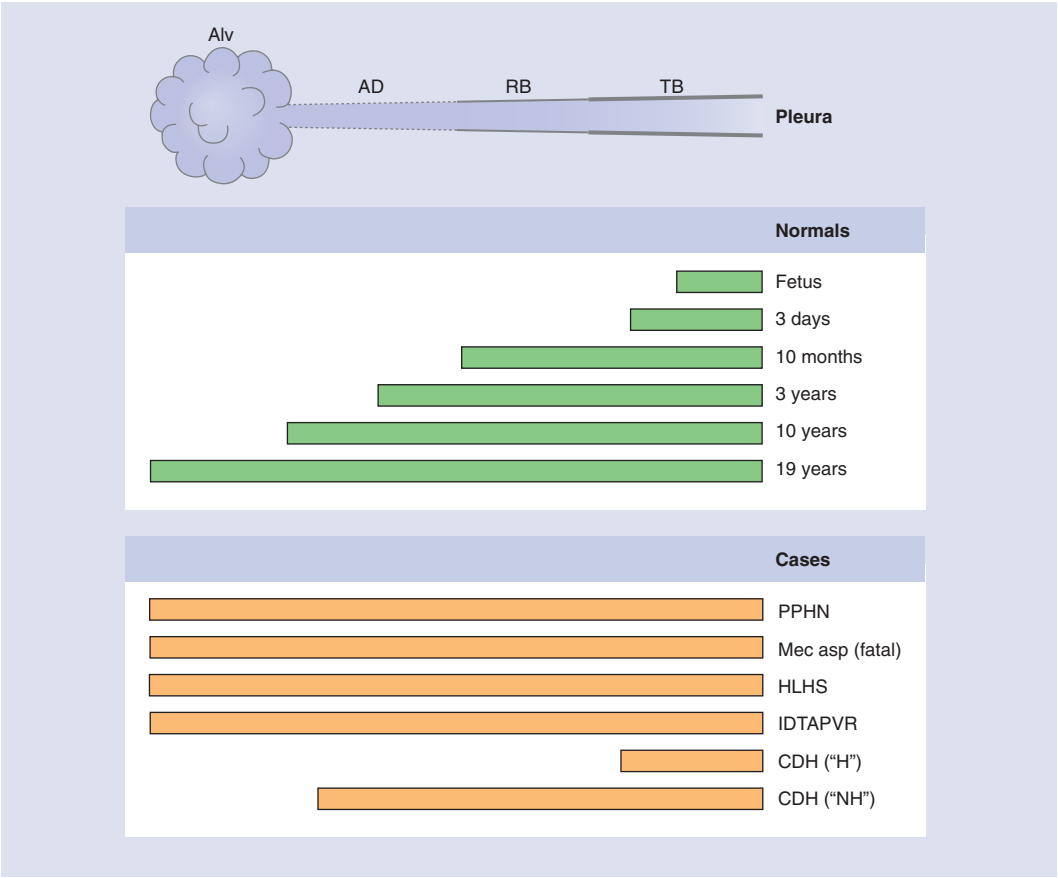

Figure 52-2 Maturational changes in the distribution of smooth muscle in the fetal and postnatal pulmonary circulation. Small pulmonary arteries that accompany the respiratory bronchioles (RB), alveolar ducts (AD), and alveoli (Alv) lack muscularization during fetal life, and extension of smooth muscle occurs throughout childhood. Neonates dying with persistent pulmonary hypertension (PPHN), meconium aspiration (Mec asp), hypoplastic left heart syndrome (HLHS), infradiaphragmatic total anomalous pulmonary venous return (IDTAPVR), and congenital diaphragmatic hernia (CDH) with and without a honeymoon period ("NH") demonstrate increased muscularization of small preacinar and acinar vessels, suggesting altered intrauterine growth. (From Reid L, Fried R, Geggel R, Langleben D: Anatomy of pulmonary hypertensive states. In Bergofsky EF [ed]: Abnormal Pulmonary Circulation. New York, Churchill Livingstone, 1986, p 227.)

ies (>200 μm) are muscularized early, and intermediate pulmonary arteries have variable medial coats, appearing either fully, partially, or nonmuscularized.[20] The apparent lack of extension of smooth muscle in small pulmonary arteries has been misinterpreted to suggest that the pulmonary circulation after premature delivery lacks the ability to vasoconstrict and that pulmonary vasospasm plays a small role in premature infants with respiratory failure. More recent studies have clearly demonstrated that high pulmonary vascular resistance (PVR) in premature neonates can be the result of active vasoconstriction, suggesting a role for vasodilator therapy in some newborns with severe hyaline membrane disease.[21]

The fetal pulmonary circulation receives less than 8% of combined ventricular output as a result of its high basal PVR, causing most of the RV output to cross the ductus arteriosus to the aorta, bypassing the lung.[22] Despite the apparent low level of pulmonary blood flow, blood flow remains essential for providing adequate substrate to allow lung growth; it has been shown that pulmonary artery ligation in the late-gestation fetal lamb causes lung hypoplasia.[23] Similarly, hypertension itself can impair lung vascular growth and decrease alveolarization in the late fetus,[24] suggesting additional mechanisms through which mesenchymal-epithelial "cross-talk" is required to achieve normal lung structure at birth.

During late gestation, pulmonary blood flow increases in proportion to lung weight and increased vascular cross-sectional area, as the number of blood vessels increases more than 10-fold. Although flow increases with advancing gestation, mean PAP increases as well, and when corrected for lung weight, PVR increases with gestational age. Mechanisms maintaining high fetal PVR include physical stimuli, such as the lack of a gas-liquid interface and rhythmic distention of the lung. In addition, low oxygen tension (normal fetal Pa_{O_2} is 20 to 25 mm Hg), low basal production of endogenous dilator products (such as prostacyclin [PGI_2] and nitric oxide [NO][25]), and increased production of vasoconstrictor substances (including endothelin-1[26-28] and leukotrienes[29]) also contribute to high PVR in utero.

In addition to the structural changes previously described, marked changes in pulmonary vascular tone and reactivity also occur with development.[30] For example, experimental

studies of maturational changes of pulmonary vasoregulation suggest that endogenous NO production modulates basal fetal PVR and that the fetal smooth muscle is responsive to vasodilators, such as NO or NO-donors, quite early in gestation.[31-33] Maturational changes in endothelial and smooth muscle function contribute to the regulation of vascular tone in fetal life (Fig. 52-3).

The distal lung develops extensively during the third trimester, including a dramatic increase in small pulmonary arteries, which continues during the first few years after birth.[34] With premature birth, the normal sequence of lung growth and development is disrupted, and at least in children requiring mechanical ventilation because of respiratory distress syndrome, lung growth may be severely impaired by hyperoxia, barotrauma, and inflammation, causing BPD.[35] In older patients dying with BPD, lung septation and capillary surface area are markedly decreased.[36-38] Impaired vascular growth may not only cause a dysmorphic pulmonary circulation in BPD, but it may also disrupt alveolarization.[19,39,40] As a result, premature birth, respiratory distress, and vascular injury during its treatment are a major cause of pulmonary hypertension in BPD (as discussed subsequently).

During late gestation, intrauterine stimuli, such as inflammation, infection, or systemic or pulmonary hypertension, can alter vascular growth, leading to striking hypertensive remodeling and decreased vessel number. Although exact mechanisms causing vascular remodeling are incompletely understood, experimental studies suggest that intrauterine hypertension may be more critical than chronic hypoxia in the pathogenesis of structural and functional impairment during the transition at birth.[41-44] Partial compression or early closure of the ductus arteriosus in fetal lambs alters vascular reactivity and lung structure, leading to the failure of postnatal adaptation at delivery, providing an experimental model of persistent pulmonary hypertension of the newborn (PPHN).[41,42]

Transitional Pulmonary Circulation

At birth, the pulmonary circulation undergoes a dramatic transition because pulmonary blood flow rapidly increases 8- to 10-fold and PAP decreases to levels approximately 50% of systemic arterial pressure.[22] Mechanisms causing this fall in PVR include establishment of an air-liquid interface, rhythmic lung distention with respiration, increased oxygen tension, and altered production of vasoactive substances.[30] Marked stimulation of endogenous NO, primarily the result of increased oxygen and shear stress, contributes substantially to the fall in PVR.[25,45] Similarly, PGI_2, largely released from increased lung ventilation and shear stress, but not increased oxygen, also contributes to postnatal adaptation.[46] Decreased production or responsiveness to local vasoconstrictors, such as leukotrienes or endothelin-1, may also contribute to the normal fall in PVR.[27] A concomitant structural reorganization of small pulmonary arteries occurs, as the vascular endothelium is flattened with high flow, and vascular dimensions change rapidly with birth.[47] Progressive pulmonary vascular dilation, recruitment, and structural adaptations are reflected by further decreases in resistance during late infancy, when adult values of PVR are achieved.

The pulmonary circulation during this transitional period (at birth and during early infancy) may be particularly sensitive to injury. Not only is this a time of rapid vessel growth, but functional changes in vascular tone and reactivity occur with age as well. Such developmental aspects of the pulmonary circulation not only are important in regard to PPHN, congenital heart disease, and BPD, but also have clinical ramifications in other settings of pediatric pulmonary hypertension. As suggested in two experimental models of chronic pulmonary hypertension, the immature or infant lung circulation may not only be more susceptible to injury, but it may also be uniquely capable of recovering more readily than adult circulation. Insight into responses of the developing lung to

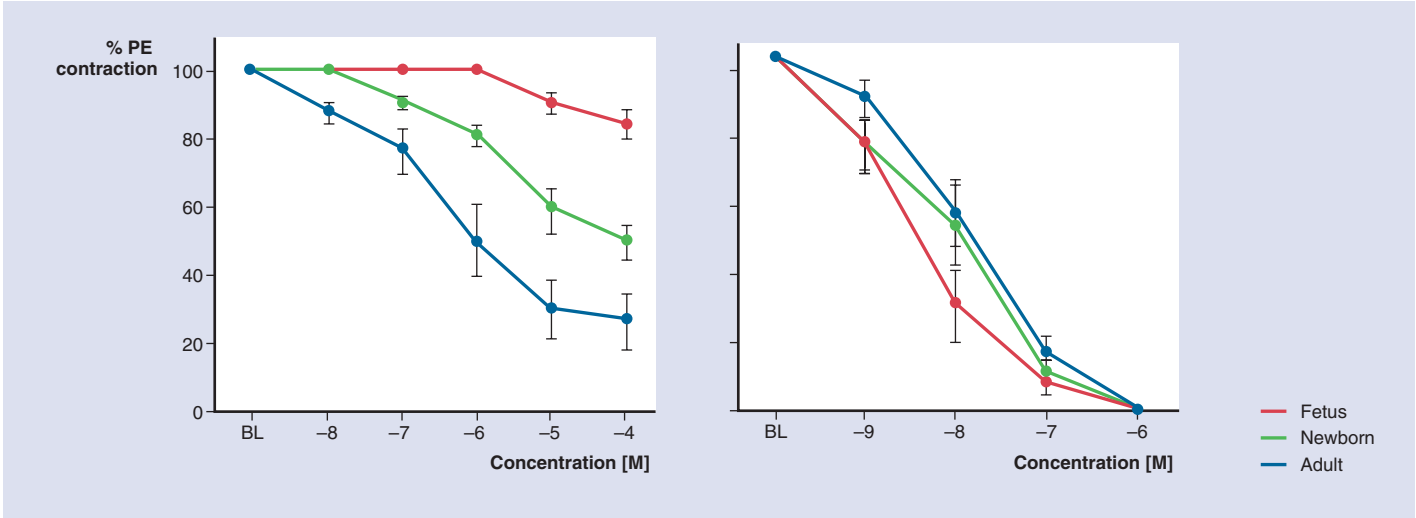

Figure 52-3 Maturation-related changes in pulmonary vasodilation to endothelium-dependent and independent stimuli. In comparison with neonatal and adult pulmonary arteries, pulmonary arteries isolated from late-gestation fetal lambs have diminished relaxation to acetylcholine (ACH), an endothelium-dependent agonist (*left*). In contrast, the relaxation to sodium nitroprusside (SNP), an agent that directly stimulates smooth muscle cell relaxation, causes marked relaxation at each age (*right*). These findings suggest that maturational changes occur in endothelial function but that vascular smooth muscle is able to respond to vasodilator stimuli early in development. (From Abman SH, Chatfield BA, Rodman DM, et al: Maturational changes in endothelium-derived relaxing factor activity of ovine pulmonary arteries in vitro. Am J Physiol 260:L280-L285, 1991.)

growth factors, vasoactive mediators, and related stimuli are likely to provide novel approaches toward the management of pediatric pulmonary hypertension.

Normal Postnatal Anatomy

Blood flow in the lung has two sources, including the pulmonary and bronchial circulations, which behave differently in health and disease states.[48] The pulmonary circulation includes the RV outflow tract, main pulmonary artery and its major branches to left and right lung, lobar branches, intrapulmonary arteries, arterioles, capillaries, venules, and large pulmonary veins. Normally, the right pulmonary artery divides into a lower branch, which supplies the right middle and lower lobes, and a smaller upper branch to the right upper lobe. The left pulmonary artery lies above the left mainstem bronchus up to the first branch, then travels behind the bronchus. Some variability exists with the distribution of smaller arterial branches.

There are striking differences in vascular growth and function of vessels throughout the pulmonary circulation, at least partly dependent on their size and location, which may be related to chronic exposure to different hemodynamic forces (discussed later). There are three types of arteries. First, elastic pulmonary arteries (>1000 μm external diameter) consist of distinctive layers of elastic fibers in a coat of smooth muscle cells in central pulmonary arteries and extralobular pulmonary arteries. Second, muscular pulmonary arteries (100 to 1000 μm external diameter) have a thin medial layer of muscle between internal and external elastic laminae, which is usually less than 5% of the external diameter of the vessel. Muscular arteries accompany bronchioles within lobules. Third, pulmonary arterioles (<100 μm external diameter) are the terminal branches of the pulmonary arterial tree and, at their origin from muscular arteries, contain a partial layer of muscle that gradually disappears. Pulmonary arterioles supply alveolar ducts and alveoli.

Two types of small pulmonary artery branches have been described, including "conventional" branches, which accompany airways, and "supernumerary" branches, which travel alone and are usually smaller. Conventional arteries branch from main arterial channels and extend to the periphery, at the end of the respiratory bronchioles. Supernumerary vessels outnumber the conventional branches, constituting 25% of the total cross-sectional area of the pulmonary arterial bed near the hilum and about 40% at the periphery. Supernumerary arteries are present at birth and can participate in gas exchange. Extensive growth of conventional and supernumerary branches accompanies the development of new alveolar ducts and alveoli and contributes to the progressive increase in surface area during the first few years of life.[34] After 18 months, the number of conventional arteries is fixed, but supernumerary arteries continue to increase with septation and formation of new alveoli (up to 3 years of age).

The microcirculation consists of small capillaries that form an extensive network in interalveolar septa. Capillaries are mostly composed of cytoplasmic extensions of endothelial cells, which, by their contiguous arrangement, form a thin vascular tube. More recently, lung vascular growth has been shown to result from angiogenesis and vasculogenesis, but the relative importance of lung vasculogenesis during postnatal life is unclear.[49] Both the endothelium and the neighboring alveolar epithelium lie on separate basement membranes. Fusion of endothelial and epithelial basement membranes cover half of the capillary border, forming the thin portion of the alveolar-capillary membrane, which provides the site for gas exchange. For the other half of the capillary perimeter, these basement membranes remain separated by an interstitial space and are sites for liquid and solute exchange.

Arterial and venous blood supplies of pulmonary lobules differ anatomically. A lobule consists of a cluster of three to five terminal bronchioles, and neighboring lobules are partly contained by connective tissue septa. Branches of pulmonary arteries and small bronchi travel together, supplying terminal respiratory units within a single lobule. In contrast, pulmonary veins drain blood from several different lobules. Normal veins have less muscularity and much thinner walls than arteries, but like arteries, veins are either conventional or supernumerary. Small intrapulmonary venules successively fuse to form increasingly larger veins until a lobar vein emerges from each lobe. The right upper and middle lobe veins usually combine; thus, there are superior and inferior pulmonary veins from each lung. Although the branching pattern of the airways increases the cross-sectional area of the bronchial tree longitudinally, the cross-sectional area of the vascular bed gets smaller from the central vessels to the arterioles or venules. Most of the blood in the pulmonary circulation is contained in large, not small, vessels. Velocity of blood flow in arteries decreases as vessels get smaller, but the decrease is not as marked as with airways.

Although the bronchial circulation normally receives only 1% to 2% of the total cardiac output, it provides flow, which is essential for maintaining normal lung growth and function.[48] The bronchial circulation is the principal source of nutrient blood and oxygen to airways (large and small), pulmonary nerves and ganglia, walls of elastic and some muscular pulmonary arteries and veins, lymph nodes and connective tissue septa, and the pleura. Bronchial blood flow may increase substantially with pathologic conditions, such as in diseases associated with chronic inflammation and injury (such as CF, BPD, and bronchiectasis).[1,50] Acute increases in bronchial flow may also contribute to lung edema with acute lung injury.[51] There is marked variability of bronchial branching patterns; 40% of children have one bronchial artery to each lung. Bronchial blood returns to the heart via bronchial veins, from branches perfusing the lobar and segmental bronchi and from branches from the pleura near the hilus. Bronchial venous blood empties into the azygos, hemiazygos, or intercostal veins and then flows into the right atrium. Veins that originate from bronchial capillaries within the lung unite to form tributaries that join pulmonary veins (bronchopulmonary veins). Blood leaving the capillary bed near terminal bronchioles flows through anastomoses with the alveolar capillaries, and the mixture of blood returns to the left atrium through pulmonary veins. About one fourth to one third of blood goes to the right atrium via bronchial veins; the remainder flows to the left atrium via pulmonary veins.

Normal Postnatal Physiology

Although the lungs normally receive the entire cardiac output, PAP remains low because of the low basal vascular resistance.

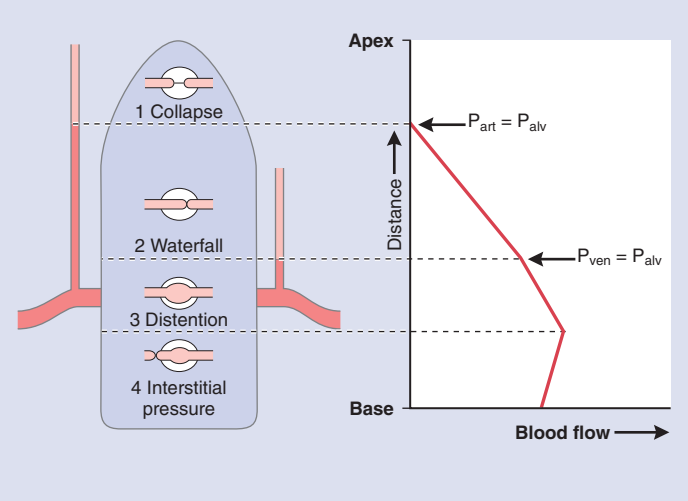

Figure 52-4 Effects of alveolar, arterial, and venous pressures on regional distribution of blood flow in the pulmonary circulation. (From Murray JF: The Normal Lung. Philadelphia, WB Saunders, 1986, pp 139-150.)

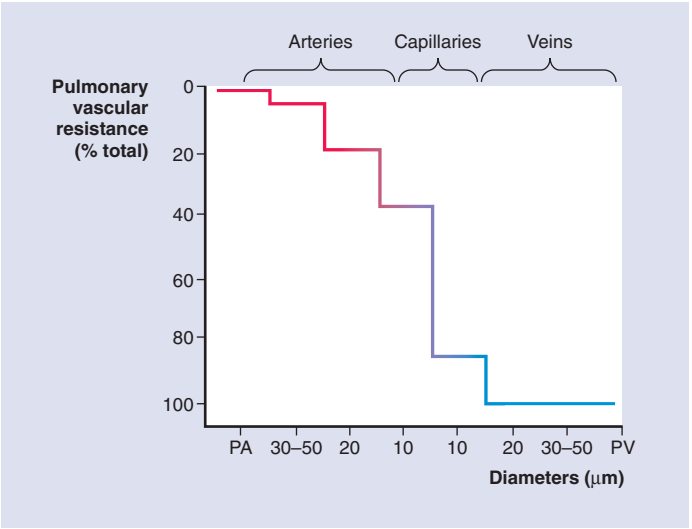

Figure 52-5 Distribution of resistance in pulmonary circulation from isolated perfused dog lung. PA, pulmonary artery; PV, pulmonary vein. (From West JB, Dollery CT, Naimark A: Distribution of blood flow in isolated lung; relation to vascular and alveolar pressures. J Appl Physiol 19:713-724, 1964.)

The distribution of pulmonary flow within the lung is nonuniform and depends partly on relationships among gravity, alveolar pressure, PAP, and pulmonary venous or left-atrial pressure.[52] Three zones have been proposed to explain regional variations in flow (Fig. 52-4). In zone 1, normal PAP is insufficient to perfuse the uppermost regions of the lung, and pulmonary capillaries are collapsed because alveolar pressure exceeds pulmonary arterial and venous pressures. Pulmonary blood flow begins at the top of zone 2, as PAP exceeds alveolar pressure, and continues to increase with increased PAP. As alveolar pressure is greater than pulmonary venous pressure, flow is determined by the difference between pulmonary artery and alveolar pressures. In zone 3, both pulmonary artery and venous pressures exceed alveolar pressure; therefore, driving pressure is determined by the difference between inflow and outflow vascular pressures. In the normal upright adult, most of the lung is in zone 3 conditions. Passive changes in PVR are affected by differences between pressures within and surrounding pulmonary blood vessels, shifts of blood into and out of the lungs, and changes in whole blood viscosity. Changing hydrostatic pressures relative to the height of the lung affect distribution of pulmonary blood flow (for example, distribution of flow is more even while supine than in the upright position). Increased pulmonary artery or left atrial pressure acutely increases flow, causing a drop in PVR. The longitudinal distribution of PVR in the normal lung using micropipette techniques demonstrated that under zone 3 conditions, the largest contribution to resistance lies in the capillaries of the alveolar septum, with most of the remaining resistance in arterioles, and little contribution from venules to veins (Fig. 52-5).[53]

Multiple mechanisms regulate vascular tone and the distribution of blood flow within the lung. Active and passive changes in PVR during exercise and the regional effects of hypoxia illustrate how the lung can alter distribution of blood flow to sustain gas exchange. Because of its low basal PVR and high compliance, the normal pulmonary circulation tolerates marked increases in flow during exercise, with only small increases in pressure and decreases in PVR. Pulmonary artery and capillary wedge pressures rise, increasing flow to the upper lobes and making overall perfusion more uniform. With high flow during exercise, low PVR is maintained by passive vascular distention, recruitment of small pulmonary arteries, and vasodilation. Patients with chronic lung disease can have marked increases in PAP because of the increase in pulmonary blood flow during exercise—even apparently during normal resting pulmonary hemodynamics.

As first described by von Euler,[54] the unique ability of pulmonary arteries to constrict with exposure to low oxygen tension plays a central role in controlling the distribution of blood flow through the lung. Although many vasoactive substances modulate the degree of hypoxic vasoconstriction, hypoxia causes contraction by direct effects on vascular smooth muscle.[55] Regional vasoconstriction redirects blood flow to lung regions with better aeration, enhancing ventilation-perfusion ($\dot{V}/\dot{Q}$) matching and preserving gas exchange.

In addition to its gas exchange function, the pulmonary circulation also provides nutritional and metabolic support for the lung and is the site for synthesis, storage, and metabolism of various circulating and local vasoactive substances. Although past studies primarily emphasized its barrier function, the endothelial cell releases multiple vasoactive products that regulate vascular tone, smooth muscle growth, angiogenesis, liquid and solute transport, thrombosis, synthesis or clearance of circulating hormones, and others. Clinical and experimental studies suggest that vascular metabolic functions are altered with pulmonary vascular injury, contributing to hemodynamic and structural abnormalities in chronic pulmonary hypertension.

DISEASE MECHANISMS

As with pulmonary hypertension in adults, numerous factors contribute to disease severity in pediatric patients, including

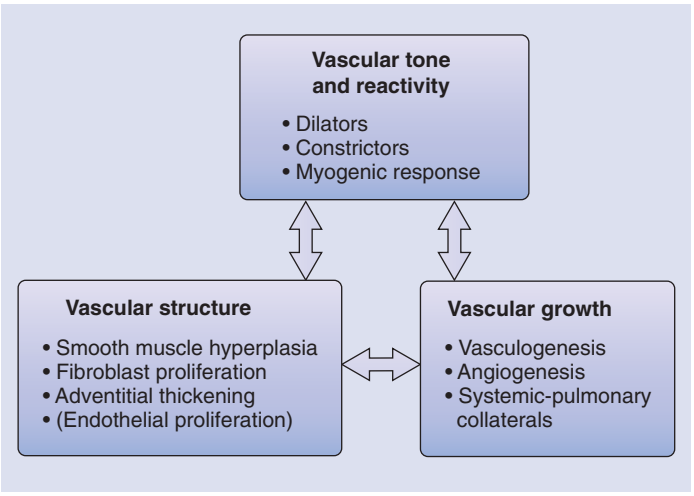

Figure 52-6 Components of pulmonary hypertension.

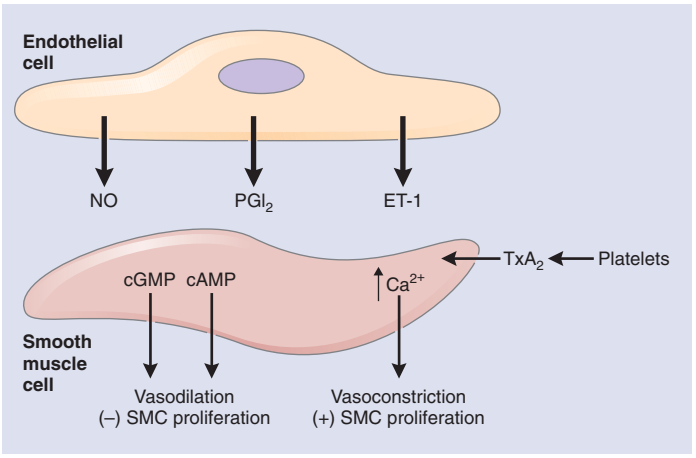

Figure 52-7 Endothelial–smooth muscle cell interactions in pulmonary hypertension. NO, nitric oxide; PGI_2, prostacyclin; SMC, smooth muscle cell; TxA_2, thromboxane.

high basal tone, abnormal vasoreactivity, thrombosis, inflammation, and altered vascular growth and remodeling (Fig. 52-6). Although pulmonary hypertension occurs in diverse clinical settings, several features are common regardless of the specific disease associated with pulmonary hypertension. First, pulmonary vascular disease is generally associated with changes in both structure and function, and the relative contribution of remodeling with changes in vascular tone is variable—even within diseases. Second, pulmonary vascular disorders are commonly associated with altered vascular reactivity, not only high basal pulmonary vascular tone, and exaggerated vasoconstriction to certain stimuli (especially acute hypoxia) is often central to pathophysiologic features. For example, altered pulmonary vasoreactivity leads to the vasolability or "flip-flopping" in patients with PPHN,[56] recurrent cyanotic episodes in apparently normal children,[57] recurrent high altitude pulmonary edema (HAPE),[58] sudden death or "dying spells" in BPD, and other disorders. Mechanisms contributing to heightened pulmonary vasoreactivity are poorly understood, but may include alterations in endothelial-smooth muscle cell interactions. Third, reduced arterial density, as typically observed in lung hypoplasia, congenital diaphragmatic hernia, BPD, Down syndrome and other settings, markedly increase the risk for advanced pulmonary hypertension. This may, in part, be due to increased hemodynamic stress of even normal cardiac output through a "hypoplastic" vasculature, and likely accounts for the accelerated pulmonary vascular disease observed in patients with BPD, Down syndrome, and other disorders, in the presence of relatively modest increases in pulmonary blood flow due to cardiac shunts.

Recent developments in vascular biology have demonstrated that the endothelial cell produces a wide variety of vasoactive compounds, including dilators such as PGI_2 and NO (Fig. 52-7). In addition, vascular endothelium can produce potent vasoconstrictors, including endothelin (ET-1), thromboxane, and other endothelium-derived contracting factors. Vascular injury from hemodynamic stresses (high flow, high pressure, shear stress, or stretch), hypoxia, or inflammation alters endothelial production of these products, creating an imbalance between vasodilators and vasoconstrictors, which favors increased basal tone or heightened vasoreactivity. Increased superoxide production may further worsen vascular tone owing to impaired NO production or endothelial injury.[59] However, in vitro studies of human pulmonary arteries suggest that impaired endogenous NO activity is likely to contribute to heightened pulmonary vasoconstriction in patients with pulmonary hypertension associated with several chronic lung diseases, including CF and chronic obstructive pulmonary disease (COPD).[60] In addition, increased immunoreactivity and gene expression of ET-1 is present in children with BPD and adults with severe pulmonary hypertension, suggesting that enhanced ET-1 production may also contribute to heightened vasoreactivity and hypertensive vascular remodeling in chronic pulmonary hypertension.[61]

Unlike the pulmonary vascular response to acute hypoxia, prolonged exposure to hypoxia causes sustained elevations of PAP that do not totally improve with the acute return to normal oxygenation. In addition to hypoxia, other mechanisms that contribute to the development of chronic pulmonary hypertension include hemodynamic stresses (increased pressure, flow, shear, stretch, and wall tension), sustained release of vasoactive products and growth factors (inflammatory, autocoids, paracrine mediators, or neurohumoral stimuli), and combinations of these stimuli. Pulmonary vascular responses to these stimuli are also dependent on the strength and duration of the stimulus, the patient's age, genetic factors, infection, inflammation, and others. Whereas the short-term responses to these agonists generally alter vascular tone and reactivity, long-term exposure to the same stimuli is likely to contribute to altered vascular growth and remodeling. Persistent elevation of PAP can be due to at least four general causes, including vasoconstriction, vessel wall proliferation and remodeling, thrombosis in situ, and decreased vessel number or surface area.

Pulmonary hypertension is commonly defined as mean PAP above 25 mm Hg, with normal values reported between 10 and 16 mm Hg. As discussed previously, mean PAP is roughly 50% of systemic arterial pressure at the end of the first day of life and gradually decreases during early infancy.[62] Determinants of PAP include cardiac output (CO), PVR, and

pulmonary capillary wedge or venous pressure. Because CO varies with body size, PVR is often indexed according to surface area (PVRI). PVR is often expressed as resistance units (mm Hg/L/min) or as dynes/sec/cm^{-5} (multiply PVRI by 80).

Diverse mechanisms may contribute to high PAP, including high PVR caused by vascular remodeling, vasoconstriction, vascular occlusion (from thromboemboli), or compression of small pulmonary arteries (for example, at high or low lung volumes during mechanical ventilation). In addition, elevated pulmonary capillary wedge pressure (PCWP) resulting from left-ventricular failure, pulmonary venous obstruction or constriction, mitral valve disease, and others can also increase PAP without marked changes in PVR. For example, assessments of transpulmonary artery pressure gradient are important in the setting of high PCWP to directly assess pulmonary vascular disease in potential candidates for cardiac transplantation because of severe cardiomyopathy. PAP may be elevated in the absence of high PVR with anatomic cardiac lesions with large left-to-right shunting. Long-standing pulmonary venous obstruction or high-flow lesions are associated with high PVR resulting from upstream pulmonary vascular disease from remodeling or vasoconstriction. Hyperviscosity and intrathoracic pressure can also influence PVR in the presence of marked polycythemia associated with chronic hypoxia and during mechanical ventilation, respectively. Positive end-expiratory pressure (PEEP) influences lung volume, depending on its effects on lung volume and intrathoracic pressure.[63] Whereas low lung volumes may elevate PVR because of the loss of the "tethering" effect of normal distention of neighboring parenchyma, hyperinflation may cause mechanical compression of intra-acinar vessels.

The earliest clinical signs of pulmonary hypertension first become apparent during exercise, even in the presence of normal or minimal increases in baseline PAP.[64,65] The normal physiologic response to exercise includes a marked increase in CO with small increases in PAP and PCWP, decreasing PVR by 60% to 70% from baseline. Increased pulmonary blood flow would markedly increase PAP if there was not a concomitant decrease in pulmonary vascular tone and an increase in vascular distention and recruitment.

With early pulmonary vascular disease, increased CO during exercise markedly increases PAP as a result of high blood flow through a restricted vascular bed and its inability to distend or dilate because of altered vascular structure and reactivity. With severe pulmonary hypertension, exercise is extremely limited because CO is unable to increase, predisposing patients to fatigue, dyspnea on exertion, and with advanced disease, syncope or sudden death. In the absence of shunt lesions, right- and left-ventricular outputs are the same.

Because PVR is normally about 20% of systemic vascular resistance, the right ventricle has a thinner wall and a greater volume and surface area than the left ventricle. This configuration is better suited to ejecting large volumes of blood with minimal myocardial shortening, providing a highly compliant chamber that better accommodates increases in filling pressure, as with normal exercise. Unfortunately, the right ventricle is poorly designed to handle rapid increases in wall tension and high systolic ejection pressure, such that an abrupt rise in RV afterload markedly increases RV end-diastolic pressure, decreasing ejection fraction, and RV output. A sudden rise in PVR rapidly dilates the right ventricle, as it attempts to improve function according to the Frank-Starling curve. Mean PAP near 50 mm Hg is poorly tolerated, leading to acute right-sided heart failure.[66] For example, although cardiac transplant patients may have tolerated moderate pulmonary vascular disease before surgery, rapid deterioration of function in the right side of the heart can occur after surgery because of the lack of adaptation of the "new" right ventricle. Interestingly, the failing right ventricle may not be able to generate enough CO to sustain elevated PAP despite high PVR, causing overt clinical signs of right-sided heart failure in some patients with only mild or moderate elevations of PAP. Reduced right coronary artery perfusion pressure, especially during systole, decreases oxygen delivery and causes subendocardial ischemia, further contributing to right ventricular dysfunction.

Experimental studies suggest that even small increases in PAP result in rapid reduction of RV stroke volume. With the gradual development of pulmonary hypertension that occurs with chronic lung disease, the right ventricle is able to adapt to increased afterload by muscle hypertrophy. Acute pulmonary hypertension does not develop until there is a 60% reduction in functional surface area.[67,68] With chronic pulmonary hypertension, smaller degrees of obstruction or loss of vascular bed increases PAP and causes RV hypertrophy. Hypertrophy represents an adaptive response that reduces ventricular compliance and increases RV end-diastolic and right-atrial pressure. High right-atrial pressure is an important marker of advanced RV failure because CO falls with right-atrial pressure above 8 to 10 mm Hg in adults.[68] Systemic venous distention, hepatomegaly, peripheral edema, and other clinical signs of right-sided heart failure can develop with acute elevations of PAP in patients with chronic mild-to-moderate pulmonary hypertension, as with respiratory syncytial virus infections in patients with BPD and congenital heart disease.

Left-ventricular function is generally well preserved in most patients with chronic lung disease despite pulmonary hypertension and suboptimal RV function.[69] However, high PVR can impair CO, especially with exercise, and in some patients, poor left-ventricular function is present, further aggravating lung mechanics and gas exchange.[70,71] High PVR causes left-ventricular dysfunction by decreasing preload and causing paradoxical interventricular septal motion (ventricular interdependence).[72] Increased RV dilation mechanically distorts the left ventricle, impedes left-ventricular filling, and decreases CO in proportion to the severity of RV failure. Histologic studies suggest remodeling of left ventricular myocytes and interstitium, suggesting that along with functional changes in left- and right-ventricular interactions, structural remodeling may also account for changes in myocardial compliance or function. Left-ventricular hypertrophy may represent an adaptive response to increased septal wall tension and is not uncommon in infants with BPD and pulmonary hypertension.[1] Mechanisms leading to the development of left-ventricular hypertrophy in BPD or other chronic lung diseases are unclear, but they may be related to systemic hypertension, β-agonist therapy, or other stimuli. Low CO is an important marker of severe pulmonary hypertension and poor long-term outcome. Decreased CO increases fluid and salt

retention as a result of increased antidiuretic hormone and aldosterone release, which may account for worsening peripheral edema and other signs of congestive heart failure.[73]

Pulmonary hypertension can alter lung mechanics and gas exchange, causing mild decreases in lung compliance and volume.[74] The direct effects of pulmonary hypertension on gas exchange are difficult to distinguish from signs and symptoms of chronic lung disease. However, patients with primary pulmonary hypertension have only mild abnormalities in ventilation-perfusion ($\dot{V}/\dot{Q}$) matching.[75] Pulmonary hypertension with chronic lung disease may further impair lung function and gas exchange by increasing pulmonary edema formation in addition to altering reactivity.

ASSESSMENT AND DIAGNOSIS

The diagnosis, evaluation, and management of pulmonary hypertension requires a methodical approach, but can vary according to the associated disease. Increased awareness of at-risk patient populations with chronic lung disease and other disorders associated with pulmonary hypertension may allow for earlier diagnosis and a greater likelihood for successful intervention. Too often, pulmonary hypertension is not recognized until overt RV dysfunction is already present. Clinically, RV dysfunction may occur at lower PAP in chronic lung disease than with patients with IPAH, making diagnosis and assessments of its contribution to the clinical picture in those with chronic lung disease difficult. Whereas patients with IPAH may tolerate mean PAP above 60 mm Hg, those with chronic obstructive lung disease often have RV dysfunction at 40 mm Hg.[76] Importantly, pulmonary vascular disease in patients with chronic lung disease can limit activity and cause exercise intolerance even in the absence of striking pulmonary hypertension by echocardiogram at rest because PAP can markedly increase with even modest activity in some cases.

Once recognized, assessment and treatment of factors that contribute to progressive pulmonary vascular disease becomes critical. For example, causes of intermittent or chronic hypoxemia, such as obstructive sleep apnea, chronic aspiration, unrecognized airway lesions, and unsuspected anatomic cardiac disease, can potentiate pulmonary vascular injury associated with any primary etiology. As with adult pulmonary hypertension, clinical symptoms and signs commonly associated with pediatric pulmonary hypertension include dyspnea, fatigue, exercise intolerance, syncope, cyanosis, chest pain, palpitations, intermittent dry cough, or vomiting. Unexplained seizures, especially in children living at or visiting high altitudes, can be a manifesting sign of reactive pulmonary hypertension. IPAH may appear to be unexplained "portal hypertension" caused by hepatomegaly,[77] recurrent cyanotic episodes, or seizures. Young infants often have feeding difficulties, including cyanosis, choking, sweating, decreased intake as a result of fatigue, and failure to thrive. Evaluations should seek a history of snoring and obstructive sleep apnea (even in the presence of underlying chronic lung disease), including inquiries regarding daytime somnolence, enuresis, and systemic hypertension.

Signs and symptoms of pulmonary hypertension in children with cor pulmonale can be nonspecific and are often difficult to distinguish from progression of the underlying respiratory problem. Such signs include dyspnea, fatigue, exercise intolerance, recurrent cyanotic or breath-holding spells, poor growth, diaphoresis, chest pain, syncope, and palpitations. Infants and young children often have poor feeding associated with choking, sweating, and cyanosis. In selected cases, unexplained seizures can be a presenting sign, especially in children with primary pulmonary hypertension. As pulmonary hypertension worsens and contributes to the underlying lung disease, progressive dyspnea, fatigue, and other signs are often attributed to exacerbations of the primary lung disease. Similarly, physical findings of pulmonary hypertension are often subtle early; neck vein distention, peripheral edema, hepatomegaly, syncope, and other problems manifest late in the course. Signs of worsening exercise intolerance or fatigue in the absence of proportionate declines in airflow limitation or lung mechanics by formal pulmonary function testing raises the possibility that pulmonary hypertension and cardiac dysfunction may be contributing factors. Physical examination may disclose signs of associated multisystem diseases that can cause pulmonary hypertension, such as cirrhosis, collagen vascular disorders, and hematologic abnormalities.

Common findings on physical examination in patients with moderate pulmonary hypertension include tachypnea, tachycardia, an increased second heart sound with narrow or fixed splitting, and a systolic ejection murmur at the left upper sternal border. Signs of advanced RV failure include RV heave, increased jugular venous distention (prominent a wave), hepatomegaly and hepatic tenderness, and peripheral edema. In patients with chronic lung disease, signs and symptoms of pulmonary hypertension are often difficult to distinguish from progressive respiratory deterioration. Fluid retention, increasing hepatomegaly, hepatic tenderness, and peripheral edema should heighten suspicion of RV failure in this setting. Although differentiating signs and symptoms from the primary lung disease versus pulmonary hypertension is difficult, awareness of the risk for pulmonary hypertension and early evaluation may lead to the diagnosis. For example, CF patients with progressive dyspnea or exercise intolerance that seems discordant with the degree of decline in pulmonary function or that persists despite aggressive antimicrobial and anti-inflammatory therapy may suggest a significant clinical contribution of pulmonary hypertension and cor pulmonale. Similarly, infants with BPD and unexplained poor growth, persistent or increased oxygen requirements, recurrent cyanotic episodes, or the lack of resolution of RV hypertrophy by ECG warrant more extensive investigation.[78]

The clinical evaluation depends on whether the evolution of pulmonary hypertension is for patients with recognized lung disease or in patients with an unknown etiology. The role of laboratory studies is to identify the presence and severity of pulmonary hypertension, to identify pathogenetic mechanisms that may contribute to its severity, and to assess response to therapeutic intervention. Although ECG, echocardiogram, and cardiac catheterization are direct assessments of pulmonary hypertension, studies such as chest radiographic examinations, chest computed tomography (CT), $\dot{V}/\dot{Q}$ scans, and pulmonary angiography provide important clinical information in many settings. Initial evaluation includes arterial blood gases (to assess chronic hypoventilation), chest radiograph, ECG, echocardiogram, $\dot{V}/\dot{Q}$ scan,

BOX 52-2 Diagnostic Evaluation of Pulmonary Hypertension

The following tests may be useful depending on the clinical features:

- Arterial blood gas
- Prolonged pulse oximetry studies (awake, asleep, exercise)
- Electrocardiogram (ECG)
- Echocardiogram
- Cardiac catheterization (including acute vasodilator testing, angiography)
- Exercise testing
- Complete blood count with platelet count, urinalysis
- Liver function tests (liver enzymes, albumin, clotting studies) plus imaging studies (ultrasound)
- Coagulation studies: DIC screen, factor V Leiden, antithrombin III, protein C, protein S, anticardiolipin IgG or IgM, antiphospholipid antibody, Russell viper venom test
- Collagen vascular disease evaluation: ESR, ANCA, ANA with profile (DNA, Smith, RNP, SSA, SSB, centromere, SCL-70), rheumatoid factor
- Complement
- Thyroid function tests
- Toxicology screen
- Chest radiographs
- Pulmonary function testing with DLCO
- Barium swallow
- Esophageal pH study
- Sleep study
- $\dot{V}/\dot{Q}$ scan
- Chest CT scan

BOX 52-3 ECG Criteria for Right-Ventricular Hypertrophy

- Right-axis deviation (RAD)
- Right-atrial hypertrophy: (p-pulmonale: P waves >3 mm)
- Increased rightward and anterior QRS vector
  - R in V_1, V_2, or aV_R > upper limit of normal (ULN) for age
  - S in I and V_6 > ULN for age
- Abnormal R : S ratio in favor of right ventricle (in absence of bundle branch block)
  - R : S ratio in V_1 and V_2 > ULN for age
  - R : S ratio in V_6 < 1 after 1 month of age
- Upright T in V_1 (in patients >3 days of age)
- q wave in V_1 (qR or qRs patterns)

Newborn

- Pure R wave in V_1 > 10 mm
- R in V_1 > 25 mm, or R in aV_R > 8 mm
- qR pattern in V_1
- Upright T in V_1 in neonates >3 days of age
- RAD > 180 degrees

sleep study, exercise testing, and others (Box 52-2). In addition to excluding the presence of parenchymal disease in patients with unexplained pulmonary hypertension, a basic laboratory work-up may include hematologic, liver function tests, clotting studies, screening for collagen vascular disease, and others.

Chest radiograph findings suggestive of pulmonary hypertension in chronic lung disease include RV enlargement with prominent appearance of dilated central pulmonary arteries. In older patients, a descending right pulmonary artery diameter greater than 20 mm and an increased hilar thoracic index are highly suggestive of pulmonary hypertension.[79] Vascular markings may appear reduced in the lung periphery, coinciding with the appearance of "pruning" detectable by angiography. Pulmonary veno-occlusive disease can appear as reticular or reticulonodular infiltrates, masquerading as interstitial lung disease. Obstruction and infiltrates may be unilateral. Irregular or marginated densities may be suggestive of pulmonary vasculitis. One of the major problems in the evaluation of pulmonary hypertension with underlying chronic lung disease is that hyperinflation masks cardiomegaly. Also, interstitial infiltrates of patchy large densities can obscure vessels. Absence of changes by chest radiograph should not limit further evaluation. Chest CT scans may help evaluate lung parenchyma for signs of early interstitial lung disease and help image pulmonary arteries. Magnetic resonance imaging (MRI) may provide an additional noninvasive method for evaluating pulmonary hypertension by assessing right-ventricular wall thickness (RVWT) and the ratio of RVWT to left-ventricular posterior wall thickness, and RV end-systolic and diastolic volume indexes.[80]

Perfusion studies using radiolabeled albumin are helpful for identifying pulmonary vascular abnormalities, such as arteriovenous malformations and intrapulmonary shunting in patients with cirrhosis. $\dot{V}/\dot{Q}$ scans aid in differentiating thromboembolic disease from other causes of pulmonary hypertension because thrombosis produces large perfusion defects in contrast with the small "moth-eaten" peripheral defects found with advanced pulmonary hypertension from other mechanisms. Pulmonary arterial angiography provides a more precise approach to the identification of vascular obstruction, the presence of structural lesions such as hemangiomatosis and arteriovenous malformations, as well as assessments of vascular pruning. Unfortunately, the degree of pruning, or distal vascular narrowing and small vessel filling, is not a sensitive method for distinguishing severe pulmonary hypertension caused by vascular remodeling versus vasoconstriction.

Detection and assessment of pulmonary hypertension and its severity primarily requires serial ECG and echocardiogram studies. Although ECG findings of RV hypertrophy or strain are diagnostically useful for patients with pulmonary hypertension, signs are usually less pronounced with chronic lung disease. This may be due to the effects of hyperinflation or the presence of milder levels of pulmonary hypertension commonly associated with lung disease. ECG findings of RV hypertrophy are present in 28% to 75% of patients with cor pulmonale.[81] Because the developmental shift from RV predominance normally occurs during infancy, diagnostic evaluations with ECG and echocardiography must take into account normal age-related changes in right-axis deviation, indices of RV hypertrophy, and other physiologic changes (Box 52-3).

Advances in Doppler and two-dimensional echocardiography have markedly improved noninvasive assessments of pulmonary hypertension. A major problem, however, is the technical difficulty of obtaining interpretable information in severe obstructive lung diseases, because marked hyperinflation and marked swings in intrathoracic pressures with respiratory efforts reduce the windows through which the right ventricle and valves can be imaged. Echocardiographic signs of pulmonary hypertension include increased RVWT, chamber size, flattening or paradoxical motion of the interventricular septum, early closure of the pulmonic valve, and incomplete tricuspid valve closure. Increased RV anterior wall thickness and interventricular septal wall thickness reflect RV hypertrophy. Paradoxical septal wall motion is a sign of impending RV failure. Quantitative assessments of pulmonary hypertension include measurements of right ventricular systolic time interval (RVSTI), tricuspid regurgitation, and the myocardial performance index (MPI, or Tei index). RVSTI is the ratio of measurements of RV pre-ejection period (PEP) to ejection time (ET). The PEP is the duration of time after electrical activation of the ventricle to the onset of ejection during systole. Right ventricular ET is measured from the time of opening to closure of the pulmonary valve during systole. Pulmonary hypertension delays pulmonary valve opening (because the valve does not open until RV systolic pressure exceeds PAP), causing prolongation of PEP and shortening ET. RVSTI increases the sensitivity of the echocardiogram and provides a noninvasive quantitative assessment for serial comparisons with subsequent clinic visits. Although several past publications used measurements of RVSTI to reflect acute changes in PAP during exposure to oxygen or vasodilators,[82] variability and lack of sensitivity makes this measurement unreliable for routine assessments of reactivity.

Perhaps a more sensitive assessment of pulmonary hypertension is the measurement of peak pulmonary artery systolic pressure obtained from continuous-wave Doppler measurements of the tricuspid jet.[83] The tricuspid insufficiency jet, as measured by pulsed Doppler echocardiography, reflects the pressure difference between the right ventricle and the right atrium. By using the Bernoulli principle (pressure = $4V^2$, where V is the peak systolic velocity in msec), the sum of this measurement with estimated or measured right-atrial pressure provides a fairly accurate assessment of RV systolic pressure. As with other echocardiographic assessments of pulmonary hypertension, imaging the tricuspid regurgitant jet can be difficult with chronic lung disease, leading to a low success rate (24%) in adults with COPD.[84] The absence of a measurable TR jet does not preclude the presence of pulmonary hypertension. The myocardial performance (or Tei) index has recently been shown as accurate in assessments of right ventricular performance in children with iPAH.[85]

Although serial studies with ECG or echocardiogram are useful during long-term follow-up, cardiac catheterization may be necessary to better define the role of pulmonary vascular disease in the clinical course. Cardiac catheterization quantifies the severity of pulmonary hypertension; to rule out anatomic cardiac lesions, structural pulmonary vascular lesions, thromboemboli, or significant hypertrophy of bronchial collaterals; to define optimal treatment levels for supplemental oxygen; to assess pulmonary vasoreactivity; and to test or select potential pharmacologic agents for long-term therapy. It is especially important to rule out LV diastolic dysfunction, which can contribute to pulmonary hypertension in some children with chronic lung disease, especially BPD.

Delays in performing cardiac catheterization in patients with chronic lung disease are common—potentially contributing to delays in diagnosis or therapy. Probe-patent foramen ovale may be present in many young children, suggesting that intracardiac shunt may contribute to the severity of hypoxemia in patients with pulmonary hypertension more often than expected. Cardiac catheterization should include angiography to avoid missing structural lesions, such as pulmonary arterial stenosis, pulmonary veno-occlusive disease, enlarged bronchial collateral vessels with chronic lung disease, diffuse pulmonary hemangiomatosis or arteriovenous shunts, and other diagnoses. Although concerns persist regarding the potential risks of angiography in precipitating pulmonary hypertensive crises or dysrhythmias in severe pulmonary hypertension, the use of newer contrast material seems to have decreased these risks. Undersedation and subsequent agitation may also increase the risk for precipitating a pulmonary hypertensive crisis.

Assessment of pulmonary vasoreactivity is an essential part of the evaluation, but it is too often not included with basal hemodynamic measurements. For example, exaggerated vasoconstrictor responses to acute hypoxia in patients with only mild baseline pulmonary hypertension may help explain episodic cyanosis or progressive pulmonary hypertension in children with recurrent cyanosis, HAPE, BPD, or other diseases (see Fig. 52-7).[86] The use of anesthesia and inadvertent oversedation, hypoventilation or hyperventilation, and hypoxia can alter basal PAP and reactivity during cardiac catheterization, potentially limiting the usefulness of clinical information. On the other hand, controlled hypoxic challenges during catheterization may provide critical insight into pulmonary vascular hyper-reactivity. For example, some patients require higher target oxygen saturations to maintain maximal decreases in PVR and to lower the risk of intermittent spikes in PAP. Whereas the vasodilator response while breathing 100% oxygen is commonly used to assess potential reversibility of pulmonary hypertension, correlation between the dilator response to oxygen and outcome is unclear. Measurement of acute hemodynamic responses while breathing high concentrations of supplemental oxygen is useful to assess vasoreactivity because of its selective pulmonary vasodilation and also because it allows adjustment of oxygen therapy. However, hyperoxia alone is not a potent vasodilator beyond its ability to reverse hypoxic vasoconstriction, and this response is often used to prognosticate on reversibility of pulmonary hypertension and outcome.

Long-term therapy with supplemental oxygen to correct hypoxia-induced pulmonary vasoconstriction will decrease the adverse effects of chronic or intermittent hypoxia and often improve clinical course. However, the response to high oxygen concentration may not be sufficient for determining the relative contributions of vasoconstriction versus structural remodeling to basal pulmonary hypertension. For example, pharmacologic vasodilators (such as inhaled NO) can often cause further vasodilation than high concentrations of inspired oxygen alone, as recently observed in infants with chronic neonatal lung disease (CNLD). Although several

agents can be used to acutely assess pulmonary vascular tone, inhaled NO may be a good choice because of its short half-life, selectivity for the pulmonary circulation (less risk for systemic hypotension, fatal dysrhythmia), and its ability to improve gas exchange, rather than worsen oxygenation, with lung disease.

Links between acute pulmonary vasoreactivity and long-term outcome require further study. Clinical decision making is often based on data from small numbers of patients with congenital heart disease because of the lack of data from patients with chronic lung disease. Conclusions regarding the relative contribution of vasoconstriction versus vascular remodeling to the severity of pulmonary hypertension presume that the degree of pulmonary hypertension remaining after administration of a vasodilator must be due to structural remodeling. This is not always true and may partially depend on the selection and relative potency of the vasodilator. Similarly, the acute response may not predict the potential for reversal of pulmonary hypertension with time. Chronic treatment with intravenous epoprostenol, a PGI_2 analog, has been shown to improve pulmonary hemodynamics and cardiac output in patients with iPAH, despite the absence of an acute vasodilator response to brief treatment.

Lung biopsies are used to assess the severity of structural changes in some cases and for further diagnostic evaluation (to rule out interstitial lung disease, veno-occlusive disease, and others). The biopsy allows grading of vascular lesions, but tissue should be obtained from multiple sites to allow for heterogeneity. In general, the histology of patients with secondary pulmonary hypertension lacks the severe intimal changes present in patients with primary pulmonary hypertension or congenital heart disease. Uncertainty exists regarding the potential reversibility of pulmonary vascular structural lesions, and further studies are needed to examine the relation between vascular reactivity, remodeling, and outcome.

MANAGEMENT

Acute management of severe right-sided heart failure requires rapid lowering of PAP to reduce RV afterload to maintain CO, systemic blood pressure, and tissue oxygen delivery. Dramatic elevations of PAP are more common in patients with iPAH, PPHN, and PAH owing to congenital heart disease than with pulmonary hypertension associated with acute respiratory failure or chronic lung disease. Patients with life-threatening acute episodes of pulmonary hypertension are managed by sedation, paralysis, hyperventilation, alkalosis, and high inspired concentrations of oxygen. Acute treatment with inhaled NO (20 ppm) may provide initial pharmacologic vasodilator therapy, especially in patients in whom RV failure is unresponsive to oxygen and general measures, or in the setting of marked pulmonary "vasolability." Extra caution is necessary to avoid the sudden discontinuation of inhaled NO in this setting because the rebound effects of inhaled NO withdrawal can cause a dramatic rise in pulmonary artery pressure, leading to a marked decrease in cardiac output, hypotension, and perhaps sudden death.

Pulmonary artery catheters provide close monitoring of PAP and PCWP, CO, systemic vascular resistance, and related hemodynamic measurements during acute therapeutic interventions. Whereas pharmacologic therapy may rapidly decrease PAP, intravenous vasodilators (such as sodium nitroprusside) can impair $\dot{V}/\dot{Q}$ mismatch in the setting of severe lung disease, causing worsening hypoxemia, or may lower systemic arterial pressure and worsen oxygen delivery. Inhaled NO may provide selective pulmonary vasodilation without adverse effects on gas exchange in children with severe pulmonary hypertension and lung disease.

The primary goal of long-term treatment of pulmonary hypertension in patients with chronic lung disease is to improve cardiac (especially RV) performance at rest and during exercise, thereby improving exercise tolerance and quality of life. In addition to managing right-sided heart failure, the long-term goal is to avoid the adverse effects of sustained pulmonary hypertension on progressive pulmonary vascular remodeling. Mechanisms leading to reversibility of pulmonary hypertension and vascular structure are poorly understood but partly depend on the severity of vascular remodeling at diagnosis and recognition of complicating factors that contribute to its progression. Thus, early anticipation and recognition of pulmonary hypertension in at-risk patients may improve outcome in many cases.

Therapy generally targets three areas: (1) optimal management of underlying lung disease (for example, lung inflammation and infection in CF, mechanical ventilation with hypoventilation and neuromuscular weakness, and others); (2) diagnosis and treatment of complicating or unsuspected cardiopulmonary abnormalities (such as aspiration, upper airway obstruction, or anatomic cardiac defects in BPD, and others); and (3) treatment of the pulmonary hypertension with oxygen and pharmacologic agents.

Because hypoxia is the most common cause of progressive pulmonary hypertension in chronic lung disease, supplemental oxygen is the mainstay of therapy. Oxygen therapy is the only treatment that has been shown to improve the clinical course of patients with pulmonary hypertension and chronic lung disease.[87,88] The British Medical Research Council study[87a] and the NIH Nocturnal Oxygen Therapy Trial (NOTT)[87b] demonstrated that adults with COPD who use supplemental oxygen for the greatest period of time each day (19 versus 12 hr/day) derive the greatest advantage in survival, and that oxygen therapy prevents further increases in PAP. Whether patients who decrease PAP during acute administration of supplemental oxygen have a better survival than nonresponders is unproven, but it has been suggested in a small clinical trial.[88] Mortality was significantly decreased by oxygen therapy in adults with COPD and slowed progression of pulmonary hypertension; these responses were directly related to the duration of daily use.

Long-term oxygen therapy may enhance oxygen delivery in addition to its effects on pulmonary vasodilation and may partially explain improved clinical outcome. In addition, long-term oxygen therapy counters the adverse effects of episodic hypoxia on intermittent elevations of PAP with sleep or activity and may influence smooth muscle cell growth or production of extracellular matrix independent of its effects on lowering pressure. Hence, an aggressive approach toward maintaining adequate oxygenation is recommended (avoidance of hypoxemia while targeting oxygen saturations above 92% to 94% while awake or asleep, and with activity) (Fig. 52-8). Recent studies have raised new questions regarding the safety of excessive levels of supplemental oxygen in former

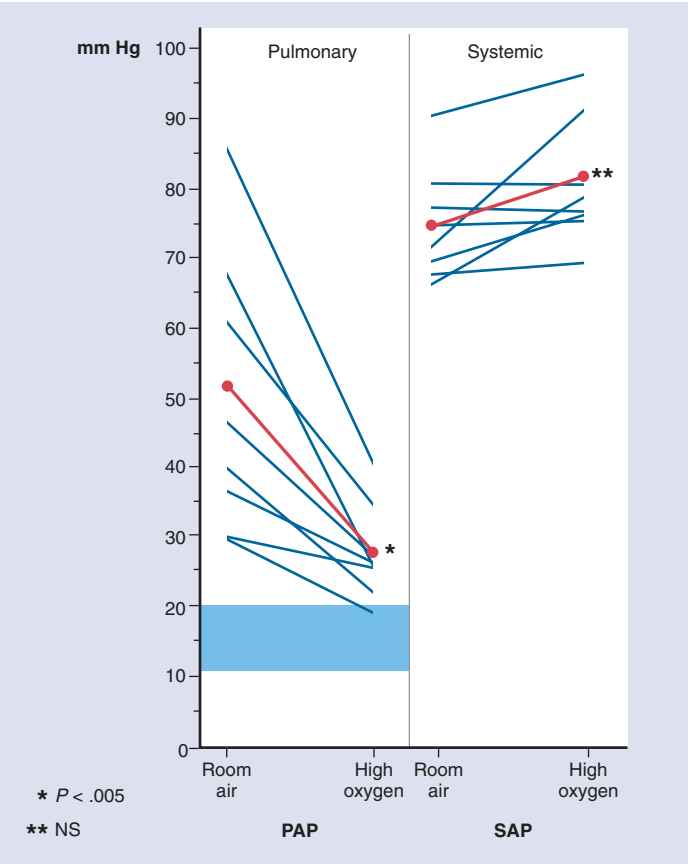

Figure 52-8 Exaggerated hypoxic pulmonary vasoconstrictor response during brief exposure to hypoxia in children with BPD. Responses of mean pulmonary artery pressures and systemic arterial pressures to high levels of inspired oxygen ($F_{IO_2} > 0.80$). (From Abman SH, Wolfe RR, Accurso FJ, et al: Pulmonary vascular response to oxygen in infants with severe bronchopulmonary dysplasia. Pediatrics 75:80-84, 1985.)

premature infants regarding adverse effects on retinopathy and worsening lung disease.

Infants with chronic lung disease require frequent noninvasive assessments of oxygenation and serial ECGs or echocardiograms while receiving supplemental oxygen, especially if signs of RV hypertrophy persist despite therapy. Monitoring of oxygenation to avoid even intermittent hypoxemia will enhance recovery or slow progression of pulmonary hypertension in children with pulmonary hypertension of many etiologies. Perhaps the clearest illustration of this strategy is in infants with BPD.[1] Chronic intermittent or persistent hypoxia blocks recovery and accelerates progression of pulmonary vascular disease. Infants with BPD are often undertreated because of fear of oxygen toxicity during the chronic stages of disease despite the presence of pulmonary hypertension. Once persistent signs of pulmonary hypertension have been identified in older BPD infants, even mild levels of hypoxia should not be tolerated. Reversal of hypoxia with supplemental oxygen in patients with chronic lung disease will acutely lower PVR in many patients and avoid intermittent episodes of hypoxic pulmonary vasoconstriction.

Progression of pulmonary hypertension in association with any disease should lead to investigation of potential contributing factors, including obstructive sleep apnea, chronic aspiration, structural airway lesions, and other problems. For example, children with Down syndrome with or without anatomic heart disease often have more severe pulmonary hypertension than other children, which is often partly due to chronic pharyngeal collapse with sleep, tracheomalacia, or other structural airway lesions. Evaluations should include sleep studies, imaging of the upper airway by flexible laryngoscopy and bronchoscopy, radiologic studies (such as barium swallow and Isovue bronchograms), pulmonary function testing, and lung biopsy in selected cases. In addition to correction of hypoxemia, acidosis and hypercarbia may contribute to progressive pulmonary hypertension. Although hypercarbia is commonly tolerated with chronic lung disease, a more aggressive ventilator therapy is recommended in patients with chronic lung disease and concomitant pulmonary hypertension.

Diuretics and digoxin are commonly prescribed in patients with chronic lung disease and cor pulmonale. Although diuretics may acutely improve gas exchange in chronic lung diseases such as BPD,[89] mechanisms underlying this response are more likely related to relief of pulmonary edema than direct improvement of pulmonary hypertension. When administered for treatment of right-sided heart failure, diuresis can acutely decrease fluid retention, especially in patients with hepatomegaly, peripheral edema, and signs of systemic venous congestion. Frequent use of diuretics in the presence of high PVR may markedly decrease RV preload, thereby decreasing pulmonary blood flow and CO. In addition, electrolyte imbalance with chloride depletion and elevated serum bicarbonate may cause metabolic alkalosis and hypoventilation. Digoxin use in cor pulmonale remains controversial. Although it may improve myocardial performance and CO in patients with impaired left-ventricular function, most patients have little clinical benefit.

DRUG THERAPY FOR CHRONIC PULMONARY HYPERTENSION

Pharmacologic agents can acutely lower PAP, but pulmonary vasodilation in the setting of parenchymal lung disease can cause hypoxemia by worsening $\dot{V}/\dot{Q}$ mismatch, limiting their usefulness in the presence of lung disease.[90] Insights into basic vascular biology, especially with regard to the NO-cGMP, PGI_2 and ET-1 systems, have led to dramatic improvements in the pharmacology of pulmonary hypertension. Multicenter randomized trials have shown striking benefits of several strategies in the treatment of IPAH and chronic pulmonary arterial hypertension associated with congenital heart disease, but in contrast, benefits of pharmacologic vasodilator therapy in the long-term management of pulmonary hypertension secondary to chronic lung disease remain unproven. Recent evidence-based guidelines from the American College of Chest Physicians (ACCP) provide clear recommendations for the treatment of severe pulmonary hypertension.[91] Overall, a step-wise approach has been outlined, based on severity of symptoms, pulmonary vascular reactivity during acute testing during cardiac catheterization, and clinical response to treatment. Whether similar approaches should be applied to patients with chronic lung disease, especially in younger children, remains uncertain, but currently provides a useful perspective.

Calcium Channel Blockers (CCBs)

Historically, CCBs have been used in patients with pulmonary hypertension who demonstrate marked acute vasoreactivity to supplemental oxygen, inhaled NO, or other agents, during cardiac catheterization—especially in patients with chronic lung disease. In the past, CCBs (such as nifedipine and diltiazem) were used primarily because of the absence of other choices. A relatively small proportion of patients with IPAH, who demonstrate a favorable response to acute vasodilator testing at the time of cardiac catheterization, initially do well with CCB therapy.[92] Sitbon and colleagues reported results of a retrospective analysis of adult iPAH patients tested acutely with intravenous epoprostenol (a PGI_2 analog) or inhaled NO.[93] Using the criteria of a >20% decrease in both mean pulmonary artery pressure (mPAP) and PVR, only 13% of patients were reactive. Of these patients, about one half demonstrated favorable long-term clinical responses to chronic CCB therapy. Thus, although true responders to vasodilators are uncommon among patients with severe iPAH, long-acting nifedipine or diltiazem, or amlodipine can be tried in this subset of patients, but caution is urged in light of negative inotropic effects in some patients, and failure to sustain clinical response should lead to the rapid transition to another agent. Because a greater proportion of patients with chronic lung disease may have acute responsiveness to vasodilator testing in the catheterization laboratory, CCBs may be a good initial choice for therapy in this population. However, there are no data comparing other oral agents (including type V phosphodiesterase [PDE-5] or ET receptor antagonists [ETRAs]) antagonists as an initial choice in patients with pulmonary hypertension.

Type V Phosphodiesterase (PDE-5) Inhibitors

Augmentation of NO-cGMP signaling with inhaled NO has been a successful strategy for the treatment of term newborns with severe pulmonary hypertension, as well as in other diseases, especially with acute pulmonary hypertension in the intensive care setting. Although noninvasive delivery of inhaled NO has been shown to be potentially effective in some cases, inhaled NO as a chronic therapy is experimental and limited by the need for multiple gas tanks and bulky delivery systems. In contrast, augmentation of cGMP through inhibition of PDE-5 provides a useful and practical approach for chronic pulmonary hypertension therapy. Sildenafil, a potent and highly specific PDE-5 inhibitor, is approved for erectile dysfunction, and has recently been approved for chronic pulmonary hypertension therapy. A double-blind, placebo-controlled study (the SUPER-1 study), randomly assigned 278 patients with symptomatic PAH (idiopathic, associated with collagen vascular disease or after repaired congenital systemic-to-pulmonary shunts) to placebo or sildenafil for 12 weeks.[94] Distance walked in 6 minutes increased from baseline in the sildenafil groups. In addition, sildenafil reduced mean PAP, and improved functional class. Side effects included flushing, dyspepsia, and diarrhea. The incidence of clinical worsening did not differ significantly between the patients treated with sildenafil and those treated with placebo. A smaller study suggested that children with pulmonary hypertension also improve during sildenafil therapy,[95] which is currently approved by the FDA for the treatment of PAH. Case reports suggest that sildenafil is well tolerated by older patients with chronic lung disease, such as idiopathic pulmonary fibrosis and CF, without worsening of gas exchange, and may be a good initial choice for treating moderate pulmonary hypertension in chronic lung disease.[96]

Endothelin Receptor Antagonists (ETRAs)

ETRAs, including bosentan, a nonselective ET A and B receptor antagonist, provide an effective oral strategy for the treatment of chronic pulmonary hypertension, but most studies have been performed in adult patients with PAH not associated with chronic lung disease.[97] Treatment with bosentan improved 6 minutes walk test, hemodynamics, and functional class. Due to the potential for abnormal liver function tests, monthly tests are needed to monitor patient safety. Bosentan has also recently been studied in children with iPAH and congenital heart disease,[98] demonstrating improvement or lack of worsening of WHO functional class in 46% and 44% of patients, respectively. Bosentan is currently approved by the FDA for the treatment of patients with WHO functional class III-IV PAH. Because the ET B receptor may also have beneficial effects in pulmonary hypertension, two newer agents that are selective inhibitors of the ET A receptor have been studied.[99,100] Sitaxsentan and ambrisentan, an oral ET A receptor-selective antagonist, have been shown to improve clinical courses in patients with pulmonary hypertension, but studies in children are lacking.

Prostacyclin (PGI_2) Analogs

EPOPROSTENOL

For patients with more advanced or poorly responsive disease, the use of intravenous PGI_2 analogs has been shown to improve survival and clinical course.[101] A 12-week, prospective trial demonstrated that when added to conventional therapy, intravenous epoprostenol improved 6-minute walk test, quality of life, hemodynamics, and survival in adult patients.[102] A multicenter, open-label study of intravenous epoprostenol in patients with scleroderma-associated pulmonary hypertension also showed improvement in exercise capacity and hemodynamics; however, improved survival was not observed.[103] Other observational studies have also shown improvement in adult patients with severe disease, and similar observations have been suggested in pediatric patients as well. Long-term PGI_2 therapy in young children and infants with IPAH or Eisenmenger syndrome is promising, but experience has been limited in patients with concomitant lung disease owing to concerns of worsening hypoxemia.

TREPROSTINIL

Numerous advances have led to the development of newer PGI_2 analogs, which have been studied as alternative approaches to intravenous epoprostenol therapy. Treprostinil (or Remodulin) has been shown to be effective for at least short-term therapy when infused subcutaneously in patients with functional class II, III, or IV PAH.[104] This effect was limited by infusion site pain and skin reactions, which led to discontinuation of therapy in several cases. Recent work suggests that intravenous treprostinil may be effective in treating severe disease, and the FDA has approved the use of intra-

venous treprostinil in patients in whom subcutaneous infusion is not tolerated.

ILOPROST

A more novel approach to the use of PGI_2 analogs is in the use of iloprost as an inhalational agent. Although several studies suggest efficacy in adults with idiopathic pulmonary hypertension,[105] the need for six to nine inhalations per day to sustain its effects may severely limit its utility. Alternate strategies include the use of inhaled iloprost with a second, oral agent, such as PDE-5 or ETRAs). Development of more potent and sustained PGI_2 analogs may decrease the need for frequent treatments, and would represent a significant advance in the field. Early experience with iloprost suggests that some children may experience acute bronchospasm during inhalation, which may limit tolerance to long-term therapy.

SPECIFIC DISEASES ASSOCIATED WITH PULMONARY HYPERTENSION

Persistent Pulmonary Hypertension of the Newborn

PPHN represents the failure of the pulmonary circulation to achieve or sustain the normal decrease in PVR at birth. High PVR in the neonate causes marked hypoxemia as a result of right-to-left shunting of blood across the patent ductus arteriosus or foramen ovale. The diagnosis of PPHN has replaced the older term *persistent fetal circulation,* and refers to a clinical *syndrome* of a wide variety of cardiovascular and pulmonary disorders, such as meconium aspiration syndrome, sepsis, pneumonia, congenital diaphragmatic hernia, or respiratory distress syndrome, or can be idiopathic. Idiopathic PPHN is characterized by severe cyanosis with tachypnea and respiratory distress in term or postdate newborns with chest radiograph findings of clear lung fields and a normal cardiothymic silhouette. Although often associated with perinatal stress (for example, maternal bleeding or asphyxia), specific etiologies are rarely identified in idiopathic PPHN. When associated with asphyxia or marked stress, meconium aspiration may be present, further complicating the clinical course. Most patients with asphyxia, intrauterine growth retardation, or meconium aspiration, however, do not develop PPHN. Etiologic mechanisms leading to the failure of postnatal adaptation are incompletely understood, but intrauterine stimuli, such as chronic hypertension or closure of the ductus arteriosus, may contribute to the characteristic alterations of pulmonary vasoreactivity and structure that are present at birth. Mechanisms underlying PPHN may include failure to release sufficient vasodilators (such as endogenous NO or PGI_2); increased vasoconstrictor production (ET-1, leukotrienes, and thromboxane); altered smooth muscle cell responsiveness to vasoactive stimuli; or altered vascular growth (smooth muscle hypertrophy and increased extracellular matrix production). Evidence supporting the hypothesis that chronic prenatal events may lead to PPHN include data from experimental animal models as well as autopsy data demonstrating extensive vascular remodeling in neonates dying with PPHN within the first days of life.[106]

Although the diagnosis of PPHN requires echocardiographic confirmation of right-to-left shunting at the ductus arteriosus or foramen ovale in the absence of anatomic heart disease, several clinical features are highly suggestive: (1) marked or "labile" hypoxemia; (2) differences in preductal and postductal Pa_{O_2} of at least 5 to 10 mm Hg (not present if shunting is predominantly at the foramen ovale); and (3) clinical improvement with hyperventilation. Treatment includes high F_{IO_2}, hyperventilation, and infusions of sodium bicarbonate (for alkalosis) and cardiotonic agents (dopamine, dobutamine) for cardiovascular support. Optimal lung inflation is essential for aggressive treatment of parenchymal lung disease that contributes to high PVR as a result of mechanical vascular compression and marked intrapulmonary shunting at low lung volumes. Pharmacologic vasodilators, such as tolazoline, prostaglandins (PGI_2 or PGE_1), and sodium nitroprusside, have been used with success in some cases. Intravenous vasodilator therapy has been limited, however, by adverse side effects, including systemic hypotension because of the lack of selectivity for the pulmonary circulation and aggravation of right-to-left shunting, and by worsening of $\dot{V}/\dot{Q}$ mismatch in patients with parenchymal lung disease. Patients failing conventional therapy often require extracorporeal membrane oxygenation (ECMO) therapy. Although lifesaving in many cases, ECMO is costly and associated with significant complications, such as intracranial hemorrhage or systemic bleeding from heparinization. It also requires carotid artery ligation, which may contribute to adverse neurologic sequelae. ECMO centers are now using venovenous ECMO in patients with stable cardiac function to avoid carotid artery cannulation. However, unrecognized or late development of myocardial dysfunction may lead to failure of venovenous ECMO, requiring conversion to a veno-arterial approach.

Recent studies have clearly demonstrated that inhaled NO can improve oxygenation and reduce the need for ECMO therapy in term newborns with acute hypoxemic respiratory failure and PPHN (Fig. 52-9).[107-111] Successful therapy is generally associated with striking increases in oxygenation with clinical and echocardiographic evidence for reversal of right-to-left shunting. Combined modalities, such as inhaled NO with high frequency oscillatory ventilation, may provide more effective therapy in some patients with parenchymal lung disease and pulmonary hypertension because responsiveness to inhaled NO appears to partly depend on achieving adequate lung inflation for delivery of NO to high resistance vessels in the distal lung. Poor responders or patients who have a prolonged need for inhaled NO may have underlying lung hypoplasia, such as alveolar capillary dysplasia, surfactant protein deficiency, or other lung disorders. PPHN survivors are at modest risk for chronic lung disease, including airways hyperreactivity and neurodevelopmental sequelae, but late pulmonary hypertension is rare.

Bronchopulmonary Dysplasia

BPD is the chronic lung disease of infancy that follows ventilator and oxygen therapy for neonatal respiratory distress. Since the earliest descriptions of BPD, pulmonary hypertension and cor pulmonale have been recognized as being associated with high mortality.[1] Mortality in BPD patients with persistent echocardiographic findings of pulmonary hypertension beyond 4 months of age has been reported as 50%.[112,113] Recent studies have reported similar mortality in selected

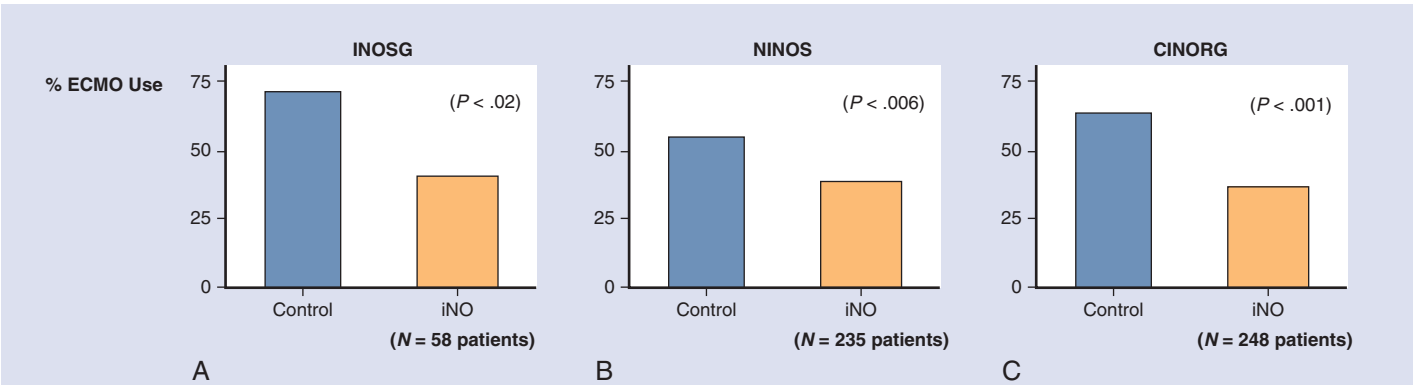

Figure 52-9 Inhaled NO decreases the need for ECMO therapy in PPHN as shown from the results of three multicenter randomized trials. ECMO, extracorporeal membrane oxygenation; NO, nitric oxide; PPHN, persistent pulmonary hypertension of the newborn. (**A,** from Roberts JD, Fineman JR, Morin FC, et al: Inhaled NO and PPHN: The inhaled NO study group. N Engl J Med 336:605-610, 1997; **B,** from Neonatal Inhaled Nitric Oxide Study Group: Inhaled NO in full term and nearly full term infants with hypoxic respiratory failure. N Engl J Med 336:597-604, 1997; **C,** from Clark RH, Kueser TJ, Walker MW, et al: Low dose NO therapy for PPHN. N Engl J Med 342:469-474, 2000.)

populations of older BPD infants with persistent pulmonary hypertension.[3] Clinically, BPD infants with severe pulmonary hypertension are prone to recurrent pulmonary edema, frequent respiratory exacerbations, congestive heart failure, and late morbidity from viral infections or sudden death.[1,113] Related cardiovascular sequelae include left-ventricular hypertrophy, systemic hypertension, and hypertrophied systemic-to-pulmonary collaterals.[1] Pulmonary vascular disease in BPD reflects the direct effects of ventilator- and hyperoxia-induced lung injury, but chronic inflammation, hypoxia, neurohumoral stimuli, and altered production of vasoactive substances contribute to the severity or persistence of pulmonary hypertension.

Physiologically, the pulmonary circulation in BPD is characterized by heightened pulmonary vasoreactivity, hypertensive vascular remodeling (increased muscularization with adventitial thickening), and decreased arterial number as a result of altered surface area caused by lung injury and decreased septation ("alveolar simplification").[36] Altered metabolic lung function, as assessed by decreased uptake of circulating norepinephrine, has been described in BPD infants with pulmonary hypertension.

As described previously, clinical management of pulmonary hypertension in BPD revolves around vigilant monitoring and aggressive use of supplemental oxygen therapy.[13] Although oxygen saturations below 90% may be well tolerated in normal children recovering from viral respiratory infections, BPD infants require better oxygenation to minimize the adverse effects of chronic hypoxic pulmonary vasoconstriction (see Fig. 52-8).[86] Based on clinical studies, oxygen saturations above 94% while awake, while asleep, and during feeding are often recommended for infants with CNLD and pulmonary hypertension.[1]

Resolution of pulmonary hypertension by ECG or echocardiographic criteria is often found with appropriate therapy over time.[112] Children with persistent RV hypertrophy require more aggressive measures to evaluate potential mechanisms complicating their recovery. These include reassessment of oxygenation levels during prolonged pulse oximetry studies; formal sleep studies; and assessment for unsuspected cardiac or lung problems contributing to the severity of the clinical course (such as aspiration, upper airway obstruction, anatomic heart disease, large bronchial collaterals causing pulmonary edema, and others). Early identification and treatment of left-to-right shunt cardiovascular lesions may enhance long-term outcome in selected BPD patients, decreasing progressive pulmonary vascular injury in a lung circulation that is already limited by decreased surface area, vascular remodeling, and vasoconstriction.

Hemodynamic improvement in BPD infants with pulmonary hypertension has been reported after brief vasodilator therapy with PGI_2[4] and nifedipine[114] during cardiac catheterization. However, PGI_2 increased CO but did not lower PAP, and although PVR fell by 23%, systemic vascular resistance decreased by 39%.[4] Similarly, the drop in mean PAP achieved during acute nifedipine treatment was similar to the response to supplemental oxygen alone.[114] Because nifedipine increased CO, however, PVR was lower after nifedipine administration than after oxygen therapy. Whether the combination of supplemental oxygen with chronic calcium channel blockers will enhance long-term outcome in selected BPD patients with pulmonary hypertension has not been studied. More recently, acute pulmonary vasodilation to inhaled NO has been demonstrated in children with BPD during cardiac catheterization, suggesting that vascular tone contributes to high PAP even late in the clinical course and that inhaled NO is effective in lowering PVR in BPD (Fig. 52-10).[115] Whether chronic treatment with PDE-5 inhibitors, including sildenafil, or ETRAs can improve long-term course in BPD patients with pulmonary hypertension without adverse effects is unknown. Thus, management of pulmonary hypertension in BPD remains largely supportive, with careful attention to the avoidance of the adverse effects of episodic hypoxia and hypercarbia on lung vascular remodeling and reactivity. In selected cases, long-term therapy with CCBs or other agents with oxygen therapy may be indicated, but patient selection would require careful initial assessment with cardiac catheterization and close follow-up.

Cystic Fibrosis

Pulmonary hypertension was first recognized as a significant clinical problem in CF more than 60 years ago,[116] but the detection and management of pulmonary hypertension in CF

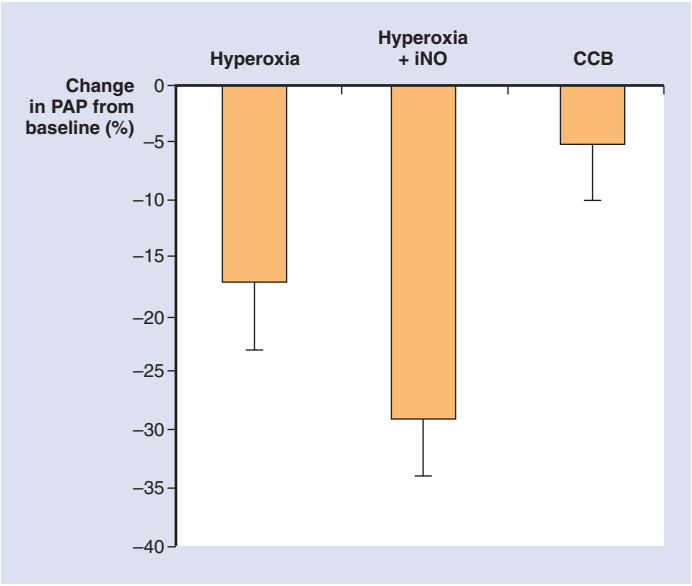

Figure 52-10 Pulmonary vasoreactivity testing in children with BPD. Brief exposure to hyperoxia lowered pulmonary artery pressure and PVR from baseline values measured during normoxia. The addition of inhaled nitric oxide (iNO; up to 20 ppm) caused further pulmonary vasodilation. Both responses were greater than the acute response to calcium channel blockade (CCB). (Adapted from Mourani PM, Ivy DD, Gao D, Abman SH: Pulmonary vascular effects of inhaled NO and oxygen tension in BPD. Am J Respir Crit Care Med 170:1005-1013, 2004.)

remains an ongoing challenge. Despite dramatic advances in our understanding of the genetics and pathophysiology of CF, little progress has been made regarding the contribution of pulmonary hypertension to mortality and morbidity in CF or its treatment.[5,6,117-119] In 1951, Royce[117] reported that 70% of patients dying with CF had marked RV hypertrophy at autopsy. In 1980, Stern and coworkers[5] found that 46% of CF patients who died after 15 years of age had clinical signs of right-sided heart failure for at least 2 weeks before death and that mean survival was only 8 months after the onset of RV failure. Whether pulmonary hypertension and RV dysfunction are markers of disease severity or directly contribute to mortality is unclear. Similarly, whether aggressive management of pulmonary hypertension could improve morbidity and long-term outcome is unknown.

Mechanisms leading to the development of pulmonary hypertension in CF include chronic hypoxia caused by severe $\dot{V}/\dot{Q}$ mismatch from severe lung disease with airways obstruction and chronic infection and inflammation. Although chronic hypoxia contributes significantly to the progression of pulmonary hypertension in CF, it is unlikely that hypoxia is the sole factor in its pathogenesis. Chronic hypercarbia with acidosis may cause intermittent spikes in PAP, leading to vascular remodeling. Exaggerated respiratory efforts can increase intrathoracic pressure, which may increase RV afterload. In addition, severe bronchiectasis with progressive interstitial disease decreases alveolar-capillary surface area, further promoting the development of pulmonary hypertension. Chronic infection and inflammation caused by increased release of vasoactive bacterial products and mediators from inflammatory cells (cytokines, lipid mediators, others) can also directly alter pulmonary vascular reactivity and structure. In its early stages, active vasoconstriction contributes to high PAP resistance in CF, which appears to predate subsequent development of hypertensive vascular remodeling found in older patients with CF. The role of vasoconstriction was first clinically demonstrated with studies of the acute pulmonary vasodilator response to supplemental oxygen and tolazoline treatment.[116-119,120] Although structural pulmonary vascular lesions contribute to cor pulmonale over time, recent in vitro studies of conduit pulmonary arteries from CF patients undergoing lung transplantation have suggested that impaired release of NO contributes to increased vasoconstriction and high PVR with advanced lung disease.[121] These findings suggest that altered pulmonary vasoreactivity persists late in the clinical course of CF and that this is, in part, due to endothelial dysfunction.

Recognition of clinical signs of cor pulmonale generally occurs late. Clinical predictors of cor pulmonale in CF include Pa_{O_2} less than 50 mm Hg, Pa_{O_2} greater than 45 mm Hg, forced vital capacity less than 60% of predicted, and right-axis deviation by ECG.[119] The degree of hypoxia while breathing room air is inversely correlated with severity of PAP. The diagnosis of cor pulmonale in CF by clinical evaluation can be masked by severe CF lung disease. Signs that are usually ascribed to right-sided heart failure, such as tachypnea, hepatomegaly, hepatic tenderness, and cyanosis, may be results of underlying lung or liver disease. Increased second heart sounds, murmurs, and gallop rhythms may not be heard during auscultation because of loud adventitious breath sounds. Peripheral edema is rarely detected, even with cor pulmonale, and is usually caused by poor nutrition with low oncotic pressure from hypoalbuminemia. Chest radiograph findings may include dilated central pulmonary arteries; heart size may appear normal as a result of hyperinflation or infiltrates. ECGs are not sensitive because RV hypertrophy may be absent by ECG even when moderate pulmonary hypertension is found with cardiac catheterization.[122]

Echocardiographic estimates of pulmonary hypertension, such as RV systolic time intervals, appear to correlate well with PAP directly measured at cardiac catheterization and RVWT at autopsy. Although echocardiograms increase the diagnostic yield of pulmonary hypertension, cardiac imaging can be difficult because of severe hyperinflation. For example, complete assessments of RV function were obtained in less than 50% of CF patients. However, longitudinal studies have reported RV wall thickening and dilation, even in some cases of mild CF lung disease. Exercise stress testing with echocardiography may further increase the diagnostic yield and may be present in patients with relatively mild CF lung disease. Radionuclide measurements of RV ejection fraction are more sensitive than echocardiogram or ECG studies of RV function.

Left-ventricular dysfunction has been identified in some patients with CF, but its role in clinical disease is unclear. Left-ventricular free wall weight can be increased at autopsy and areas of myocardial fibrosis have been reported. Echocardiography can demonstrate flattening or compression of the left ventricle along its minor dimension by a massively dilated right ventricle. RV enlargement could produce left-ventricular dysfunction in severe CF.[123] Left-ventricular compression and abnormal interventricular septal motion can cause dyskinetic contraction and relaxation, which could contribute to diminished stroke volume.

Therapy includes liberal use of supplemental oxygen while continuing aggressive management of the underlying lung disease. In theory, improved lung function will enhance gas exchange, decrease regional hypoxia, and slow the progression of pulmonary hypertension. Similarly, relief of airways obstruction and reduction of lung infection and inflammation should decrease lung injury and alter production of vasoactive mediators or growth factors that contribute to pulmonary vasoconstriction, structural remodeling, and loss of vascular surface area. Supplemental oxygen therapy should be administered to avoid episodic or persistent hypoxemia; target Pa_{O_2} is generally recommended to be maintained above 60 to 65 mm Hg, or oxygen saturations by pulse oximetry greater than 94% during sleep and while awake. Oxygen therapy may further attenuate increases in PAP during acute or subacute respiratory deteriorations. Serial evaluations of CF patients with ECG and echocardiogram should be performed regularly to monitor for signs of RV hypertrophy, especially with moderate lung disease, even in the absence of overt signs of cor pulmonale. Echocardiograms before and immediately after cardiopulmonary exercise testing (CPET) may provide a more clinically-useful assessment of underlying pulmonary vascular disease, even in the absence of high baseline PAP by echocardiogram.

Sleep-associated hypoxemia should be sought and treated in CF patients with early morning headaches, signs of obstructive sleep apnea, or in the presence of RV hypertrophy. Recent changes in ECG or echocardiogram, excessive fatigue, poor exercise tolerance, cardiac signs on examination, hepatomegaly, right upper quadrant tenderness, and declines in pulmonary function or CPET may warrant further evaluations, such as cardiac catheterization.

Most recommendations for the use of supplemental oxygen therapy in CF are based on clinical observations or data from studies of other chronic lung diseases. No published data have demonstrated benefits from early and long-term oxygen therapy in CF. One study that examined the effects of nocturnal oxygen therapy on the short-term (6-month) course of CF patients with advanced lung disease reported no improvement.[124] In this study, however, patients were treated only with nocturnal oxygen despite having hypoxia (room air Pa_{O_2} less than 65 mm Hg) while awake. In addition, no documentation of sleep-associated hypoxemia or its resolution with therapy was present, and ECG and echocardiographic assessments of pulmonary hypertension were not included. Whether early and aggressive use of supplemental oxygen improves clinical outcome, reduces pulmonary hypertension, and enhances the quality of life in CF patients remains speculative.

Data on the role of drug therapy are also limited. Acute diuretic therapy improves signs of systemic venous congestion in CF patients with severe cor pulmonale, decreasing mean PAP without changing CO.[125] Whether long-term diuretic therapy sustains clinical improvement is unclear. Aggressive diuresis could potentially worsen hemodynamic status by dropping RV preload, further decreasing pulmonary blood flow and systemic CO. If diuretics are used, careful monitoring of fluid and electrolyte status are important to avoid the dangers of marked hypokalemic, hypochloremic metabolic alkalosis, and aggravation of chronic CO_2 retention. Digoxin has been used in some patients with severe right-sided heart failure and may be of benefit in selected patients with signs of left-ventricular dysfunction.

Several studies have examined acute hemodynamic responses to vasodilators, including CCBs. Davidson and colleagues[126] compared the acute effects of supplemental oxygen and CCBs in eight CF patients with mild clinical disease. Increased F_{IO_2} lowered mean PAP by 23%, and PVR by 21%; nifedipine did not alter PAP but lowered PVR by increasing cardiac index by 30%. Diltiazem lowered mean PAP by 24% without changing cardiac index. The degree of oxygen-induced pulmonary vasodilation was not predictive of responses to CCBs. In some cases, supplemental oxygen lowered mean PAP to normal values, reflecting the relative lack of structural remodeling in early disease. Geggel and coworkers[127] also reported a favorable acute hemodynamic response to oxygen but no improvement with calcium-channel blockers. Sustained improvement in exercise tolerance has been reported in some CF patients. A recent report describes a favorable response to sildenafil therapy in a patient awaiting lung transplantation.[96] Whether chronic therapy will improve long-term outcome, exercise tolerance, or the quality of life in CF patients with cor pulmonale is not known.

Pulmonary Hypertension and High Altitude

Studies of physiologic adaptations to acute and chronic exposure to high altitude provide unique insights into mechanisms of human diseases associated with hypoxia.[128] In most clinical settings, chronic hypoxia accompanies severe lung disease, making it difficult to differentiate the effects of hypoxia itself on lung function. To determine the direct cardiopulmonary effects of severe hypoxia, extensive studies of adult volunteers were performed before and during exposure to hypobaric hypoxia by simulating altitude of 8848 meters.[129] These investigators demonstrated that high altitude increased PAP (from 15 to 33 mm Hg); decreased forced vital capacity, which was interpreted as reflecting a restrictive defect caused by increased central blood volume and edema; altered $\dot{V}/\dot{Q}$ mismatch caused by continued perfusion of poorly ventilated regions; and normal cardiac function at rest and with exercise. These findings demonstrate that chronic hypoxia, in the absence of underlying lung disease, markedly impairs respiratory function.

In children living at altitude, the normal postnatal decline in PAP is delayed.[130] For example, infants living above 4200 meters in Peru have higher mean PAP (45 mm Hg at 1 to 5 years; 28 mm Hg at 6 to 14 years) than do children at lower altitudes. Children living at high altitude have persistence of RV predominance by ECG; increased RV weight; increased muscularization of small pulmonary arteries; and increased incidence of patent ductus arteriosus. However, there is marked individual variability in basal PAP in long-term residents of high altitude.[131-134]

Although acute hypoxia generally increases mean PAP from 13 to 17 mm Hg in normal adults, the pulmonary vasoconstrictor response is markedly heightened in some individuals, even in the absence of underlying cardiopulmonary disease. For example, some children develop severe symptomatic pulmonary hypertension while living at high altitude. Khoury and Hawes[130] described 11 infants (younger than 2

years of age) residing above 3000 meters in Leadville, Colorado. Symptoms included cyanosis, dyspnea, poor growth, cough, sleeplessness, oliguria, seizure, syncope, and cyanotic spells. Cardiac catheterization revealed suprasystemic or near systemic levels of pulmonary hypertension. At autopsy, advanced hypertensive pulmonary vascular lesions (Heath-Edwards grade 3 to 6) were common. To determine mechanisms that may contribute to severe pulmonary hypertension, a subsequent study examined pulmonary vascular responses to acute hypoxia in a similar study group from Leadville.[58] Although mean PAP was only mildly elevated while breathing room air (mean, 24 mm Hg), PAP increased dramatically (to 81 mm Hg) while the group was exposed to an hypoxic gas mixture (16% F_{IO_2}). Marked pulmonary vascular hyperreactivity has been observed in children with chronic lung disease and early in the course of primary pulmonary hypertension. This exaggerated responsiveness is likely to contribute to progressive pulmonary vascular injury associated with these diseases and may be present in occasional cases of children with unexplained cyanotic spells. High altitude can have dramatic effects on pulmonary vascular disease in chronic heart and lung disease. For example, more advanced pulmonary vascular disease was experienced in patients with anatomic shunt lesions such as ventricular septal defect or patent ductus arteriosus at high altitude—suggesting that the combined effects of hypoxia with high flow may accelerate vascular injury.

Mechanisms causing altered pulmonary vasoreactivity to hypoxia in patients without underlying cardiopulmonary disease are unknown. Pulmonary vascular responses to high altitude depend on multiple factors, including age, genetics, severity of elevation, duration of exposure to high altitude, presence of triggering factors (for example, viral infection), and the presence of underlying chronic cardiovascular or lung disease. Although acute hypoxic pulmonary vasoconstriction is primarily due to direct effects of low oxygen tension on the vascular smooth muscle, various mechanisms play a vital role in modulating vascular tone and reactivity (discussed previously). Local mediators (such as NO, PGI_2, endothelin, endothelium-derived contracting factors, and lipid mediators) and various neurohumoral stimuli modulate the degree of pulmonary vasoconstriction. For example, an inability to produce increased NO to attenuate the severity of pulmonary vasoconstriction may lead to more sustained, severe pulmonary hypertension during acute hypoxia. The contribution of genetics to exaggerated pulmonary vasoreactivity and increased susceptibility to hypoxic pulmonary hypertension has been suggested by animal and clinical studies. Grover and colleagues[133] identified increased severity of hypoxic pulmonary hypertension ("brisket disease") in some cattle strains. Similarly, human infants who are born at sea level but later moved to high altitude (3600 meters) in Lhasa, Tibet, develop severe pulmonary hypertension and right-sided heart failure within weeks to months. Massive RV hypertrophy and hypertensive pulmonary vascular remodeling is present at autopsy. This disease (called subacute infantile mountain sickness) represents the failure of lowlanders of Han origin to adapt to hypobaric hypoxia.[134] Other Hans have lived in Lhasa for generations, but are apparently well adapted to high altitude, demonstrating biologic variability. Polymorphisms of the endothelial NO synthase gene that contribute to impaired NO production may increase susceptibility to poor tolerance of high altitude.

HAPE primarily occurs in previously healthy individuals ascending to altitudes, usually above 2400 meters. Typically, patients have made a rapid ascent from sea level. Additional risk factors include poor conditioning, increased activity at altitude, underlying viral illness, lack of progressive adaptation to altitude by gradually increasing altitude, sleep apnea, and alcohol intake. HAPE often occurs in patients who have previously tolerated altitude and with re-ascent of some long-term altitude residents after travel for a few days at a lower altitude. The incidence of HAPE is unclear, but severe disease occurs in less than 0.1% of visitors to Summit County, Colorado; however, mild disease is unlikely to require medical attention. Clinical signs include severe dyspnea, fatigue, weakness, dry cough, and anxiety or restlessness. Some patients develop hemoptysis. A viral illness is often initially suspected in young children with HAPE because of such nonspecific signs as anorexia, vomiting, and low-grade fever. The differential diagnosis also includes congestive heart failure, pneumonia, pulmonary embolus, alcohol consumption, viral syndrome, severe exhaustion, or carbon monoxide poisoning. On examination, patients have tachypnea, tachycardia, cyanosis, and diffuse crackles. Chest radiographs generally show fluffy densities, which may appear unilateral early, along with pulmonary artery enlargement, normal heart size, and progressive alveolar infiltrates. ECG studies often show tachycardia, peaked p waves, right-axis deviation, ST-T changes, and perhaps RV hypertrophy. Arterial blood gas tensions show severe hypoxia with low CO_2 (early). If cardiac catheterization is performed, marked pulmonary hypertension with normal PCWP and normal left-sided heart function is often found. Follow-up studies generally report normal or mildly elevated baseline PVR, which increases dramatically with acute hypoxia.[58]

Detection of high concentrations of albumin in bronchoalveolar lavage fluid confirms that HAPE is characterized by permeability edema[135,136] and is associated with increased inflammation, as reflected by increased inflammatory cells and products, including leukotrienes.[143] Mechanisms that disrupt the alveolar-capillary barrier leading to increased permeability are unclear but may be related to the direct effects of hypoxia on endothelium through altered cyclic adenosine monophosphate (cAMP) activity. Although pulmonary edema in HAPE may not be primarily caused by pulmonary hypertension per se, elevation of microvascular pressure contributes to the severity of edema formation in the presence of increased permeability. Patients with a history of HAPE have marked hypoxic pulmonary vasoconstriction, which is likely to accelerate edema formation. Thus, the sequence of events contributing to the pathophysiology of HAPE may be as follows: at high altitude, alveolar hypoxia disrupts the alveolocapillary barrier, promotes lung inflammation, causes intense vasoconstriction, and worsens $\dot{V}/\dot{Q}$ mismatch. Overperfusion of some nonconstricted capillaries may cause stress failure, worsening vascular injury and increasing interstitial and alveolar edema formation. Etiologic factors contributing to HAPE include exposure to high altitude, nonspecific triggers (such as viral illness), and genetics. Because a marked individual variability in susceptibility and recurrence risks for HAPE exists, the role of genetic factors has been suggested. Hypoxic

ventilatory drive is often diminished in individuals with recurrent HAPE, perhaps because of altered nocturnal respiratory patterns. Nocturnal hypoxia caused by hypoventilation may contribute to the development of acute mountain sickness and HAPE.

Treatment of HAPE includes early recognition of its signs and symptoms, rapid descent to lower altitude, administration of supplemental oxygen, cautious use of diuretics, and bed rest. There is no role for digoxin or antibiotics. Although treatment is simple, mortality is high if untreated; early treatment should lead to full recovery. With severe symptoms, nifedipine and inhaled NO can lower PAP and hasten recovery.[137] In anticipation of ascent to high altitude, gradual increases in altitude with limited activity is recommended. Dexamethasone, sildenafil, and CCBs often provide effective prophylaxis in HAPE-susceptible individuals.

Chronic Upper Airway Obstruction

Pulmonary hypertension develops in children with upper airway obstruction or obstructive sleep apnea caused by repeated episodes of marked hypoxia. Diverse etiologies of upper airway obstruction share common pathophysiologic features of episodic hypoxia, causing intermittent elevations of PAP, which can eventually lead to sustained pulmonary hypertension and RV hypertrophy. Although airway obstruction can lead to striking cor pulmonale in otherwise healthy children, it can accelerate pulmonary hypertension associated with chronic lung and heart disease. Every child with significant pulmonary hypertension should be evaluated for upper airway obstruction and obstructive sleep apnea. Clinical signs include noisy breathing, snoring, restless sleep with frequent arousal, appearance of air hunger, and retractions with sleep. Other signs include excessive daytime somnolence, deteriorating school performance, behavioral changes, enuresis, systemic hypertension, and morning headache. Failure to thrive is not uncommon, with growth improving with therapy. Similarly, correction of hypoxia can improve neurodevelopmental delays in children with chronic obstruction, as in infants with Pierre-Robin syndrome. Diagnostic evaluations include pulse oximetry and arterial or capillary blood gas tension (to evaluate $PaCO_2$), sleep studies, flexible bronchoscopy, barium swallow, and other studies as indicated. Management depends on the cause and severity of obstruction, whether hypoxia is easily corrected with supplemental oxygen, and the severity of pulmonary hypertension. The roles of tonsillectomy with adenoidectomy, oxygen therapy, repeat sleep studies, nasal continuous positive airway pressure (CPAP) or bilevel positive airway pressure (BiPAP) ventilation, tracheostomy, and other strategies are discussed elsewhere. Although pulmonary hypertension from upper airway obstruction can be severe at presentation, diagnosis and therapy usually lead to complete resolution with time.

Pulmonary Circulation in Liver Disease

Pulmonary vascular disease associated with chronic liver disease includes two strikingly different clinical abnormalities, including (1) low-resistance vascular lesions with marked hypoxemia and (2) high PVR, often with extensive structural remodeling (often with "onion-skinning").[138] Hypoxemia with chronic liver disease may be due to lung disease, including decreased lung volumes, pleural effusions, atelectasis, or pulmonary edema. However, up to one third of patients with chronic liver disease have hypoxemia without underlying cardiac or lung disease. Patients with hepatopulmonary syndrome have severe dyspnea on exertion, shortness of breath, clubbing, cyanosis, and cutaneous spider nevi. Hypoxemia is often severe and is aggravated in the upright position (orthodeoxia) and with exercise. Hypoxemia may precede the onset of severe liver disease, and there is little correlation between the degree of hypoxemia and severity of hepatic function. Chest radiographs may be normal or show increased interstitial markings with more prominence in the bases. Pulmonary function tests may demonstrate restrictive or mixed abnormalities. Diffusing capacity for carbon monoxide (DLCO) is abnormal. Chest CT shows increased central and peripheral vascularity without interstitial abnormalities. Diagnosis is confirmed by perfusion lung scans using technetium Tc 99m-labeled macroaggregated albumin, in which radiolabeled albumin particles, 20 to 60 microns, are injected intravenously. With normal pulmonary capillaries, which are 8 to 15 microns in diameter, the particles are trapped in the pulmonary microcirculation and do not pass to the systemic circulation. Increased activity in extrapulmonary sites as detected by scanning over the kidneys or brain implies the presence of marked right-to-left cardiac or intrapulmonary shunting. Echocardiography rules out intracardiac shunting. Pulmonary angiography is usually not necessary for diagnosis but would show a diffuse (spongy) arterial phase or discrete focal arteriovenous communications.

Hypoxemia and exercise intolerance in the hepatopulmonary syndrome is partly due to low $\dot{V}/\dot{Q}$ zones at the lung bases from airway closure during tidal volume breathing. Impaired hypoxic pulmonary vasoconstriction has been demonstrated in patients with cirrhosis, suggesting that an inability to redistribute blood flow to match ventilation further contributes to $\dot{V}/\dot{Q}$ inequality.[139] Lack of marked improvement while breathing 100% oxygen in these patients, however, implies that $\dot{V}/\dot{Q}$ alone does not account for severe hypoxemia. Intrapulmonary shunting through dramatically enlarged or dilated vessels in the microcirculation causes refractory hypoxemia The marked increase in vessel diameter increases diffusion distance for oxygen from the alveolus to capillary blood; equilibrium may not be achieved, especially with exercise. Alternatively, the low resistance in these vessels may decrease perfusion of distal microcirculation within the lung periphery. Pulmonary vascular lesions are associated with spider angiomas on the skin and pleura, suggesting that an unknown systemic factor contributes to altered vascular function or growth. Past unsuccessful medical therapies have included drug treatment with estrogens, β blockers, cyclooxygenase inhibitors, and somatostatin. Almitrine, a drug that augments hypoxic pulmonary vasoconstriction, has little effect in these patients. Although in the past hypoxemia was considered a contraindication for liver transplantation, recent evidence has suggested that hypoxemia, clubbing, and related signs of hepatopulmonary syndrome improve after transplantation.

In contrast with the low-resistance shunt vessels in the lung microcirculation, some patients have severe unexplained pulmonary hypertension. The presence of portal hyperten-

sion may be a critical factor among cirrhotic patients who develop pulmonary hypertension because pulmonary hypertension has complicated portal hypertension in the absence of underlying liver disease. Pulmonary hypertension is not restricted to specific types of liver disease and can be present in the absence of portal hypertension. The pathogenesis is unknown, but it has been speculated to be related to an autoimmune process or related to circulating mediators with potent vasoconstrictor or growth-stimulating effects that may be produced in excess or not cleared by the diseased liver. Clinically, patient evaluation should include a work-up for portal vein thrombosis and hypercoagulability. Moderate pulmonary hypertension may serve as a contraindication for liver transplantation because of the risks of graft dysfunction from severe postoperative right-sided heart failure as well as the difficult hemodynamic management of these patients in the immediate perioperative period. Preoperative evaluation may be aided by assessing pulmonary vasoreactivity in these patients; however, whether the acute hemodynamic response to vasodilators predicts a favorable outcome is unproven.

Acute Respiratory Distress Syndrome

Current treatment of acute hypoxemic respiratory failure, including acute respiratory distress syndrome (ARDS), is often unsuccessful, with mortality at 50% to 75%. Although death is commonly associated with multiple organ failure, progressive respiratory failure contributes to poor outcome. Injury to the pulmonary circulation during acute respiratory failure leads to increased permeability, leading to pulmonary edema with surfactant inactivation, low lung compliance, and decreased gas exchange. In addition, the pathophysiology of ARDS is characterized by pulmonary hypertension and altered pulmonary vasoreactivity, which worsens $\dot{V}/\dot{Q}$ mismatch, accelerates pulmonary edema formation, and may cause RV dysfunction. Despite the presence of pulmonary hypertension, vasodilator therapy has been limited by the inability to selectively lower PAP without causing systemic hypotension or worsening gas exchange by increasing perfusion of underventilated lung regions. The contribution of pulmonary vasoconstriction to the pathophysiology of ARDS has been recently demonstrated in studies examining the response to inhaled NO.[140-142] Inhaled NO selectively lowers PAP and improves gas exchange in many patients with severe ARDS, and can improve cardiac output in the setting of moderate to high PVR. Despite improvement in oxygenation, inhaled NO has not been shown to improve long-term outcomes such as mortality or ventilator-free days.

RESPIRATORY COMPLICATIONS OF CARDIAC DISEASE

Because chronic lung disease contributes to pulmonary hypertension, altered cardiac function can also adversely affect lung function. Many respiratory complications accompany cardiac disorders, complicating acute management following surgical repair of anatomic heart disease as well as long-term outcome. Three general categories of cardiovascular lesions cause concomitant abnormalities in lung function: first, vascular anomalies that obstruct large airways; second, high pulmonary blood flow caused by large volume left-to-right shunts; and third, inflow or outflow obstruction to the left (systemic) ventricle. Central airways obstruction resulting from vascular compression can be caused by structural lesions such as double aortic arch, right-sided aortic arch, aberrant right subclavian artery, anomalous innominate artery, and pulmonary artery sling. These can accompany congenital cardiac lesions and should be sought in clinical settings of stridor, recurrent or persistent wheezing, cough, apnea, and feeding difficulties. In addition, structural abnormalities of the central airways can also be associated with cardiac lesions, such as complete tracheal rings and narrowing (with agenesis of right lung or pulmonary sling). Structural abnormalities of small airways may also accompany some cardiac lesions. Small airway obstruction with heart disease is commonly caused by mechanical compression by small pulmonary arteries, pulmonary edema, bronchial edema, or bronchoconstriction (discussed later).

Increased pulmonary blood flow occurs with large left-to-right anatomic shunts, such as with ventricular septal defects, patent ductus arteriosus, atrioventricular canals, single ventricle, aortopulmonary window, or truncus arteriosus. High pulmonary blood flow distends small pulmonary arteries and increases PAP. High flow also increases left-ventricular end-diastolic volume and pressure, which raises left-atrial and pulmonary venous pressures. Increased blood flow with elevated pulmonary arterial and venous pressures contribute to peribronchial and interstitial edema, causing small airway obstruction and "cardiac asthma," which is characterized by clinical signs of high airway resistance as a result of small airway obstruction. Airway edema causes mechanical obstruction of small airways as a result of peribronchial and mucosal swelling. Distended pulmonary arteries cause extrinsic compression of small airways, which can occur with high flow even in the absence of overt heart failure. Bronchoconstriction and altered bronchial reactivity may further contribute to small airways narrowing.[143] Chronic elevation of pulmonary blood flow may also be associated with increased peribronchial wall thickening caused by smooth muscle hypertrophy and increased extracellular matrix production.

Along with increased airways resistance, high pulmonary blood flow decreases lung compliance and increases work of breathing, especially when associated with mean PAP above 25 mm Hg.[144,145] Marked left-atrial enlargement can compress the left or right mainstem bronchi, causing airflow obstruction and hyperinflation. Clinical findings include tachypnea with shallow breathing, which may increase physiologic dead space. Other signs are retractions, rhonchi, and wheezing. Chest radiograph findings include hyperinflation or, in some cases, lobar emphysema or atelectasis. Therapy includes medical management of pulmonary edema and failure (diuresis, digoxin), and acute assessment for clinical improvement after an inhaled bronchodilator. These patients are at marked risk for severe respiratory failure with superimposed lower respiratory infections, including respiratory syncytial virus bronchiolitis. Surgical correction of the underlying lesion should improve respiratory signs, but in some cases, airways obstruction persists.

Inflow or outflow obstruction to the left (or systemic) ventricle, from pulmonary veno-occlusive disease, total anomalous pulmonary venous return, mitral stenosis, cor triatriatum, and left-ventricular obstruction caused by coarcta-

tion of the aorta, interrupted arch, aortic stenosis, or atresia and cardiomyopathy, can also impair lung function. Pulmonary venous obstruction or hypertension initially increases pulmonary blood volume and interstitial edema, causing many of the effects on lung mechanics discussed previously. Clinically, children can present with clinical signs of airways obstruction, but more commonly, they present with "interstitial lung disease," with marked tachypnea, cyanosis, and rales. Chest radiograph usually shows a normal cardiac silhouette with increased venous or interstitial markings. Asymmetry may suggest unilateral venous obstruction. Prolonged pulmonary venous hypertension over time can subsequently lead to striking structural venous and arterial changes, contributing to severe pulmonary hypertension.

PLASTIC BRONCHITIS

Plastic bronchitis (PB) is a relatively rare but frustrating cause of airways obstruction and respiratory distress in children with diverse cardiac and respiratory conditions, including congenital heart disease, lymphangiectasis, sickle cell anemia, asthma, and others.[146-148] PB is characterized by respiratory signs caused by the formation of large mucinous or gelatinous airway casts that can plug and obstruct medium-sized or small airways. These casts can be discovered at the time of bronchoscopy for persistent atelectasis or unexplained deterioration in respiratory course, or can be expectorated spontaneously. In many patients with PB, symptoms may persist and lead to recurrent episodes of respiratory distress and, in some cases, have been attributed as the cause of death.

The prevalence of PB is unknown, but multiple reports and small case series have been published. PB is associated with a wide range of diverse diseases, and its pathogenesis is unclear. Most often, it is observed in postoperative cardiac patients who have undergone palliative repair for cyanotic heart disease, including Fontan, Glenn and Blalock-Taussig procedures. PB has also been observed in the setting of lymphatic obstruction associated with chylous effusions, lymphangiectasia, lymphangiomatosis, or lymphatic obstruction associated with total anomalous pulmonary venous return. PB has also been found in diseases not associated with cardiovascular disease, such as asthma, allergic bronchopulmonary aspergillosis, sickle cell anemia during acute chest syndrome, collagen-vascular disease (such as systemic lupus erythematosus) and others.

Clinically, patients with PB present with dyspnea, wheezing, or pleuritic chest pain, and may have fever. Auscultation may yield focal wheezing or asymmetric breath sounds. Chest radiograph often reveals focal collapse of the involved lobe or segment with compensatory hyperinflation, or consolidations with volume loss. PB should be considered in patients with pleural effusions in the setting of cyanotic heart disease after palliative surgery or with chylothorax. Although patients can spontaneously expectorate casts, the diagnosis of PB is generally made during bronchoscopy, in which casts of the airway can be pulled from the airway. These casts often have a rubbery texture, and have often been characterized as either "inflammatory" or "noninflammatory." This classification may not be helpful, and even in the absence of inflammatory cells, it is believed that airway inflammation may be a significant initiating trigger. Currently, there are no unifying theories that link lymphatic obstruction, cyanotic congenital heart disease, or other diseases with PB. Treatment is empirical, with bronchodilators, inhaled or systemic steroids, and airway clearance methods typically used. With marked obstruction, bronchoscopy is warranted for removal of casts, which act as "foreign bodies." Some advocate the use of inhaled heparin, urokinase, tissue plasminogen activator (TPA), or dornase alfa, but experience is limited to case reports, and treatment failures with each approach have been noted. Oral macrolide antibiotics have also been proposed to modulate mucus production, but efficacy is uncertain. The natural history and clinical course is closely linked with the associated disease, as the highest mortality is noted in patients with severe complex cyanotic heart disease.

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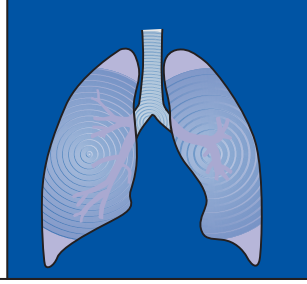

CHAPTER 53

Pulmonary Arterial Hypertension

Eli Gabbay, Robert G. Weintraub, and Lewis J. Rubin

TEACHING POINTS

- A new classification for pulmonary hypertension based on mechanisms and etiology allows more useful description of natural history and response to treatment.
- *Idiopathic pulmonary arterial hypertension* has replaced the term *primary pulmonary hypertension.*
- Idiopathic pulmonary arterial hypertension arises from an interplay of genetic and environmental factors.
- A greater understanding of the pathogenesis of pulmonary arterial hypertension has led to the development of various classes of treatments that have improved quality of life, exercise capacity, and survival.
- Future therapeutic options include newer classes of drugs, combinations of existing therapies, and gene and stem cell therapy with the potential to improve prognosis.

Pulmonary arterial hypertension (PAH) refers to a group of diseases that have in common narrowing of the small pulmonary arteries and arterioles resulting in progressive elevation of pulmonary vascular resistance (PVR) and potential development of right ventricular failure and death.[1-3] The last few years have seen major changes in the classification of pulmonary hypertension, a greater appreciation of its prevalence, and improved understanding of the pathogenesis that underlies the clinical syndrome. As a result, newer therapies have been developed and, although still a life-threatening disease, the prognosis for patients with PAH has improved considerably.

DEFINITION AND CLASSIFICATION

PAH is defined by a sustained elevation of mean pulmonary arterial pressure to a level greater than 25 mm Hg at rest or greater than 30 mm Hg during exercise, with a normal pulmonary artery wedge pressure less than 15 mm Hg.[1-3] Previously, pulmonary hypertension was further described as primary pulmonary hypertension (PPH) or secondary pulmonary hypertension.[4] However, the term *secondary* was confusing because it referred to heterogeneous diseases including diseases that resemble PPH but had known associations such as pulmonary hypertension in association with anorexigen use as well as diseases that are very different from PPH, such as cardiac diseases (e.g., pulmonary hypertension secondary to left ventricular dysfunction) and parenchymal lung disease (e.g., cor pulmonale).

As a result, the World Health Organization–sponsored Expert Working Group suggested replacing the terms *secondary* and *primary* pulmonary hypertension with a new classification (Table 53-1).[5] This classification distinguishes pulmonary hypertension by a combination of mechanisms and etiology and is more useful when considering the natural history, prognosis, and potential therapies of the different causes of pulmonary hypertension.

In this classification, the term PPH has been replaced by the terms *idiopathic pulmonary arterial hypertension* (iPAH) and *familial pulmonary arterial hypertension* (fPAH). This chapter focuses on that group of diseases in group 1; iPAH, fPAH, and conditions known to be associated with PAH (APAH).

Although similarities exist in the diagnosis, prognosis, and therapeutic options for patients with pulmonary hypertension secondary to congenital systemic to pulmonary shunts (Eisenmenger syndrome), these syndromes are significantly different from iPAH in terms of their pathogenesis and natural history and are dealt with elsewhere in the text. However, in some children, the differentiation between iPAH and Eisenmenger syndrome is less clear. For example, children with small atrial septal defects may develop PAH without ever manifesting large left-to-right shunts and it may be more appropriate that such patients are considered to have iPAH.[6]

Within the group of conditions classified under the heading PAH, there are two rare conditions in which pulmonary arterial changes are associated with significant venous or capillary involvement. In both pulmonary veno-occlusive disease (PVOD) and pulmonary capillary hemangiomatosis (PCH), similar changes to iPAH are found in the pulmonary arterioles and the clinical presentation is similar.[7,8] The major difference and the importance of differentiating them from iPAH is that life-threatening pulmonary edema may result from epoprostenol and other therapies that are often used in the treatment of iPAH.

Persistent pulmonary hypertension of the newborn (PPHN) is a separate entity arising from failure of the PVR to decrease after birth.[9] In the fetus, PVR is very high and little blood flows through the fetal lung. At birth, with the onset of ventilation, the increased oxygen tension in the alveoli results in pulmonary vasodilatation, reduced pulmonary pressure, and increased pulmonary blood flow. PPHN or *persistent fetal circulation*, as it is also known, may arise as a result of abnormally strong pulmonary vasoconstrictive response to hypoxemia and is often seen in association with conditions that result in neonatal hypoxemia, such as con-

Table 53-1
Revised Clinical Classification of Pulmonary Hypertension

Pulmonary arterial hypertension (PAH)
Idiopathic (iPAH)
Familial (fPAH)
Associated with (APAH)
Collagen vascular disease
Congenital systemic-to-pulmonary shunts
Portal hypertension
HIV infection
Drugs and toxins
Other (thyroid disorders, glycogen storage disease, Gaucher disease, hereditary hemorrhagic telangiectasia, hemoglobinopathies, myeloproliferative disorders, splenectomy)
Associated with significant venous or capillary involvement
Pulmonary veno-occlusive disease (PVOD)
Pulmonary capillary hemangiomatosis (PCH)
Persistent pulmonary hypertension of the newborn
Pulmonary hypertension with left heart disease
Left-sided atrial or ventricular heart disease
Left-sided valvular heart disease
Pulmonary hypertension associated with lung diseases and/or hypoxemia
Chronic obstructive pulmonary disease
Interstitial lung disease
Sleep-disordered breathing
Alveolar hypoventilation disorders
Chronic exposure to high altitude
Developmental abnormalities
Pulmonary hypertension caused by chronic thrombotic and/or embolic disease
Thromboembolic obstruction of proximal pulmonary arteries
Thromboembolic obstruction of distal pulmonary arteries
Nonthrombotic pulmonary embolism (tumor, parasites, foreign material)
Miscellaneous
Sarcoidosis, histiocytosis X, lymphangiomatosis, compression of pulmonary vessels (adenopathy, tumor, fibrosing mediastinitis)

From Simonneau G, Galiè N, Rubin LJ, et al: Clinical classification of pulmonary hypertension. J Am Coll Cardiol 43:5-12, 2004.

genital diaphragmatic hernia, meconium aspiration, pneumonia, and acute respiratory distress syndrome.[10]

Pulmonary hypertension may also arise as a result of chronic thromboembolic disease.[11] Although an important differential in the assessment of pulmonary hypertension, chronic thromboembolic pulmonary hypertension (CTEPH) represents a different mechanism of disease when compared to PAH. The natural history and prognosis is different and most importantly treatment is predominantly surgical,[12] although medical therapy may be effective in selected cases.[13-16] It is discussed in greater depth in the chapter on pulmonary embolism.

Pulmonary hypertension can complicate left heart disease and can occur in association with lung disease and/or hypoxemia. The mechanisms differ from those of PAH and treatment is directed to the underlying cause and correction of hypoxemia. However, it may yet transpire that in lung conditions associated with pulmonary hypertension, medical treatment with specific PAH therapies (see later) may have a role in selected patients[17-19]

EPIDEMIOLOGY

Idiopathic Pulmonary Arterial Hypertension

The incidence and prevalence of iPAH is uncertain. The reported incidence of iPAH is 1 to 2 per million per year but this may represent an underestimate of the true incidence. It is likely that some patients die without a diagnosis and many others are managed without referral to a hospital clinic. A recent study examining prevalence in Scotland found that in adults between 16 and 65 years of age there was a prevalence of 2.5/million/yr in males and 4/million/yr in females.[20] Autopsy studies in unselected patients have suggested that in 0.13% of cases changes compatible with PAH are found.[21] Idiopathic PAH is more common in women[22] (female to male ratio of between 1.7 and 3.5) and although it has a peak incidence in the third decade of life in women and fourth decade in men, it can manifest at all ages.[23] No ethnic predisposition is apparent, but the disease may have a worse prognosis in African Americans and Asians compared to whites.[24]

Familial PAH

The incidence of PAH is higher in certain families. Familial PAH accounts for between 6% and 10%[23,25,26] of all patients, and close family members of patients with PAH have a significantly increased risk of developing PAH (see later).

Associated PAH

CONNECTIVE TISSUE DISEASE

Pulmonary arterial hypertension has been found in association with almost every type of connective tissue disease.[27] The presence of a connective tissue disease may also be associated with other potential causes of pulmonary hypertension such as interstitial lung disease, direct proliferative lung vascular involvement, or left ventricular dysfunction. However, isolated PAH can occur in 10% to 33% of patients with scleroderma depending on the diagnostic criteria used,[28,29] and is most significantly associated with the limited cutaneous form, often referred to as CREST syndrome.[30] PAH complicates the clinical course 5% to 10% of patients with systemic lupus erythematosus (SLE)[31,32] and 10% to 15% of patients with mixed connective tissue disease.[33] It can rarely complicate rheumatoid arthritis, dermatomyositis, and polymyositis.

PORTOPULMONARY HYPERTENSION

The prevalence of PAH in patients with chronic liver disease varies from 1 in 140 in an autopsy study[21] to as high as 1 in 15 referred for liver transplantation.[34] The development of PAH appears to be related to the duration of portal hypertension rather than the development of cirrhosis per se.[34-37]

DRUGS AND TOXINS

The use of the anorexigens aminorex fumarate, fenfluramine, and dexfenfluramine has been associated with the development of PAH.[35,38,39] The risk is greatest with prolonged use but has been described after only 3 to 4 weeks' exposure.[40] In one review, if fenfluramine was taken for greater than 3 months, there was a 23-fold risk of developing PAH.[35] Other agents likely to be associated with PAH include contaminated rapeseed oil,[41,42] L-tryptophan,[43] cocaine,[35,43] amphetamines, and meta-amphetamines.[44] Certain chemotherapeutic agents, especially mitomycin-C, carmustine, etoposide, and cyclophosphamide, have been linked with PVOD.[45]

HIV INFECTION

PAH complicates HIV infection in approximately 1 in 200 cases.[46] The longer the duration of HIV infection, the greater appears the risk. Many patients with HIV infection may have coexistent portopulmonary hypertension from hepatitis B and C infection or thromboembolic pulmonary hypertension from intravenous drug use. In the absence of these factors, co-infection with human herpes virus 8 (the causative agent of Kaposi sarcoma) may be central to the development of PAH.

HEMATOLOGIC DISORDERS AND SPLENECTOMY

Pulmonary hypertension is seen with a greater prevalence than in the general community in myeloproliferative disorders,[47] myelodysplasia, POEMS syndrome,[48] and thrombocytosis.[49] This relationship is, in part, due to the development of platelet emboli, previous splenectomy[50] (a risk factor in its own right), chemotherapy-induced PVOD, and infiltration of the pulmonary parenchyma by hematopoietic cells—but isolated PAH appears to be more frequent even in the absence of these confounders. PAH complicates sickle cell disease in 8% to 30%[51] of patients and is an important predictor of mortality in these patients. In β-thalassemia, PAH was found to be present in as many as 75% of patients, but because this study relied entirely on echocardiographic indices, it probably represents an overestimate.[52]

GENETIC AND METABOLIC DISEASES

PAH appears to be more prevalent in poorly controlled thyrotoxicosis[53] and may occur in up to 15% of patients with hereditary hemorrhagic telangiectasia.[54] It also complicates the rare storage diseases, Gaucher's[55] and von Gierke disease.[56]

In children, PAH associated with congenital heart disease is more prevalent than in adults, but PAH associated with connective tissue disease, portal hypertension, HIV infection, and drugs and toxins is less prevalent.[2] Chronic thromboembolic pulmonary hypertension is rare in children.[2,57]

PATHOLOGY AND PATHOGENESIS

The normal pulmonary circulation is a low-pressure system attributable to the large combined surface area of the small pulmonary arteries. The thin muscle layer of these arteries and arterioles ensures that they are compliant and can usually accommodate large changes in blood volume.[58] The resistance across the total pulmonary circulation is usually between one tenth and one fifteenth of the systemic circulation. In PAH, the arterial luminal area is reduced by a combination of vasoconstriction, vascular remodeling, and thrombosis.[59] The vascular remodeling includes smooth muscle proliferation, intimal and adventitial thickening, and formation of plexiform lesions (Fig. 53-1).[4,7] There is distal extension of

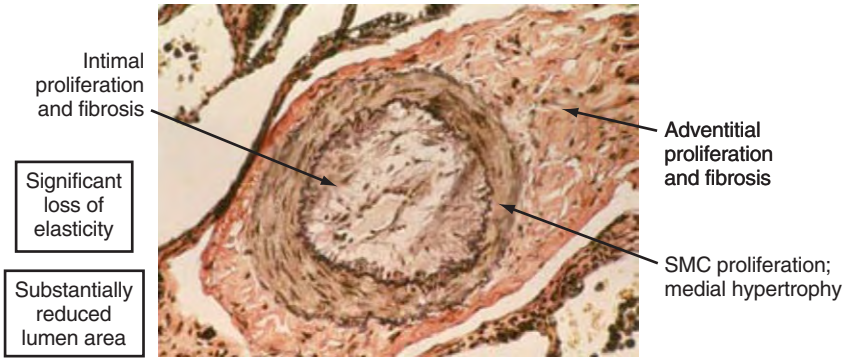

Figure 53-1 Microscopic features seen in pulmonary arterial hypertension. A, High-power view of small pulmonary artery showing smooth muscle proliferation and intimal and adventitial thickening. **B,** A plexiform lesion is shown. PPH, primary pulmonary hypertension; SMC, smooth muscle cell. (From Gaine S, Rubin L: Primary pulmonary hypertension. Lancet 352:719-725, 1998.)

smooth muscle into the smallest normally nonmuscular pulmonary arterioles. This progressive luminal obstruction leads to elevation of pulmonary vascular resistance. In response to increased afterload, there is hypertrophy of the right ventricle that may result in bowing of the intraventricular septum and compression of the left ventricular wall (Fig. 53-2). Eventually the right ventricle will begin to fail.

CELLULAR CHANGES AND MOLECULAR ABNORMALITIES

Although there remains much that is unknown about the pathogenesis of PAH, what is clear is that PAH arises from a complex interplay of several cellular changes and associated molecular and genetic abnormalities.[60] The main cellular changes involve the endothelium, platelets, smooth muscle cells, and adventitial fibroblasts. These abnormalities lead to vasoconstriction, remodeling, and thrombosis via an imbalance between vasodilators and vasoconstrictors, between growth inhibitors and mitogenic factors, and between antithrombotic and prothrombotic mediators (Table 53-2).[61] It remains unclear if the abnormalities in these cellular groups represent changes in local cells or reflect bone marrow–derived progenitor endothelial and smooth muscle cells and fibroblasts that migrate to the pulmonary arteries in response to abnormal stimuli.[62]

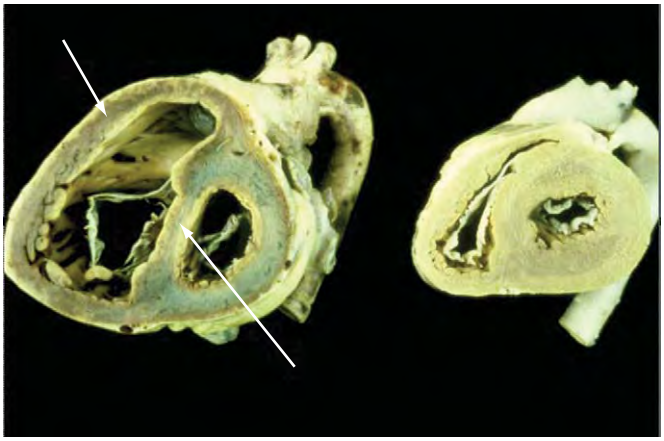

Figure 53-2 Macroscopic view of a heart removed at autopsy from a patient with pulmonary arterial hypertension. When compared to the smaller normal heart, there is evident right ventricular hypertrophy (*short arrow*) and bowing of the intraventricular septum resulting in a D-shaped left ventricle (*long arrow*).

ENDOTHELIAL CELL DYSFUNCTION, PROSTACYCLIN, NITRIC OXIDE, VASOACTIVE INTESTINAL PEPTIDE, AND ENDOTHELIN

The initiating factor, at least in the majority of cases of PAH, appears to be endothelial cell injury—although other cellular components are important and interrelated. In iPAH, the cause of endothelial dysfunction is unknown.

Endothelial cell dysfunction leads to monoclonal expansion of endothelial cells in plexiform lesions.[59,63] Further, there is an imbalance in concentration of mediators normally produced by the endothelium, with reduced production of prostacyclin (PGI_2), nitric oxide (NO) and vasoactive intestinal peptide (VIP) and upregulation of endothelin-1 (ET-1). This imbalance in mediators results in the abnormal proliferation and contraction of pulmonary smooth muscle cells via three pathways that are potential targets for therapy (Fig. 53-3).[64]

ET-1 acts via the two receptors endothelin receptor A and B and, as well as its effects on pulmonary smooth muscles, it also contributes to fibroblastic proliferation and inflammation.[65] ET-1 levels in the serum and expression of ET receptors within the plexiform lesions are increased in PAH and correlate with the severity of hemodynamic changes and prognosis.[66,67]

As well as its antiproliferative and vasodilatory effects on pulmonary vascular smooth muscle cells, PGI_2 normally acts to reduce platelet aggregation. Reduced production of PGI_2 coupled with increased platelet release of the prothrombotic mediator thromboxane (TXA_2),[68] as well as abnormalities in the clotting cascade and impaired fibrinolysis, potentiates the development of in situ thrombosis. Nitric oxide is a potent vasodilator and platelet inhibitor, and reduced levels of endo-

Table 53-2
Cellular, Genetic, and Molecular Mechanisms Involved in Pulmonary Arterial Hypertension*

Cell	Molecular/Genetic Abnormality	Pathobiology
Endothelial cell	↓ NO, PGI_2, VIP	Procoagulant
	↑ ET-1 and TXA_2	Platelet aggregation
	↓Growth suppressor genes	Endothelial proliferation
	↑ VEGF	Smooth muscle proliferation
Smooth muscle	Dysfunctional K^+ channels	Vasoconstriction
	↑ Angiopoietin-1	Smooth muscle proliferation
Platelets	↑ Release of serotonin	Platelet aggregation
	↑ Release of PDGF and VEGF	Vasoconstriction
		Smooth muscle proliferation
Adventitial fibroblast	↑ Elastase	Migration of myofibroblasts and formation of neointima
	↑ MMPs	Smooth muscle proliferation
	↑ L-Allele of 5HTT	
Inflammatory cells	↑ Expression of fractalkine	Cell recruitment and inflammation

*Although described separately, there is significant interaction between the cellular, molecular, and genetic abnormalities.
ET-1, endothelin; 5HTT, serotonin transporter; MMPs, matrix metalloproteinases; NO, nitric oxide; PDGF, platelet-derived growth factor; PGI_2, prostacyclin; TXA_2, thromboxane; VEGF, vascular endothelial growth factor; VIP, vasoactive intestinal peptide.

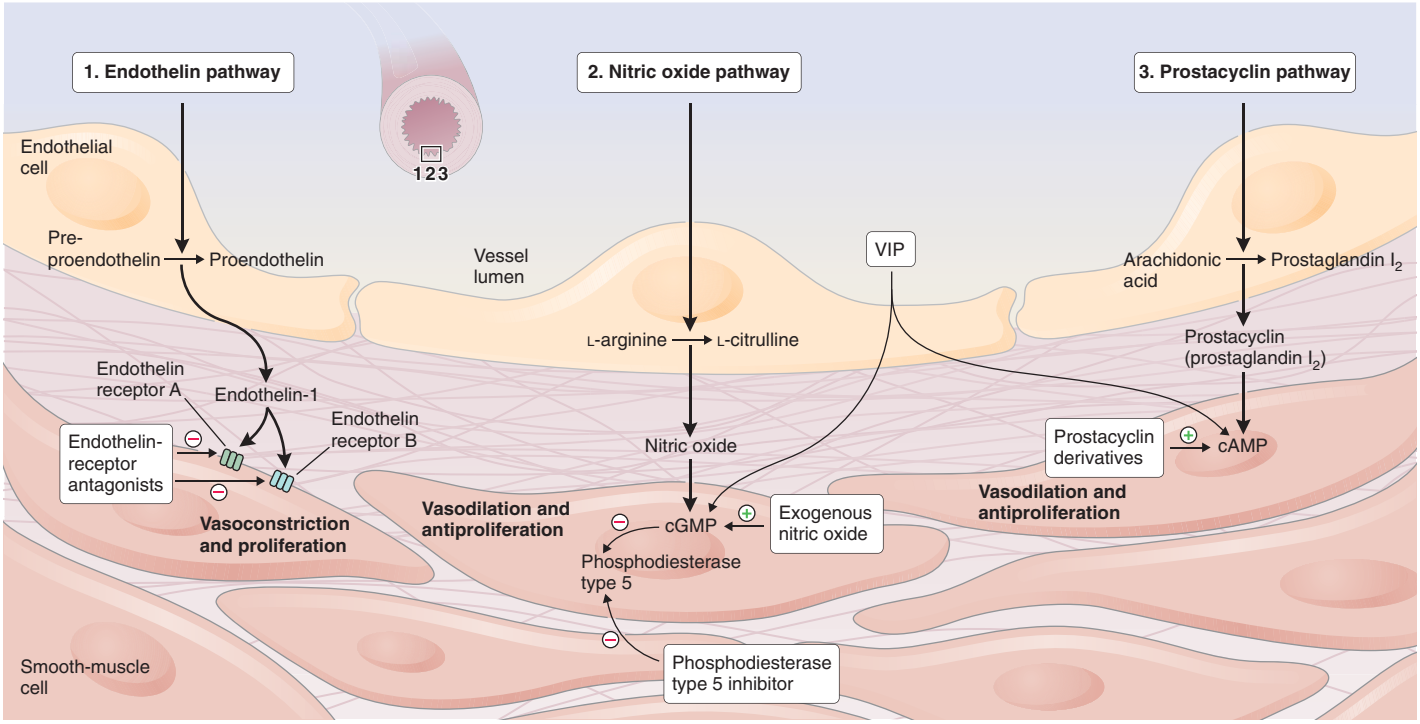

Figure 53-3 Consequences of endothelial dysfunction on pulmonary vascular smooth muscle showing potential targets for therapy. Three major pathways and associated therapeutic targets in abnormal proliferation and contraction of smooth muscle cells are shown. Dysfunctional endothelial cells have decreased production of prostacyclin and endogenous nitric oxide and increased production of endothelin-1. This imbalance of mediators along with decreased production of vasoactive intestinal peptide (VIP) results in a condition favoring vasoconstriction and proliferation of pulmonary artery smooth muscle cells. In addition to their actions on smooth muscle, these mediators have other properties including antiplatelet effects of nitric oxide and prostacyclin and profibrotic and proinflammatory effects of endothelin. + denotes an increase in intracellular concentration; – reflects blockage of a receptor, inhibition of an enzyme, or a decrease in the intracellular concentration; cAMP, cyclic adenosine monophosphate; cGMP, cyclic guanosine monophosphate. (Modified from Humbert M, Sitbon O, Simonneau G: Drug therapy: Treatment of pulmonary arterial hypertension. N Engl J Med 351:1425-1436, 2004.)

thelial NO synthetase are seen in the lungs of patients with PAH, resulting in decreased NO production.[69,70]

PLATELETS, SEROTONIN, VASCULAR ENDOTHELIAL GROWTH FACTOR, AND PLATELET-DERIVED GROWTH FACTOR

In addition to their role in coagulation, platelets release serotonin and vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF). PAH is characterized by an increased platelet release of serotonin.[71] Precisely how serotonin affects the pulmonary vessels is uncertain, but it appears likely to contribute to smooth muscle vasoconstriction and proliferation.[72,73] Selective serotonin reuptake inhibitors (SSRIs) block serotonin transport and activity and have a potential role in therapy of PAH.[74]

VEGF is important in the normal homeostasis of the pulmonary vasculature, helping to maintain normal endothelial cell function. Whereas the VEGF A isoform is protective and appears a likely candidate for gene transfer therapy,[75] the VEGF B isoform may exacerbate endothelial cell dysfunction.[76] In the plexiform lesions, VEGF expression is increased along with its receptors, whereas signaling molecules that are important to the normal response to VEGF are downregulated.[63,77,78] It appears likely that dysregulation of this pathway is part of an abnormal response allowing clonal expansion of endothelial cells.[78] PDGF and other growth factors such as epidermal growth factor (EGF) and insulin-like growth factor-1 are upregulated in PAH[78] and also may contribute to endothelial cell dysfunction and proliferation, as well as abnormal smooth muscle and adventitial proliferation.

SMOOTH MUSCLE CELLS, POTASSIUM CHANNELS, AND ANGIOPOIETIN-1

The vascular smooth muscle is a target for growth factors and mediators that promote abnormal contraction and proliferation, but changes within the smooth muscles themselves appear to be central to the pathogenesis of vasoconstriction and vascular wall remodeling and endothelial dysfunction.

Within the smooth muscle cells, loss of some of the normal voltage-gated potassium (K^+) channels leads to increased intracellular calcium and resultant vasoconstriction and smooth muscle proliferation.[79] It remains unclear if these K^+ channel abnormalities are genetically determined or acquired. Further, abnormal K^+ channels in platelets may contribute to the increased serotonin release seen in PAH.[80]

Angiopoietin-1 is a vascular growth factor that is essential for lung vascular development.[81] Produced by smooth muscle cells, its receptor is present only on endothelium and after development is completed is present in only very small quantities in the lung. One study has suggested that it is

upregulated in PAH[82] and another study has suggested that it directly contributes to vascular remodeling in experimental forms of PAH.[81] Alternatively, another study has suggested that it has a protective role.[83]

ADVENTITIA, NEOINTIMA, MATRIX METALLOPROTEINASES, AND PROTEOLYSIS OF EXTRACELLULAR MATRIX

In PAH, fibroblast proliferation leads to adventitial thickening, and a layer of myofibroblasts and extracellular matrix develops in the neointima between the endothelium and internal elastic lamina. The matrix metalloproteinases (MMPs) are matrix-degrading enzymes involved in extracellular matrix (ECM) turnover. Changes in the balance of these and related enzymes and their inhibitors contributes to migration of myofibroblasts, deposition of excess ECM, and may interact with growth factors, leading to enhanced smooth muscle proliferation.[84-86]

MMP2 and MMP9 are gelatinases that break down basement membrane and allow the migration of myofibroblasts from the adventitia through the media and into the neointima. Upregulation of MMP2 and MMP9 occurs in PAH, and increased release of smooth muscle–derived serine elastase contributes to the increased activity of MMP2 and MMP9. Further, the upregulation of MMPs and serine elastase may lead to the formation of breakdown products that interact with EGF leading to smooth muscle cell proliferation. The increased deposition of ECM may arise from an imbalance between collagenase MMP1 and its inhibitor (tissue inhibitor of metalloproteinase 1 [TIMP-1]).[85]

The importance of the role of dysfunctional proteolysis in PAH is highlighted by the observation that serine elastase inhibitors reverse vascular changes in experimentally induced severe PAH.[87]

INFLAMMATORY MECHANISMS

Inflammatory mechanisms are likely to be important, at least in certain forms of PAH. Inflammatory infiltrates are commonly seen within plexiform lesions, and increased expression of the chemokines RANTES and fractalkine, as well as their receptors, have been observed in PAH.[88] Patients with PAH have higher serum concentrations of IL-1 and IL-6, which upregulate endothelin and PDGF and may have procoagulant activity.[89] Immunosuppressive medications have been shown to be effective in some forms of PAH.[89]

ANGIOTENSIN-CONVERTING ENZYME

Within both the intima and plexiform lesions seen in patients with PAH, angiotensin-converting enzyme (ACE) expression is upregulated.[90,91] ACE leads to the production of angiotensin II, a potent vasoconstrictor and activator of smooth muscle proliferation. However, the role of ACE in the pathogenesis of PAH is unclear[92] and clinical studies with ACE inhibitors have failed to find a benefit.

Genetic Abnormalities

Familial PAH shows an autosomal-dominant inheritance but with only 10% to 20% penetrance.[22] At least 80% of those who receive the abnormal gene do not develop disease. Inheritance shows genetic anticipation, with the disease developing at a younger age and often with greater severity in successive generations.[3,22,93]

Underlying the development of both fPAH and iPAH are genetic mutations in the TGF-β receptor family. Proteins encoded by these genes are central to vascular remodeling. The first candidate gene identified in PAH encodes bone morphogenetic protein receptor type 2 (BMPR-II).[94,95] Binding of ligand to this receptor activates intracellular pathways acting via the SMAD group of proteins and mitogen-activated protein kinases (MAP kinase), which suppress the growth of vascular smooth muscle cells. In 50% to 60% of patients with fPAH, mutations in BMPR-II have been identified.[94,95] However if postsomatic mutations are included, then BMPR-II gene abnormalities are found in at least 90% of patients with fPAH.

In contrast to fPAH, only 10% to 26% of patients with iPAH have mutations in the BMPR-II gene.[94-96] The absence of BMPR-II mutations in the majority of sporadic cases suggests that other genes probably also contribute to the development of PAH. Genetic mutations linked to PAH have been discovered in other genes in the BMPR-II/TGF-β superfamily. These include ALK-1 and endolgin in hereditary hemorrhagic telangiectasia[54,97] and mutations that directly affect SMADs, MAP kinase, and nuclear transcription factors.[98,99] In the plexiform lesions, the monoclonal endothelial cells show defects in the growth suppressor genes TGF-β receptor and Bax, suggesting that such mutations allow clonal expansion of endothelial cells.[100]

The precise interactions at different levels in this pathway are complex. However defective BMP signaling and loss of its antiproliferative effects appears to be central to the development of both iPAH and fPAH. The role of BMPR-II mutations in conditions associated with PAH is less clear, with such mutations not identified in studies of scleroderma-associated PAH and HIV-associated PAH—but probably of some significance in PAH seen with anorexigen use.[101-103]

Other than genetic mutations arising directly within the TGF-β superfamily, there are likely to be other modifier genes in other pathways that interact with the primary mutation and influence whether or not PAH develops. One study has suggested that upregulation of angiopoietin-1 occurs in PAH and that acting via its receptor TIE2 on endothelium may contribute to defective BMPR-II signaling.[80] This raises the possibility that a gene in this pathway is a suitable candidate to be such a modifier gene.[81]

Another gene pathway likely to be important in PAH is the serotonin (5-HT) pathway. Plasma levels of serotonin released from platelets are increased in PAH and may contribute to pulmonary vasoconstriction and increased proliferation of pulmonary vascular smooth muscle cells. A polymorphism in the 5-HT transporter (5-HTT) has been found. The L-allele (long form) induces a greater rate of synthesis of the transporter and has been found in 65% of patients with iPAH but only 26% of controls.[104]

Another potential modifier gene encodes plasminogen activator inhibitor type 1 (PAI-1), dysfunction of which leads to impaired fibrinolysis and a procoagulant state of the pulmonary vessels. Other candidate genes include those that encode prostacyclin synthase, NO synthetase, serine elastase, MMP2 and MMP9, voltage gated K^+ channels, angiotensin-converting enzyme, and VEGF and VIP.[105]

Environmental Factors

PAH develops in only a small percentage of the carriers of the BMPR-II, ALK-1, and 5HTT mutations, suggesting that environmental triggers are probably required for the development of disease. Clues as to the nature of these stimuli are evident from the known associations of PAH and act via cellular and molecular mechanisms important in PAH.

Acute hypoxia causes pulmonary vasoconstriction, in part via upregulation of endothelin and serotonin and by K^+ channel dysfunction.[106,107] Although changes are initially reversible, chronic hypoxia results in proliferation of vascular smooth muscle and matrix, resulting in irreversible changes. Therefore, chronic hypoxia may contribute to the PAH seen in people living at high altitude but also may be relevant to the ongoing remodeling of the pulmonary vasculature with disease progression.

In connective tissue diseases, especially SLE, the presence of antinuclear antibodies and deposition of complement fraction in the vascular smooth muscle wall suggest an immunologic mechanism.[108] Further, antiendothelial cell antibodies specific to certain receptors on the pulmonary vasculature are present in patients with the limited cutaneous form of scleroderma.[109] In connective tissue diseases, PAH often occurs in association with Raynaud phenomenon—suggesting a similar pathogenesis.[110]

Anorexigens increase plasma serotonin levels by inducing platelet serotonin release or inhibiting its metabolism.[111] Additionally, they block K^+ channels.[112] This combination may contribute to vasoconstriction and vascular smooth muscle proliferation. It is likely that in the presence of portal hypertension, the presence of portosystemic shunts might allow vasoactive substances such as serotonin to bypass the liver, where they are normally metabolized, and reach the pulmonary circulation in greater concentration.[113] In HIV, co-infection with HHV-8 may allow clonal expansion of endothelial cells by dysregulatory cell growth.[114]

In sickle cell disease, destruction of nitric oxide by increased concentrations of free hemoglobin may be important to the development of PAH,[115] and it is plausible that in the myeloproliferative diseases, increased release of platelet-derived serotonin and growth factors contributes directly to pulmonary vascular smooth muscle proliferation.

The environmental stimulus/stimuli that underplay iPAH remain elusive, although two interesting observations may give some insight. The presence of antiendothelial cell antibodies in patients with iPAH raises the prospect of immune mechanisms at play, and the finding of HHV-8 infection in plexiform lesions of 10 out of 16 patients with iPAH suggests that vasculotropic viruses may be important triggers in some individuals.[116]

It is evident that one genetic mutation and/or one environmental stimulus cannot explain all forms of PAH, and it is likely that development of disease requires interplay between multiple genetic and environmental factors. This has led to the development of a multi-hit hypothesis,[61] requiring primary gene abnormalities which are influenced by modifier genes and environmental stimuli, to develop into clinically evident PAH.

Clinical Features

SYMPTOMS

Common symptoms of pulmonary hypertension include lethargy and reduced exercise capacity. Anorexia, chest pain, syncope, and congestive heart failure may also be present. Syncopal episodes are usually related to exertion or emotional upset and may culminate in a brief generalized seizure.

Although intended primarily for adults with pulmonary hypertension, the WHO classification of functional status of patients with pulmonary hypertension provides a useful framework for describing symptom severity in children as well[117]:

Class I: Patients with pulmonary hypertension in whom there is no limitation of usual physical activity; ordinary activity does not cause increased dyspnea, fatigue, chest pain, or presyncope.

Class II: Patients with pulmonary hypertension who have mild limitation of physical activity. There is no discomfort at rest, but normal physical activity causes increased dyspnea, fatigue, chest pain, or presyncope.

Class III: Patients with pulmonary hypertension who have a marked limitation of physical activity. There is no discomfort at rest, but less than ordinary activity causes increased dyspnea, fatigue, chest pain, or presyncope.

Class IV: Patients with pulmonary hypertension who are unable to perform any physical activity at rest and who may have signs of right ventricular failure. Dyspnea and/or fatigue may be present at rest and symptoms are increased by almost any physical activity.

PHYSICAL EXAMINATION

Cyanosis is usually absent unless there is intrapulmonary shunting, or reversed shunting through a congenital septal defect or arterial communication. The jugular venous pressure may be elevated with visible a waves present. The peripheral pulses may be reduced in volume if cardiac output is low. The right ventricular impulse is usually forceful and pulmonary valve closure may be palpable at the upper left sternal edge. On auscultation the pulmonary component of the second heart sound is louder than normal and may narrowly split from the aortic component or, more commonly, may overlap with aortic closure so that the second heart sound is both loud and single. The murmurs of tricuspid and pulmonary valve regurgitation may be audible at the left lower and upper sternal edge, respectively. Signs of right ventricular failure include hepatomegaly, ascites, and occasionally peripheral edema. Because of ventricular interdependence and altered left heart filling, there may be signs of biventricular heart failure, with tachypnea also present, particularly in young infants.

DIAGNOSIS AND ASSESSMENT

The clinical features of PAH are nonspecific and, therefore, it is important to consider the possibility of pulmonary hypertension in any patient presenting with unexplained progressive breathlessness or fatigue, especially when more common causes such as anemia, obstructive lung diseases, and left heart failure are excluded.[3,4,118]

The diagnosis of iPAH is one of exclusion. The assessment involves establishing the precise diagnosis using the WHO classification (see Table 53-1), determination of potential contributing factors, and assessment of prognosis and response to therapy. A full medical history should be taken to elicit the presence and duration of symptoms, prior illnesses, exposure to drugs or medications, and the presence of other family members with similar symptoms. Clues to the possibility of pulmonary hypertension may be found in the physical examination, in an abnormal ECG and/or chest radiograph, although all three can be normal especially in the early stages. The following investigations are standard in the work-up of someone with known or suspected pulmonary hypertension.[117]

Electrocardiogram

This typically shows right atrial enlargement and right ventricular hypertrophy, manifest as tall R waves and upright T waves in the right chest leads and deep S waves in the lateral chest leads. If severe, ST and T wave changes may be present in the anterior and lateral leads and there may be intraventricular conduction delay. In isolation, the ECG is an inadequate screening tool for the detection of PAH.[117]

Chest Radiograph

The chest radiograph may be normal especially early in the presentation.[117] However, as the disease progresses, changes are usually seen. The main pulmonary artery is usually enlarged, as are the branch pulmonary arteries. The cardiac silhouette may appear abnormal in shape, with late right atrial and right ventricular enlargement. Decreased peripheral lung vasculature may be present but is often subtle.

Echocardiogram

The best screening tool for detection of pulmonary hypertension is a transthoracic echocardiogram (TTE). The patient should be relaxed and comfortable and with appropriate family members present, especially with younger children. Sedation may be required but should be used judiciously. A segmental approach is required to the visualization of all normal structures and exclusion of potential cardiac defects.

Right ventricular systolic pressure (RVSP) and pulmonary artery diastolic pressure can be estimated from the velocity of the tricuspid and pulmonary regurgitant jets if present. RVSP is calculated from the formula:

$$\text{RVSP} = 4V^2 + \text{right atrial pressure}$$

where V = velocity of the tricuspid regurgitant jet. The absence of adequate tricuspid regurgitation does not exclude the presence of pulmonary hypertension.

TTE can also detect other features of pulmonary hypertension including right ventricular wall thickness and dilatation, right atrial dilatation, flattening of the intraventricular septum and right ventricular function, although there is no fully validated measure of right ventricular systolic function on routine echocardiography.[119] A patent foramen ovale or a modest secundum atrial septal defect is commonly found in subjects with atrial dilatation, with any pattern of interatrial shunting possible, and may be secondary rather than representing the primary cause. Right ventricular free wall thickness does not vary much between early infancy and adult life, and right ventricular hypertrophy is usually present but the amount of right atrial and right ventricular dilatation can be variable.

In experienced hands, TTE should be able to reliably exclude congenital cardiac malformations associated with pulmonary hypertension, including anomalies of pulmonary venous return, left heart inflow obstruction (mitral stenosis, cor triatriatum, septal defects, patent ductus arteriosus and aortopulmonary window). Agitated saline may be used to detect evidence of intracardiac shunting. TTE is a valuable tool to detect features of left ventricular or other left-sided heart disease.[120] TTE is less reliable in detecting diastolic dysfunction of the left ventricle. Occasionally a transesophageal echocardiogram (TOE) is useful to highlight cardiac malformations.

Tests to Exclude Other Causes

Abdominal ultrasound and liver function tests should be undertaken to exclude liver disease and portal hypertension. Pulmonary function testing, arterial blood gas assessment, and a sleep study are undertaken to exclude lung disease and various forms of sleep apnea.[121]

Computed tomography of the chest or a nuclear ventilation perfusion test to exclude thromboembolic disease are standard among older subjects presenting with pulmonary hypertension, and at least one of these is usually undertaken in young children.

Hepatitis C, HIV, scleroderma, SLE and other connective tissue disorders, as well as hematologic abnormalities, should be excluded with appropriate blood studies. If there is evidence of thromboembolic disease, then testing for a hypercoagulable disorder should be performed.

Measurements of Exercise Capacity

A 6-minute walk test (and less commonly, a shuttle walk test) is usually undertaken in older subjects (adolescents and adults) but prior practice on the part of the patient is required in order to ensure a reproducible result. This test is not required for the diagnosis of pulmonary hypertension but does provide a useful baseline and measure of functional status.[122] More sophisticated cardiopulmonary exercise testing, with measurement of gas exchange, has also been used,[123] but is not essential for diagnosis or management. Both the 6-minute walk test and WHO functional class can be used to monitor response to therapy, and improvements in these parameters with therapy suggest a better prognosis.[124]

Cardiac Catheterization

Right heart catheterization should be undertaken in almost all subjects in whom PAH is suspected. In children, this investigation should be undertaken in an institution that has experience with both pediatric cardiac catheterization and the assessment of pulmonary hypertension. An experienced pediatric anesthetist should be available to manage sedation requirements, and general anesthesia is best avoided in subjects with advanced right ventricular dysfunction.

Cardiac catheterization is required to confirm the presence of pulmonary hypertension and to ensure that the pulmonary wedge pressure is normal. It is valuable in excluding

congenital heart disease and/or determining intracardiac shunt fraction. A complete assessment requires not only measurement of pulmonary pressure but also measurement of cardiac output indexed to body surface area, measurement of right atrial pressure, and mixed venous oxygen concentrations, all of which help determine the severity of disease and the prognosis in an individual patient.[125]

At the time of catheterization it is possible to assess the response to a selective pulmonary vasodilator (inhaled nitric oxide, infusion of prostacyclin or intravenous adenosine). A positive acute pulmonary vasodilator response is defined as a fall in mean pulmonary artery pressure >10 mm Hg to reach a mean pulmonary artery pressure <40 mm Hg, with an increase or unchanged cardiac output in response to an acute pulmonary vasodilator challenge.[117] A positive response is more common in the pediatric population and can help guide initial therapy.[126] Pulmonary angiography is required to determine if thromboendarterectomy should be performed in patients with chronic thromboembolic pulmonary hypertension.[127]

Other Investigations

There have been numerous reports using serum markers such as brain natriuretic peptide[128] and von Willebrand factor[129] in assessing prognosis and response to therapy. Cardiac MRI may be helpful in defining the cardiac anatomy and assessing prognosis.[130] Measurements of quality of life are used in clinical trials of new therapies but are rarely practical in routine clinical practice.[123]

A thoracoscopic lung biopsy is very rarely performed because of the significant risk of mortality associated with this procedure in this population.[131] It is occasionally used when other tests indicate the possibility of an unusual interstitial lung disease or pulmonary vasculitis and on occasions when PVOD or PCH is suspected.

THERAPY

In recent years the therapeutic options for various forms of PAH have proliferated (Fig. 53-4). The level of evidence differs for various therapies, with most evidence coming from studies of affected adults. It remains unclear if subjects with stable, mild PAH require treatment. However, the outcome for children with iPAH is poor, with data indicating a median survival of only 9 months.[126,132]

Conventional Therapy

General measures include management of underlying or contributing factors, avoidance of pregnancy, early treatment of intercurrent respiratory infections with antibiotics and oxygen as required, and the use of diuretics and digoxin if there are signs and symptoms of congestive heart failure. Nonsteroidal anti-inflammatory medications are usually avoided when possible because of their potential effects on renal function and fluid balance.

The evidence for efficacy of anticoagulants is based on single center, retrospective studies.[133,134] Several studies noted improved survival of treated subjects when compared with controls. Long-term systemic anticoagulation has become routine in subjects with all forms of PAH because of the predilection for pulmonary microthrombi in this condition, regardless of underlying etiology.

With the advent of specific PAH therapies, the role of the nonselective vasodilators, calcium channel blockers has been redefined. Improved clinical status and survival have been noted in subjects with iPAH who demonstrated acute reactivity in response to pulmonary vasodilator testing, and who received high-dose calcium channel blockers.[126,132,134] The observed difference in survival may have been due to the poorer prognosis of control subjects who did not demonstrate acute reactivity. Calcium channel blockers are reserved for subjects with class II and III symptoms who display acute reactivity and remain stable.[135] Recent data suggest that of both children and adults, who are initially suitable for treatment with calcium channel blockers, at least one half will require additional therapy within 5 to 10 years of presentation.[136]

Specific PAH Therapies

The current understanding of the mechanisms underlying PAH has led to the development of therapies that have favorably influenced survival, exercise capacity, hemodynamics, and quality of life. These agents have protean effects on the pulmonary vasculature. They are effective, in part, because they redress the imbalance of mediators in PAH which favors not only vasoconstriction but also vascular remodeling and thrombosis. There are four main classes acting upon three main intracellular pathways (see Fig. 53-3).[64]

1. *Synthetic prostacyclin (epoprostenol) and prostacyclin analogs:* Epoprostenol has been tested in two randomized controlled trials of subjects with iPAH.[137,138] Improvement in symptoms, exercise capacity, and hemodynamics was demonstrated in treated subjects. To date, epoprostenol remains the only agent that has been shown, in a randomized, controlled trial, to improve survival in subjects with iPAH.[138] The long-term use of epoprostenol has been shown to significantly improve survival when compared to historical controls.[124,139] Improved survival has also been reported in retrospective trials of children with iPAH and those with congenital heart disease.[140]

Use of intravenous epoprostenol is limited by the need for a continuous intravenous infusion pump and associated problems of line sepsis, as well as flushing, gastrointestinal disturbance, and headaches, which may occur as a direct effect of the medication.

Several randomized controlled trials have been performed with prostacyclin analogs. Both continuous subcutaneous infusion of treprostinil and inhaled iloprost, which has to be given at least eight times per day, have been shown to improve exercise capacity and hemodynamics in 3-month randomized trials.[141,142] Beraprost, an orally active analog, showed improvement in exercise capacity and clinical events in a randomized trial at 6 months but the benefit was not sustained at 12 months.[143]

2. *Endothelin-1 receptor antagonists:* Two randomized trials of bosentan, a dual endothelin receptor antagonist, have shown improvement in multiple parameters including exercise capacity, functional class, hemodynamics, and time to clinical worsening.[144,145] Preliminary data for both sitaxsentan and ambrisentan, orally active endothelin A receptor antago-

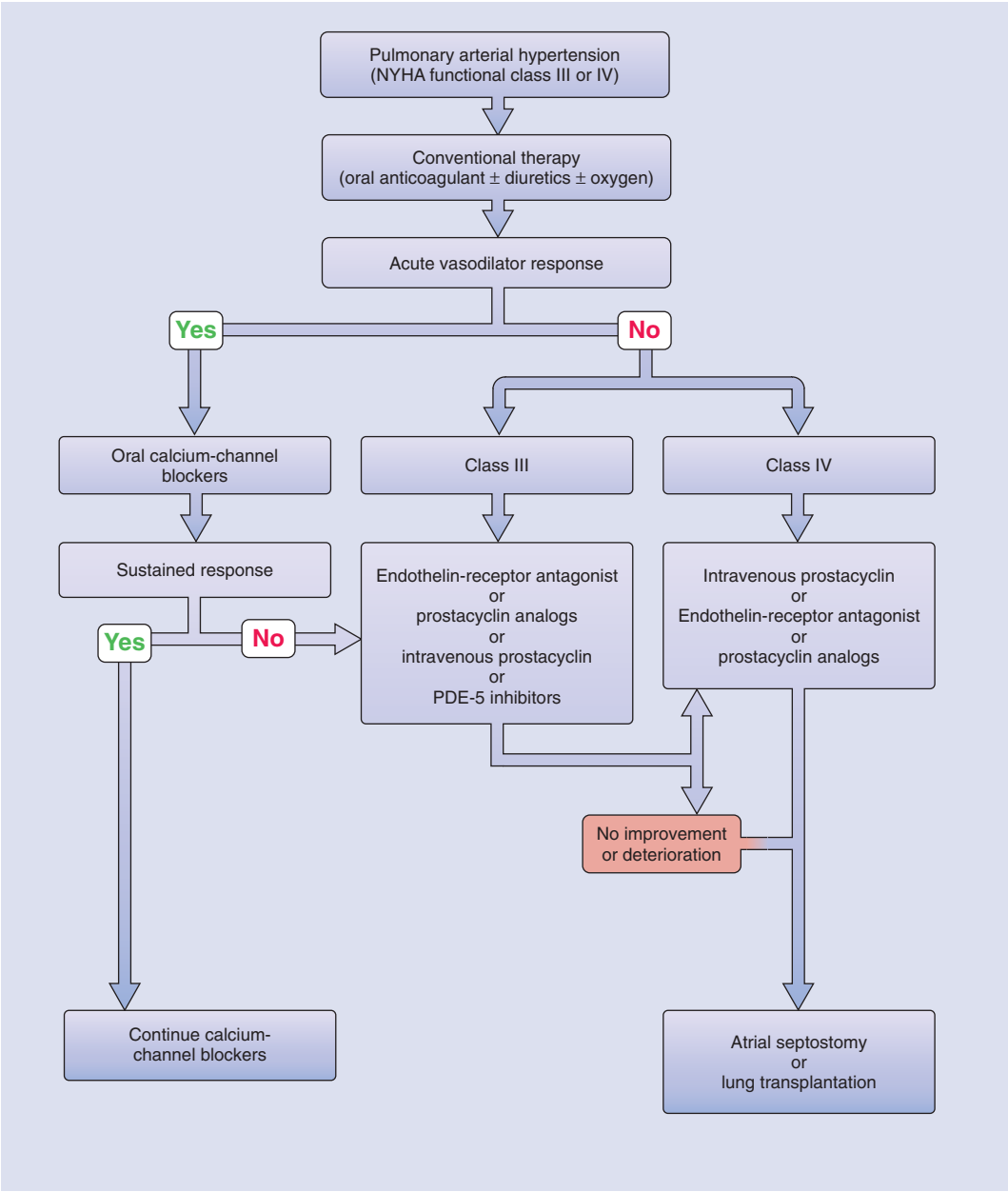

Figure 53-4 Algorithm for the treatment of pulmonary arterial hypertension. This algorithm applies only to patients in NYHA functional class III or IV, because very few data are available for patients in NYHA function class I or II. The treatments have been evaluated mainly in idiopathic (primary) pulmonary arterial hypertension and in cases associated with systemic sclerosis or with exposure to anorectic agents. The drugs of choice for testing of acute vasoreactivity are short-acting agents (e.g., intravenous prostacyclin, intravenous adenosine, or inhaled nitric oxide). Patients with a sustained benefit from calcium-channel blockers are defined as those in NYHA functional class I or II who have near-normal hemodynamic values after at least 1 year of follow-up. Most experts recommend that patients in NYHA functional class IV receive continuous intravenous epoprostenol. The experience with phosphodiesterase type 5 (PDE-5) inhibitors, including sildenafil, is preliminary, and controlled studies are ongoing to determine its efficacy and safety. The combined use of drugs with different mechanisms of action warrants further investigation. Lung transplantation is considered an option for all eligible patients who remain in NYHA functional class IV after 3 months of receiving epoprostenol. Atrial septostomy is proposed for selected patients with severe disease.

nists, suggest improved exercise capacity and hemodynamics comparable to bosentan.[135]

3. *Phosphodiesterase-V inhibitors:* Several preliminary reports and one randomized crossover study of sildenafil[146] have reported improvement in symptoms and exercise capacity in subjects with PAH. A placebo-controlled trial has reported improvements in 6-minute walk test, WHO functional class, and hemodynamics.[147] The role of sildenafil in the treatment algorithm for subjects with PAH is as yet unclear but it may be a reasonable alternative to bosentan or nebulized iloprost, especially in patients in WHO functional class II or III.

4. *Nitric Oxide (NO) and NO donors:* Inhaled NO is a potent selective pulmonary vasodilator and can lower pulmonary pressures, improve hemodynamics, and improve oxygenation in the ventilated patient.[148] Outside of this setting, its use is limited by the toxic product of its metabolism and practicalities inherent in delivering it by the continuous inhaled route.[149]

L-Arginine is the substrate from which NO is produced and trials of L-arginine suggest that although it may have limited effects on pulmonary pressures,[150] overall it probably provides no clear benefit.[149]

The number of available therapies for patients with iPAH has led to the development of suggested treatment algorithms as shown in Figure 53-4. Whatever therapies are employed it is important to carefully monitor the patient by use of symptoms, serial echocardiography, measurements of exercise tolerance and, occasionally, repeat cardiac catheterization. This will help guide escalation or gradual reduction in therapy, allow better assessment of prognosis, and consideration of timing for listing for transplantation.

TREATMENT OF ASSOCIATED PAH

It is important to diagnose or exclude conditions that are known to be associated with PAH, not only because these conditions warrant therapy in their own right, but also because treatment of the underlying condition may itself improve pulmonary pressures and associated hemodynamics.

There is increasing evidence for the use of the specific PAH therapies discussed above to control PAH when it is associated with the connective tissue diseases, especially scleroderma,[145,151,152] and when it is seen in association with HIV infection,[153] portopulmonary hypertension,[154,155] and hematologic abnormalities.[156] The role for anticoagulation in these conditions is less clear, and the risk-to-benefit ratio needs to be assessed in scleroderma because of associated reflux esophagitis and also in portopulmonary hypertension and some myeloproliferative disorders because of coagulopathy, thrombocytopenia, and other risks of bleeding.[2] In terms of specific therapies, in portopulmonary hypertension, although potentially effective, there is an increased risk when using bosentan or other drugs with hepatic toxicity.[2] Further, beta-blockers, which are normally used to treat portal hypertension and reduce risk of variceal bleeding, should be used with caution because of their negative inotropic effects on the right ventricle. The phosphodiesterase inhibitors such as sildenafil are contraindicated in patients who are receiving highly active antiretroviral therapy (HAART) for HIV disease because of reports of sudden death owing to markedly increased plasma levels.

In PAH associated with connective tissue diseases, there are reports of improvement in pulmonary pressures with immunosuppressive therapy.[157-159] This is more likely to be seen with SLE and mixed connective tissue disease, and there is little indication for corticosteroid and/or other immunosuppressive therapies in scleroderma-associated PAH—unless there is associated pulmonary fibrosis.[160,161] Treatment of thyrotoxicosis, where present, may help reduce pulmonary pressures.[53] Whole-lung radiotherapy has been shown to reduce pulmonary pressures where extramedullary hematopoiesis was found to be contributing to elevated pulmonary pressures seen in some patients with myeloproliferative disorders.[162] Corticosteroid therapy was shown to contribute to reduction in pulmonary pressures in a series of patients with POEMS syndrome.[48] The withdrawal of anorexigens has been associated with improvements in pulmonary pressure.[163] Chelation therapy may be helpful in β-thalassemia–associated PAH[164] and hydroxyurea helpful in the PAH associated with sickle cell disease.[51,156] There have been case reports suggesting improved pulmonary hemodynamics following HAART in HIV-associated PAH.[46,165]

In patients being assessed for liver transplantation, the presence of portopulmonary hypertension is associated with increased perioperative risk and is usually considered a contraindication to transplantation.[166] However, treatment with selective PAH therapies may reduce PVR sufficiently to allow transplantation to be performed successfully.[167,168] Further, if hepatic transplantation is feasible in these patients, then this may result in improvements in pulmonary pressures.[169]

Patients with PVOD and PCH may benefit from specific PAH therapies but these need to be used with great caution because of the high risk of developing pulmonary edema—especially with epoprostenol. The only curative therapy for these two conditions is lung transplantation.[2]

Atrial Septostomy

The observation that patients with iPAH and a patent foramen ovale (PFO) have a survival advantage over those without a PFO has led to the therapeutic intervention of balloon atrial septostomy, which results in the formation of an intra-atrial right-to-left shunt.[170] In patients with severe iPAH, this shunt allows decompression of the volume-overloaded right ventricle, thereby reducing signs and symptoms of right heart failure, and results in increased left ventricular preload, improving systemic cardiac output, and reducing symptoms such as syncope.[171] Further, despite a fall in systemic arterial oxygen tensions, the increased cardiac output allows greater systemic oxygen delivery.[172] Studies have shown improvements in cardiac index following atrial septostomy from between 15% and 58%,[172-175] which appear to correlate with improved functional class, exercise capacity, and possibly survival.[172,174] Occasionally the procedure needs to be repeated because of subsequent closure of the defect.[172]

However, atrial septostomy is associated with a mortality of between 5% and 50% depending on the center's experience and patient selection.[176] Therefore, its role is probably limited to highly experienced centers where septostomy is performed with low morbidity, and reserved for patients with severe iPAH suffering from recurrent syncope or right heart failure and in whom other therapies are unavailable or have failed or as a bridge to transplantation.[177]

Lung Transplantation and Combined Heart and Lung Transplantation

Either single (SLT) or bilateral lung transplantation (BLT) or heart-lung transplantation (HLT) have been employed for patients with severe iPAH and may improve survival and quality of life.[178] Benefits from transplantation are limited by a lack of suitable organs[179] (a problem compounded in children), by relatively high rates of early mortality when compared to transplantation for other indications, and by the development of chronic graft dysfunction or bronchiolitis obliterans syndrome.[178,180-182]

The international survival figures following transplantation for iPAH are 65%, 46%, and 25% at 1, 5, and 10 years, respectively.[178] Overall median survival is approximately 4 years with a slight trend to better survival for BLT that does not reach statistical significance. Survival figures are generally worse for pediatric recipients compared to adult recipients. Transplantation is best reserved for selected patients with functional class III or IV who deteriorate despite medical therapy. The timing of listing is complicated by the unpredictability of the period on the waiting list. A recent study found that for those being treated with epoprostenol for at least 3 months, persistence of functional class III or IV and failure of PVR to fall by more than 30% from baseline, as well as presence of right heart failure, were associated with a poor prognosis. The authors recommended that the presence of any of these factors should give rise to consideration of listing for transplantation.[124]

Combined liver and lung or heart-lung transplantation has occasionally been performed for portopulmonary hypertension.[183] Transplantation for PAH in association with scleroderma is not offered by many centers because of generally poor results, and the presence of HIV disease is usually considered an absolute contraindication to transplantation.[184]

PROGNOSIS

Prior to the advent of epoprostenol and the other specific PAH therapies, the prognosis for patients with iPAH had been well defined by several studies including the National Institute of Health (NIH) registry.[125] There was an estimated median survival from presentation of 2.8 years. Prognosis was worse the lower the cardiac index, and the higher the mean pulmonary artery pressure and mean right atrial pressure.

Treatment with epoprostenol has impacted favorably on survival.[124,139] Typical results from adults receiving a continuous epoprostenol infusion have suggested a median survival in excess of 5 years. Similar improvements have been seen in children.[140] Use of first-line bosentan has also been shown to improve survival in a group of patients in WHO functional classes III and IV.[185] In this study, the 2-year survival was 89% compared to a predicted 2-year survival of 57% for historical controls from the NIH registry.

The prognosis for patients with HIV-associated PAH and scleroderma-associated PAH appears to be worse than for iPAH. Survival for patients with Eisenmenger syndrome is superior than that for iPAH.[186]

FUTURE DIRECTIONS

Although the outlook for patients with PAH has improved considerably, PAH is incurable and many patients still die.[1-3,57] Even in those who obtain a good response to therapy, the hemodynamics often will not normalize. Better outcomes are likely to result from further improving the understanding of the disease process. It is still not fully understood which cells initiate the process and why. Further, it remains unclear if, once established, this process is inexorably progressive or if it requires ongoing stimuli with the potential for reversal.[105]

Screening for Disease

On most occasions, PAH is diagnosed late in the disease with most patients having significantly reduced exercise capacity and increased PVR by time of diagnosis. Diagnosing patients earlier in their disease course is an attractive proposition because earlier treatment may be more effective and prevent onset or progression of disease. This has led to the development of screening programs for those at risk, such as patients with scleroderma[187] or family members of affected individuals.[1] The role of exercise echocardiography and other noninvasive screening tests to help establish the disease in asymptomatic or minimally symptomatic individuals requires further evaluation.[188,189] Because of incomplete penetrance, genetic testing of family members, if offered, should include careful and detailed counselling.[1]

Combination Therapies

Current therapies act on three intracellular pathways, nitric oxide, prostacyclin, and endothelin, known to be abnormal in PAH (see Fig. 53-3). A logical extension is to use a combination of two or more of therapies—each acting on a different one of these pathways.[190,191] Such an approach is successful in systemic hypertension, and uncontrolled case series in PAH have suggested that this may be beneficial but further work is required.[192,193]

Emerging and Potential Therapies

There are data suggesting that tackling other pathways known to be involved in the pathogenesis of PAH may be promising. Tackling the serotonin pathway has led to the use of SSRIs, which inhibit serotonin transport. These have been shown to protect against hypoxia-induced pulmonary hypertension.[74]

Inhalation of vasoactive intestinal peptide may be efficacious.[194] Given the importance of platelet aggregation in the pathogenesis of PAH, there is potential benefit in the use of aspirin or other platelet inhibitors as well as other anticoagulants with less toxicity than those currently available.[195,196]

The hydroxy methyl glutaryl-coenzyme-A reductase inhibitors or statins have pleiotropic effects on the vascular wall, including preventing downregulation of endothelial NO synthetase and repressing the vascular smooth muscle proliferative effects in response to PDGF.[197,198] Statins are known to protect against experimental forms of PAH[199] and case reports of their use suggest promise.[200]

Tyrosine kinase is central to the actions of the growth factors PDGF, EGF, and VEGF. The tyrosine kinase inhibitor imatinib (Glivec) reverses two experimental forms of PAH[201] and has been shown to improve exercise capacity and hemodynamics in a patient who was deteriorating despite established therapies.[202] Elastase inhibitors ameliorate experimental forms of PAH[87,203] but clinical studies are required. Additionally, targeting the angiotensin pathway[204] and abnormalities in the K^+ channels may provide useful alternatives,[60] as might inhibitors of the chemokine fractalkine.[88] IL-1 inhibitors reverse PAH in animal models induced by inflammation and warrant further study.[205]

Further, the use of VEGF gene transfer has promise, as do other forms of gene therapy.[60] Increasing data show that bone marrow–derived progenitor cells such as progenitor endothe-

lial cells, fibroblasts, and smooth muscle cells migrate to the pulmonary vasculature and contribute, at least in part, to pulmonary vascular remodeling.[62] Therefore, a future therapeutic option may include stem cell and bone marrow transplantation.[105]

Pharmacogenomics

The relation between genetic and environmental factors in the pathogenesis of PAH is complex and likely not to be the same in all forms of PAH. Understanding which genetic factors are important in an individual may influence which therapies are likely to be more effective; therefore, there is potential application for pharmacogenomics in the future treatment of PAH.

CONCLUSIONS

Despite advances, pulmonary arterial hypertension remains an incurable disease, which is usually diagnosed late in its clinical course. Therefore, it is important to consider the possibility of pulmonary hypertension in any patient presenting with unexplained dyspnea and/or fatigue. There is a potential that screening programs in at-risk groups may allow earlier diagnosis at a time when treatment may be more effective.

When a patient is found to have pulmonary hypertension, it is necessary to establish whether the problem is pulmonary arterial hypertension or another cause (as per the WHO-sanctioned classification), consider possible contributing factors, and assess the prognosis. If pulmonary arterial hypertension is diagnosed, the clinician has several effective treatments available and once treatment is commenced, patients require ongoing careful assessment to determine if there is a need to increase therapy and consider listing for transplantation. With the advent of newer therapeutic strategies, it remains to be seen if pulmonary arterial hypertension can become a chronic manageable problem with prolonged survival and minimal impact on quality of life.

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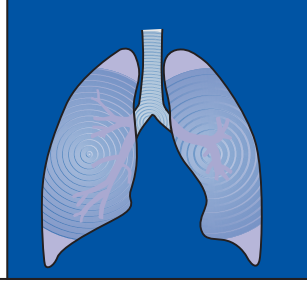


CHAPTER 54 Pulmonary Embolism

Brenda Wittman and Richard Donnerstein

TEACHING POINTS

- Although a pulmonary embolism is unusual in children, the diagnosis is frequently missed.
- Most pediatric patients with a pulmonary embolus will have one or more significant risk factors.
- Although most patients will be symptomatic, clinical findings are generally nonspecific and are frequently attributed to an underlying disease.
- The primary diagnostic imaging modalities are selective pulmonary angiography, ventilation/perfusion scanning, and computed tomography.
- In most cases, the object of therapy is to prevent clot extension and recurrence through the use of anticoagulants. Early treatment is with unfractionated or low molecular weight heparin followed by longer therapy with warfarin or low molecular weight heparin. The use of thrombolytics is controversial.
- If diagnosed and treated early and appropriately, mortality from a pulmonary embolus in children is significantly less than in older individuals.

Pulmonary thromboembolism is defined as pulmonary arterial obstruction by embolism or local thrombus. Although pulmonary emboli may be caused by air, fat, amniotic fluid, tumors, infected masses, or foreign bodies, as well as thrombus, this chapter refers primarily to thromboemboli.

EPIDEMIOLOGY, RISK FACTORS, AND PATHOGENESIS

Although it has been more than 140 years since Löschner described a case of a pulmonary thromboembolism in a 9-year-old child,[1,2] pulmonary embolism is infrequently clinically diagnosed or treated in children.[2-4] The reported incidence of pulmonary embolism in childhood depends on the population investigated, diagnostic techniques, and clinical suspicion. Results from registries, hospital discharge data, and autopsy series differ.[3-9] Excluding autopsy data, studies have suggested an annual incidence of thromboembolic disease of about 0.5 to 0.8 per 100,000 children beyond the neonatal period, with about 10% to 20% of these having a pulmonary embolus.[5,7-9] Hospital discharge data from the United States estimated an incidence of about 0.9 per 100,000 children per year with the rate in African-American children 2.4 times higher than that in European-American children.[6] However, autopsy data suggest that the incidence of pulmonary embolism in infants and children is likely to be underestimated to a significant degree.[3] There is a bimodal age distribution of thromboembolic events with the highest incidence in neonates followed by a peak in adolescence.[5-8,10-14] When pulmonary embolism is specifically investigated, the incidence appears to be significantly higher in select populations such as children with nephrotic syndrome or with long-term central venous lines.[15,16] Although it is a common event in adults, fatal pulmonary embolism is a relatively unusual occurrence in infants and children.[3,17] Nonetheless, autopsy series have suggested that most clinically significant pulmonary emboli in children are not recognized before death.[3]

Virchow noted more than 150 years ago that the risk of thrombosis is increased with stasis of blood flow, injury to the vessel wall, and hypercoagulability of blood.[15,18] Specific processes in younger patients that result in stasis, vascular injury, or hypercoagulability differ from those in adults. High-risk factors in children and adolescents include infection, malignancy, trauma, immobility, pregnancy or use of oral contraceptives, nephrotic syndrome, ventriculoatrial shunts for hydrocephalus, central venous catheters, congenital coagulation disorders, and cardiac diseases—particularly cardiomyopathies or the presence of a right heart bypass procedure such as the Fontan.[2-6,11,15,16,19-25] Although many thromboses in neonates are associated with indwelling central catheters, these are frequently related to other risk factors such as maternal disease, peripartum asphyxia, dehydration, septicemia, trauma, congenital heart disease, or recent surgery.[5,12,26]

Whereas nearly 30% of adults may have no identifiable cause for a thrombosis, significant risk factors are found in almost all children with a thrombosis.[5,7,16,17,21,27] Children and infants in intensive care settings are at particular risk for thromboembolism because of the high incidence of immobility, central venous catheterization, and recent operations.[2,28] Advances in pediatric critical care and more frequent use of central venous lines have increased the incidence of pulmonary embolic disease.[17,29,30] Central venous catheters have become the most important acquired risk factor for thrombotic disease in children and neonates and are the leading cause of death from pulmonary emboli.[7,30] Possible mechanisms for catheter-induced thromboemboli include damage to the vessel wall, infused substances, blood flow obstruction, and thrombogenic catheter materials.[16]

Multiple defects in the hemostatic system have been associated with thromboembolism.[19,31,32] Inherited deficiencies

of the endogenous anticoagulants protein C, protein S, factor V Leiden, and antithrombin III have been observed in some patients with thromboembolism.[13,20,31,32] Numerous other congenital defects of the coagulation system such as activated protein C resistance, dysfibrinogenemia, or prothrombin 20210 mutations have also been identified.[11,13,16,20,32] Increased levels of lipoprotein(a) and homocysteine may also be risk factors.[13,20,32] Thrombophilia may also be acquired from conditions such as systemic lupus erythematosus, antiphospholipid syndrome, or nephrotic syndrome.[20,31,32] Screening is indicated for children with spontaneous thrombotic events where a significant proportion have been found to have prothrombotic disorders but remains controversial in the presence of other significant risk factors.[11,13,18,20,21,31,32] Patients with homozygote or multiple inherited disorders are at significantly higher risk.[13,20]

As in adults, pulmonary embolism in children is frequently associated with a deep vein thrombosis. The anatomic sites of venous thrombi associated with pulmonary emboli in children differ from those in adults. Similar to adults, the child described by Löschner had a symptomatic thrombus of a lower extremity.[1,2] However, when compared with thrombi in adults, venous thrombi in children are often asymptomatic and are less likely to involve the veins of the pelvis or lower extremities and more likely to involve the upper venous system.[1,7,12,27,30]

An acute increase in pulmonary vascular resistance associated with right-ventricular failure and shock is the principal cause of death after pulmonary embolism.[15] In the absence of preexisting pulmonary hypertension, mean pulmonary pressure increases approximately in proportion to the degree of obstruction of the pulmonary arteries.[33] Because of the limited ability of the normal right ventricle to respond to an acute increase in afterload, a right-ventricular systolic pressure greater than 60 mm Hg, or a mean pulmonary artery pressure of 30 to 40 mm Hg, represents severe pulmonary artery hypertension.[33-35] However, patients with underlying chronic pulmonary hypertension may generate right-ventricular pressures near or greater than systemic pressures.[33,35] Although vasoactive substances and baroreceptor reflexes may affect pulmonary vascular resistance after pulmonary embolism, vascular obstruction by the embolus is probably the major cause of the pulmonary hypertension.[33] Inflammatory mediators may alter capillary permeability and surfactant function, which can significantly compromise pulmonary function.[17,25]

Acute changes in ventilation and perfusion result in abnormalities of gas exchange.[22,33,36] Following a pulmonary embolus there is a redistribution of blood flow from obstructed to nonobstructed lung units. An increase in alveolar dead space, resulting from a ventilated but poorly perfused lung, can affect CO_2 elimination.[33,36] However, except for the most severe pulmonary embolism, hyperventilation compensates for this increased dead space, and many patients are hypocarbic.[22,33,36,37] This hyperventilation and resulting hypocapnia are rarely eliminated by the correction of hypoxemia with supplemental oxygen, suggesting that it is a reflex response of proprioceptors or chemoreceptors to stimuli other than oxygen or carbon dioxide.[33] Abnormalities of ventilation and perfusion, right-to-left shunting through a patent foramen ovale, right ventricular failure, and decreased mixed venous saturation caused by a low cardiac output may all contribute to an abnormally low PaO_2.[22,33,36,38] When resulting atelectasis and pulmonary edema contribute to hypoxemia caused by a pulmonary embolus, supplemental oxygen or positive airway pressure may help alleviate the hypoxemia.[33,36,38] Arterial blood gas abnormalities such as hypoxemia or hypocarbia may not be as prominent in adolescents and young adults as they are in older adults.[22] This is probably because of the more intact pulmonary bed and cardiopulmonary reserve in most younger patients.[15,22]

Pulmonary infarction is unusual following a pulmonary embolus[33]—probably because of multiple sources of oxygen supply to the lung tissue. When infarction does occur, it may be due to obstruction of distal pulmonary arteries and hemorrhage into the airways.[33]

CLINICAL FEATURES

Most small pulmonary emboli are asymptomatic.[15] The presentation of a symptomatic pulmonary embolus may often be subtle and nonspecific, and this is probably especially true for younger patients.[18,22,25,27] Because most children will have significant risk factors, the presence of a primary disease may further complicate the diagnosis.[17,18,27,30] For many reasons, a diagnosis of pulmonary embolism is frequently delayed in children.[18,23] Clinical diagnosis may be particularly difficult in infants because underlying respiratory disease is common.[21] The most common symptoms of pulmonary embolism, such as chest pain (pleuritic or nonpleuritic), shortness of breath, cough, tachycardia, hemoptysis, and diaphoresis, are nonspecific and may occur in a variety of disease states—including acute respiratory infections.[3,4,18,20,22,28] Moreover, the diagnosis of pulmonary embolism is often masked by the underlying disease, or concomitant sedation, muscle relaxation, or artificial ventilation. Although patients may present with acute right heart failure, hypotension or even sudden death,[27] signs of pulmonary or cardiac dysfunction are less common in younger patients than in adults.[22] Nonetheless, data from two large registries have shown that almost all children with a significant pulmonary embolus will be symptomatic.[5,17] Chest pain is the most common presenting complaint in teenagers.[4,18] The nonspecificity of the signs and symptoms makes diagnosing a pulmonary embolism solely on clinical grounds hazardous.[4] Nonetheless, this diagnosis should be considered in the evaluation of unexplained shock, pulmonary hypertension, respiratory insufficiency, or other pulmonary symptoms in children—particularly in the presence of risk factors.

DIAGNOSIS

Prompt diagnosis and therapy can significantly reduce mortality in patients with a pulmonary embolus. Unfortunately, because symptoms are frequently nonspecific, clinical diagnosis is not reliable and this diagnosis is often not considered in children. The relatively low incidence of pulmonary embolism and problems of long-term anticoagulation in the pediatric age group make accurate diagnosis essential.[17] Chest radiographs and electrocardiograms are often normal in young patients with a pulmonary embolus, and abnormalities, if present, are usually nonspecific.[15,17,22,25,27] Although most

patients will have some degree of hypoxemia, a significant proportion will have a normal $\mathbf{PaO_2}$ and the alveolar-arterial oxygen tension difference, $P(A\text{-}a)O_2$, is a more sensitive indicator of problems with gas exchange.[22,37,39]

D-Dimer quantification is a sensitive technique for detecting conditions in which thrombus is formed.[25,28,40] Although it is highly sensitive for excluding a pulmonary thromboembolic event in adults with a low pretest probability, a positive test lacks specificity and may not be helpful.[15,40] This is particularly true in children because D-dimer levels may be elevated owing to their underlying disease.[27] In children considered at high-risk, a negative result should not alter the decision to pursue further evaluation.[17,28]

Much of the information regarding imaging modalities available for the diagnosis of pulmonary emboli in children has been derived from adult experience. Currently available techniques include pulmonary angiography, ventilation/perfusion ($\dot{V}/\dot{Q}$) scans, computed tomography (CT), magnetic resonance imaging (MR) and echocardiography.[16,20]

Selective pulmonary angiography remains the standard and should be considered in children and adolescents with a suspected pulmonary embolus (Fig. 54-1).[15,17,18,20,21,25,27,40] Nonetheless, because of the relative invasive nature and risks of pulmonary angiography, other imaging modalities are now more frequently used.

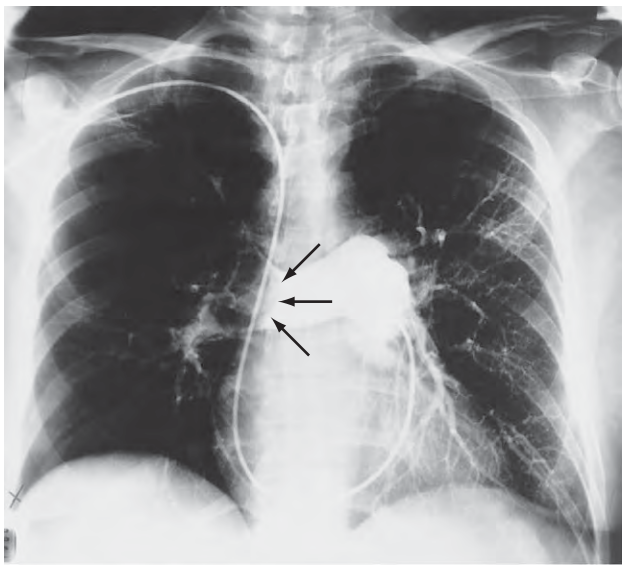
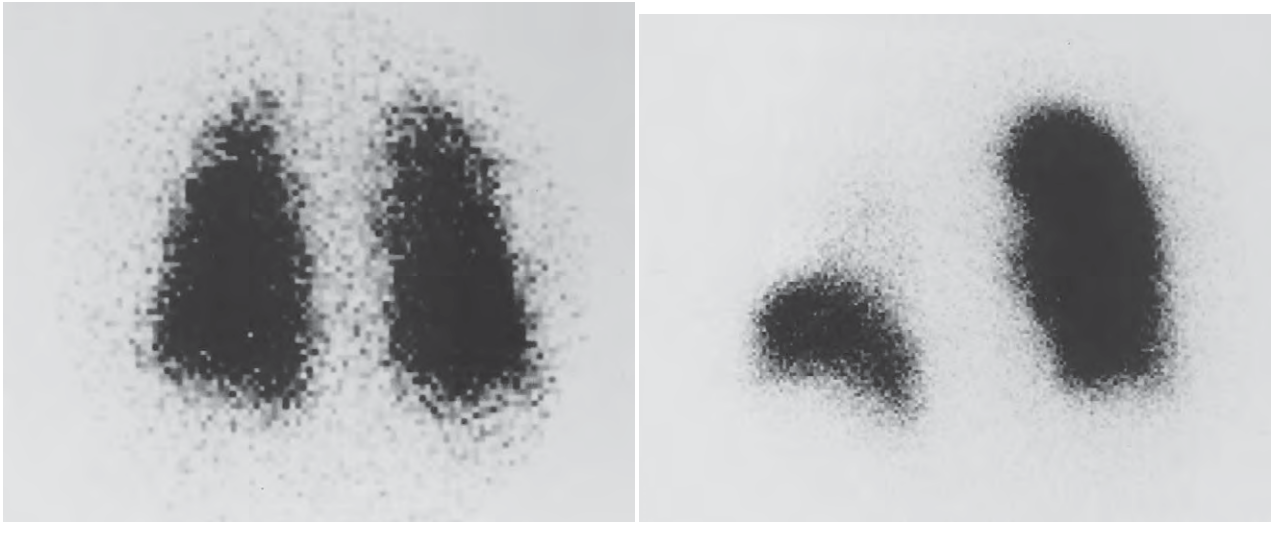


Figure 54-1 Pulmonary angiography in a patient with pulmonary embolism. A large filling defect is seen in the proximal right pulmonary artery (*arrows*). Smaller filling defects are seen in branches of the left pulmonary artery.

In the presence of obstructed pulmonary vessels caused by pulmonary embolism, **ventilation and perfusion radionuclide studies** would be expected to show mismatched defects with areas of absent or abnormal pulmonary perfusion associated with normal ventilation (Fig. 54-2). Whereas a high-probability scan strongly suggests pulmonary embolism, a significant portion of adult patients with proven pulmonary embolism will not have a high-probability scan.[15,40] Patients with normal scans rarely have a clinically significant pulmonary embolus.[15] However, the majority of scans are nondiagnostic.[17,27,40] Although a matched defect (abnormal ventilation and perfusion) suggests other pulmonary disease, a pulmonary embolus cannot be excluded.[2] These studies are frequently used in children[15,17,18,20,21,27] and may be highly suggestive of the diagnosis. However, scans are often not definitive for the diagnosis of pulmonary embolism,[17,27] and other imaging methods may be necessary.

Magnetic resonance imaging and **computed tomography** may detect significant emboli in the central pulmonary arteries.[15,17,21,27] Modern multidetector CT scanners have significantly improved diagnostic capability when compared to earlier generations, and spiral CT pulmonary angiography is now commonly used as the initial imaging modality to diagnose pulmonary thromboemboli (Fig. 54-3) in adults[15,40,41] as well as children.[17,18,27] In adults, they yield fewer nondiagnostic results when compared to $\dot{V}/\dot{Q}$ scans.[15,27]



A B

Figure 54-2 Ventilation and perfusion scans from a patient with pulmonary embolism. **A,** Posterior view of the ventilation scan shows normal xenon-133 distribution in both lungs. **B,** Posterior view of the perfusion scan demonstrates markedly decreased perfusion of the left upper lobe with smaller filling defects of the right lung.

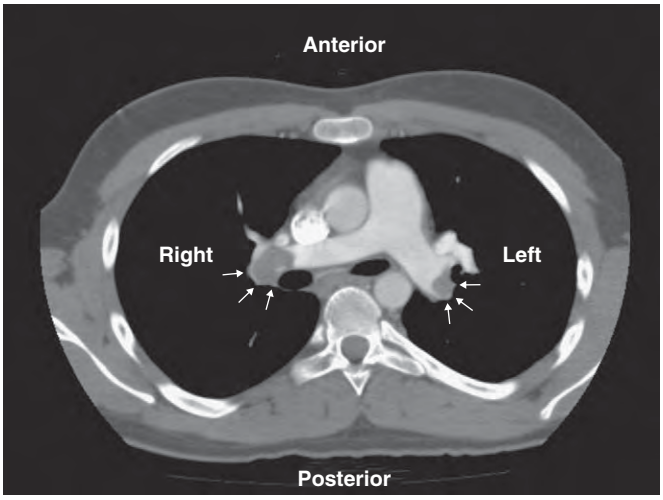


Figure 54-3 Computed tomographic angiography in a patient with pulmonary embolism. Large thrombi are seen in both the right and left pulmonary arteries.

Disadvantages include the need for contrast agents requiring satisfactory renal function, significant radiation exposure,[15,27] and insensitivity to small, subsegmental thrombi.[17,27,40] Although it is considered reasonable to withhold treatment in adults with a negative spiral CT scan, it is unclear whether this is also true for children, especially in a high-risk patient.[15,17]

Magnetic resonance angiography has also been shown to be an effective imaging modality with high specificity and reasonable sensitivity for the diagnosis of a pulmonary embolus.[15,27] Although it may be insensitive to small emboli, it has the advantages of being noninvasive and requiring no radiation.[27] Disadvantages include long imaging times and difficulties in obtaining the study in some acutely ill patients. It is likely that continued advances in computed tomography and magnetic resonance imaging will further improve their usefulness for diagnosing pulmonary emboli in the pediatric population.[25]

Transthoracic **echocardiography** has poor sensitivity for diagnosing pulmonary embolism.[42,43] However, this technique is useful for detecting signs of acute right-ventricular overload or failure, and many patients with a significant pulmonary embolus will have detectable echocardiographic abnormalities.[18,42,44,45] Even if pulmonary embolism is diagnosed by other means, echocardiography should be performed to assess right-sided hemodynamics.[44-46] In adults, significant hemodynamic changes suggest obliteration of more than one third the pulmonary arterial bed.[25,35,42,44] When acute right-ventricular afterload is excessive, right-ventricular failure will ensue with passive venous congestion and a decrease in forward cardiac output. Echocardiography may help identify those patients with significant hemodynamic compromise before the onset of clinically apparent cardiogenic shock and assist in stratifying risk and assessing response to therapy.[42,45-47] Two-dimensional echocardiographic findings that suggest a pulmonary embolus include dilation or hypokinesis of the right ventricle, abnormal ventricular septal motion, or decreased left ventricular diastolic size.[42] Thrombi within the right-sided cardiac structures such as the right atrium, right ventricle, or proximal pulmonary arteries, as well as the venae cavae, may also be detected.[18,34,35]

Doppler echocardiography can accurately estimate pulmonary pressures in the presence of tricuspid or pulmonary regurgitation.[34,35] Many normal individuals and most patients with acute pulmonary embolism and right-ventricular failure will have some degree of tricuspid regurgitation. In the absence of structural heart abnormalities, flow velocities of tricuspid regurgitation can be used to estimate systolic right-ventricular, and therefore, systolic pulmonary artery pressures, whereas pulmonary regurgitation flow velocities can be used to estimate diastolic pulmonary artery pressures.[34] Color-flow Doppler or contrast echocardiography can be used to assess for the presence of a patent foramen ovale as a source of right-to-left shunting.[42]

TREATMENT

Mortality from pulmonary emboli can be significantly reduced if promptly diagnosed and treated.[20] Unfortunately, there are no large randomized controlled pediatric trials for thrombolytic and anticoagulant agents, and most recommendations for children have been extrapolated from adult studies.[18,21,28,48-52] Because the coagulation and fibrinolytic systems are age-dependent, infants and children respond to anticoagulation and thrombolytic agents differently than adults and regimens should consider both weight and age.[7,11,17,52-54] However, definitive protocols for treatment of pulmonary emboli in children will almost certainly lag behind those of adults because of the scarcity of pediatric patients diagnosed and treated for pulmonary embolism.

Because a major objective of treatment for pulmonary embolism is to prevent clot extension and recurrent emboli, anticoagulation is used in most patients.[16,18,19,21,55] When possible, a pediatric hematologist with experience in treating thromboemboli should be involved in the care of these patients.[48,52,55] **Unfractionated heparin** (UFH) has the advantage of a short half life and is easily reversible if bleeding develops or if the patient needs an emergent invasive procedure.[52,55] UFH may be started with an initial bolus of 75 to 100 U/kg over 10 minutes followed by continuous infusion at a rate of 20 U/kg/hour for children over 1 month of age and 28 U/kg/hour if younger than 1 month of age.[14,19,21,52,55] Premature infants and neonates as well as patients with deficiency of antithrombin III may require even higher doses to achieve adequate anticoagulation.[55] The infusion rate should be adjusted to maintain an anti-Xa level of 0.35 to 0.70 or a PTT prolongation to two to three times the baseline value.[14,17,21,52,55] Heparin can be rapidly reversed by administering protamine sulfate.[55]

Pediatric hematologists are using **low molecular weight heparin** (LMWH) more frequently because it has the advantages of subcutaneous administration, fewer adverse effects than unfractionated heparin,[19] and less frequent monitoring of levels.[11,15,17,21,28,52] For enoxaparin, a suggested regimen for children greater than 1 year of age is 1 to 1.25 mg/kg/dose subcutaneously every 12 hours[14,17,19-21,25,52,55] and for infants 1 to 12 months of age 1.5 mg/kg/dose subcutaneously every 12 hours.[14,19-21,25,52,55] Neonates and infants younger than 1 month of age may require initial doses as high as 1.65 mg/kg/dose.[55] When using LMWH, a therapeutic goal for anti-

Xa is 0.5 to 1.0 U/mL in a sample taken 4 to 6 hours after injection.[14,17,19,25,28,52]

When a patient has achieved adequate anticoagulation with heparin, oral therapy with **warfarin** is subsequently started if not contraindicated.[17,19,52,55] The initial dose for children is 0.2 mg/kg/day and then adjusted according to published nomograms.[52] Warfarin therapy should be titrated to obtain an international normalized ratio (INR) of approximately 2.0 to 3.0.[11,19-21,25,28,52] However, warfarin dosages may vary widely between patients and may be difficult to manage in infants and young children. Because of dietary changes, changes in physiologic levels of vitamin K–dependent proteins, and frequent changes in other medications, INR must be monitored closely.[21,25,52,56] Warfarin therapy should overlap therapy with UFH or LMWH, which can then be discontinued when the INR is therapeutic.[14,52] Anticoagulation is generally continued for at least 3 to 6 months and possibly longer if the underlying cause is still present.[17,19,25,52,55] Shorter times may be appropriate for neonates.[52] Long-term LMWH may be used in lieu of warfarin and, for practical reasons, may be easier to manage in neonates and young children.[11,14,28,52]

Although still investigational for pediatric patients, three thrombolytic agents (urokinase, streptokinase, and recombinant tissue plasminogen activator) have been used to dissolve vascular clots and pulmonary emboli in children.[15,19,25,48,51,52,57] Although these agents have been shown to facilitate clot lysis, their use has been limited because of bleeding and other complications.[44,49,51,52,58,59] Short-term results using thrombolytics in children and adults have demonstrated rapid dissolution of the embolus and improvement of hemodynamics.[58,60,61] However, studies in adults have not found a significant long-term difference between the outcome of patients routinely treated with thrombolytic agents or heparin for pulmonary embolism.[44,59,62-65] Except for severe pulmonary embolism with hemodynamic compromise, these results have discouraged the use of these agents for routine therapy in patients with pulmonary emboli and decisions to use it should be individualized.[18,28,44,50-52,60-62,66] When it is thought that potential benefits of thrombolytics outweigh risks, human recombinant tissue plasminogen activator (rt-PA) has become the most common thrombolytic agent used in children.[21,25,28,50,52,54,58,60,67] Suggested infusion rates for rt-PA range from 0.1 to 0.6 mg/kg/hour over a period of 6 hours,[25,50-52,60] but recent studies have suggested that lower doses (0.03 to 0.1 mg/kg/hour for 24 to 96 hours) may be effective in children and have fewer complications than standard doses.[25,51,55,58,60,67] Directed thrombolytic therapy through a pulmonary artery catheter does not appear to be safer or more effective than delivery through a peripheral vein.[52] Concomitant anticoagulation with low-dose unfractionated heparin has been used in some studies, and the patients should be closely monitored and receive replacements of platelets, fibrinogen, or other clotting factors as needed.[51,55,58,60]

Embolectomy can be considered in the presence of a massive pulmonary embolism if thrombolytic therapy is contraindicated, if severe hemodynamic compromise limits the time for response to thrombolytic therapy, or if the patient shows hemodynamic deterioration despite thrombolytic therapy.[25,65,68] Both surgical[15,25,69-73] and transcatheter[15,25,72,74,75] techniques have been reported in infants and children.

Venous filters have been used in children at risk for a pulmonary embolus if their vessels are large enough to accommodate the device.[15,19,76,77] Depending on associated risk factors, these can be positioned in either the inferior or superior vena cava.[66]

CLINICAL COURSE AND PROGNOSIS

The clinical course in a child with a pulmonary embolus is frequently related to the underlying disease and treatment as well as to the embolus itself. Although some evidence is accumulating regarding overall mortality,[5,7,8,29] at this time the long-term risks of complications such as recurrence and pulmonary hypertension remain unknown.[5,8,15,25] The lung has an effective fibrinolytic system and most pulmonary emboli will spontaneously resolve.[46,78] Because of their better underlying cardiopulmonary fitness, when properly diagnosed and treated, mortality from pulmonary embolism in children and younger adults appears to be significantly lower than in older individuals.[7,17,22]

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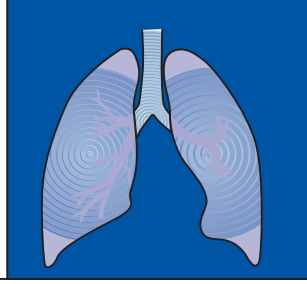

CHAPTER 55 The Global Burden of Asthma

Paulo Márcio Condessa Pitrez, Renato T. Stein, and Fernando D. Martinez

TEACHING POINTS

- Childhood asthma prevalence seems to have reached a plateau after 2 decades of persistent increases.
- Asthma affects children in both developed and developing countries, but the predominant etiology seems to be different in the two areas: atopic asthma is more prevalent in school children of better-off countries, whereas nonatopic asthma is more prevalent in poorer societies.

Asthma is a chronic airway disease occurring at all ages worldwide—frequently beginning in childhood. The prevalence has increased over the last 4 decades in some countries and there are very few places in the world untouched by this illness. It is currently the most common chronic disorder in children. However, it has been demonstrated that the distribution of childhood asthma varies significantly between countries (2% to 33%).[1] Given that asthma is a heterogeneous condition with different phenotypes, its complex genetic-environmental interactions explain the particular expression in different subjects and populations. Despite its uneven distribution, asthma still poses a major global health problem, resulting in extraordinarily high morbidity.[1,2]

It is estimated that around 300 million people currently suffer from asthma in the world. It has been demonstrated that the prevalence of asthma increases as populations become more urbanized and developed.[3,4] This illness brings a significant burden on patients, families, health systems, and society in general. In developing countries, regardless of different prevalence rates, the burden of asthma may be even more serious because of economic, social, and educational limitations associated with poverty and inadequate health care facilities.

The assessment of the impact or burden of a disease on society is essential to improve quality of life, decrease mortality, and reduce costs. This burden can be estimated using parameters such as prevalence, severity/mortality, medical visits, treatment regimens, quality of life, and costs. A new approach was recently developed using a standard unit, called the disability-adjusted life year (DALY). DALY assesses the years of healthy life lost because of a disease—combining information about morbidity and mortality in terms of healthy years lost. World asthma accounts for approximately 1% of all DALYs lost and it is estimated to be about 15 million/year. Moreover, the number of DALYs lost due to asthma is similar to that for diabetes, liver cirrhosis, or schizophrenia.[5]

PREVALENCE

The prevalence of asthma has increased steadily over the last decades. Considering that these changes in prevalence have occurred concomitantly with massive urbanization worldwide, it is estimated that there will be an additional 100 million people with this illness by 2025.[4] There is no clear or unique explanation for these marked increases in prevalence, occurring in a relatively brief period of time. English-speaking countries have the highest prevalence of asthma-related symptoms, ranging between 17% and 30% in the United Kingdom, New Zealand, and Australia. The general trend for asthma to be more prevalent in such affluent nations has suggested the so-called *hygiene hypothesis*, which postulates that the degree of exposure to microbial products, especially in early life, is a major determinant of the likelihood of developing allergies and asthma.[2] It is clear, however, that other factors must be at play, because the ISAAC study has also shown that some developing countries in Latin America have a high prevalence of asthma-related symptoms.[1] Of interest is the fact that, in these countries, the most prevalent form of asthma is one not associated with sensitization to aeroallergens, suggesting that the factors that have determined the observed increases in the prevalence of asthma are heterogeneous and have an impact beyond the presence of atopy.

Despite the fact that the frequency of asthma appears to have peaked in some developed countries,[6,7] asthma continues to be a major health problem in both the developed and developing nations,[8] and addressing its impact on the lives and well-being of children worldwide is a high public health priority.

MORTALITY AND SEVERITY

Data on asthma mortality is difficult to assess and is often unreliable, especially in areas where the health care system is less well organized. Even so, it is estimated that 250,000 people die from asthma every year worldwide. In Europe and the United States, asthma mortality seems to be slightly decreasing over the last 2 decades.[9,10] However, even considering the relative lower prevalence, mortality is higher in developing countries, where diagnosis is not properly carried out and therapy is not widely available.[4] In Brazil, for

example, mortality has been estimated to be 2200 deaths per year over a period of 5 years, which is a much higher frequency when compared with data from more affluent communities. The highest mortality rates in Latin America were found in Mexico and Uruguay.[11,12]

In children from developed countries, asthma often presents racial disparities and a disproportionate burden among the poor. In the United States, black children, and especially those living in inner cities, have a higher risk of developing asthma and visiting emergency departments because of this illness.[13] Moreover, Puerto Rican children have a higher prevalence of lifetime asthma (26%) and recent asthma attacks (12%) when compared with non-Hispanic blacks (16% and 7%, respectively), non-Hispanic whites (13% and 6%, respectively) and Mexican-American children (10% and 4%, respectively).[14] The factors that determine these differences in prevalence and severity between children with distinct ethnic backgrounds from the same population are not well understood. Nevertheless, recent interventional studies to decrease exposure to allergens and other indoor contaminants in inner cities in the United States have suggested that decreasing these exposures may be an effective therapeutic strategy to lessen the burden of disease in these communities.[15]

Hospitalizations are not uncommon in children with asthma. Admissions are a marker of the quality of a health care system. Admission rates for asthma are higher in infants and toddlers. On the other hand, the length of hospital stay increases with age. In developing countries, asthma hospitalization rates and length of stay are higher than in more affluent communities.[16] In Finland, the implementation of a national asthma treatment program has decreased the number of hospitalizations.[17]

Visits to an emergency department (ED) are common in children regardless of asthma severity. In a 2-year survey (2000 to 2001), 67% of acute asthma in EDs occurred in children younger than 15 years.[18] The highest rates of ED visits for asthma in children are among those aged between 1 and 4 years. The peak of visits to EDs occurs in winter. The number of visits to EDs is a good marker of failure of an asthma prevention strategy in a population.

IMPACT ON THE PATIENT AND THE FAMILY

Quality of life is a very important issue in any disease process. Asthma in childhood has a significant impact on the lifestyle of patients and their families. Several factors are directly associated with quality of life. Fear, stress, anxiety, and depression are common psychological features associated with asthma among children. Missed school days, interference with social activities, unscheduled visits to physicians and visits to EDs also have a strong impact on family life. Nearly 50% of the children with asthma report missing one half day or more of school in the last month and 30% reported one or more ED visits in the last year for asthma-like symptoms.[19] Sleeping difficulties are also common and occur in nearly 50% of children with asthma. Tobacco use and alcohol consumption can be higher among asthmatic adolescents.[20] Allergic rhinitis and passive smoking are preventable and treatable factors that are highly prevalent among asthmatics, thereby increasing morbidity.

Questionnaires may be useful to measure quality of life in chronic diseases. Based on clinical experience with the Asthma Quality of Life Questionnaire (AQLQ), Juniper and colleagues developed the Pediatric Asthma Quality of Life Questionnaire (PAQLQ).[21] This questionnaire was developed as a tool to evaluate quality of life in children with asthma and was validated in many countries.[22-25] Further studies comparing quality of life of asthma in childhood are required to pursue better strategies of treatment and prevention of disease.

The uncertainty and unfamiliarity of many characteristics of asthma in children brings significant anxiety and apprehension to the family. Therefore, asthma education must be a continuous process and should be emphasized in every medical consultation. The need for long-term prophylactic treatment, fear of severe attacks, and doubts about adverse effects of medications are some of the major issues that should be constantly stressed in family asthma education.

The cost of treatment is an important issue to be considered in asthma management, and this is especially true among nonaffluent populations for whom available resources are limited. Aggressive policies providing free access to prophylactic treatment for every child with moderate to severe asthma would have a significant impact on the patient's and family's quality of life.

COSTS TO SOCIETY

The economic costs of asthma to society are substantial. Between 1990 to 2000, costs for asthma care increased approximately 50% in the United States, with inpatient costs declining and outpatient costs, especially for asthma medications, increasing. In 1998, the costs of asthma were estimated to be 12.7 billion dollars.[3,26] The financial burden of asthma is both direct in health care costs and indirect in personal burden for the patient and family. Medical consultations, hospitalizations, and prescribed medications are some of the most important direct costs to the society. Time lost from school or work and premature death are very important indirect costs that play a role in the burden of disease. Low quality of life because of asthma is very difficult to measure, but the cost is certainly substantial for any population

HOW TO REDUCE THE BURDEN OF DISEASE

There are different strategies that can be implemented to reduce the impact of the disease in both an individual and on a community level. An approach taken by many health-related institutions is the organization of international or national-based guidelines on the management of asthma for both adults and children. These widely publicized guidelines, such as GINA, the NHLBI Asthma Guidelines, and the British Thoracic Society guidelines, are probably the ones with the greatest public impact.[27-29] Many other local initiatives have been taken in the same direction, but the positive impact of these publications on the burden of disease is not clearly established.

National or local programs have been shown to have some impact on asthma burden, but this impact has been surprisingly less than expected. Despite the fact that the guidelines have been widely publicized, outpatient management of

asthma remains inadequate in most locales.[30] This situation may be the consequence of limited access of the guidelines by physicians or because of their complex format. It seems that education plays a key role in reducing the impact of disease, so the greatest challenge is to produce simplified guidelines that are accessible in different locales, either by physicians or patients and their families. The best strategy seems to be the development of partnerships between health care providers and local communities, in which the need to prescribe and use pharmacologic and environmental preventive measures is not imposed but understood and encouraged. An example of such successful partnerships has been the dramatic decreases in the prevalence of smoking in communities where this collaborative approach has been adopted.

Some studies have shown that low-income urban minority neighborhoods present the highest rates of asthma hospitalizations.[31,32] Many factors may contribute to the correlation between proportion of low-income minority populations in a neighborhood and high rates of asthma hospitalizations. However, asthma hospitalization rates may not necessarily reflect asthma prevalence. It is possible that higher rates of hospitalizations in neighborhoods of low socioeconomic status with predominantly low-income minority residents can result from a high proportion of individuals with severe disease, poor levels of education, mistrust of the health care system, and/or lack of access to preventive medical care. It is not known which factors are the strongest contributors to the urban asthma epidemic. Race/ethnicity, income, and local environmental factors have been associated with these observed high asthma levels, especially in urban areas, for the past 3 decades.[33,34]

Other than possible environmental exposures, perhaps more frequently in low-income communities, differences in health insurance status, access to proper preventive care, and medication utilization/availability may contribute to increased asthma hospitalizations.[35] There are valid data showing that low-income minorities are more likely to obtain asthma care from EDs, a place where they are less likely to receive asthma education on prevention techniques.[36]

There is strong evidence indicating that community-based education for asthma management could have a strong impact in lowering asthma morbidity. Two major needs today are the development of locally adapted, simple management guidelines and access to free preventive medications for all children with asthma. Given the impact that such measures could have in reducing suffering among children worldwide, the very limited accessibility to these resources in most communities is morally unacceptable. Making these resources widely available is, therefore, a high priority for all those who care for children with asthma.

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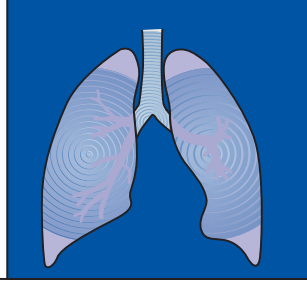

CHAPTER 56 Genes, Environment, and Their Interactions

Peter N. Le Souëf

TEACHING POINTS

- The environmental factors that caused the increase in asthma in the late 20th century are still largely unknown.
- Known or suspected gene by environment interactions have been reported and these can be short-, medium- or long-term.
- Host response to an acute respiratory virus infection is genetically determined and may be impaired in those with atopic genotypes.
- Host response to vaccines is genetically determined and impaired in those with pro-Th2 alleles.
- Exposure to farm animals, cats, and dogs and the associated reduction in susceptibility to asthma is genetically determined.
- Adverse effects of environmental tobacco smoke exposure are influenced by genetic factors, particularly in the genes for glutathione-S-transferase.
- Long-term interactions may act through natural selection—tropical parasitic infections may be critical in these interactions.
- With regard to finding new approaches to the treatment or prevention of asthma, the most promising areas of gene by environment research are exposure to acute viral respiratory infection, animals, and tobacco smoke exposure.
- Nearly one half the world's population live in the tropics and owing to long-term adaptation of the immune system to helminthic infections could be at a much greater risk of developing asthma than those from more temperate climates.

Over the last 10 to 20 years, rapid advances in DNA technologies have allowed an exponential expansion in the number and variety of studies investigating the genetics of disease. With respect to respiratory disease, the great majority of studies have been directed at asthma, chronic obstructive pulmonary disease (COPD), and cystic fibrosis. Cystic fibrosis is very different from asthma and COPD in that it is a single gene defect disease and its genetics are covered in Chapter 61. Asthma and COPD are polygenic diseases with many genes contributing to their susceptibility. As an example of a polygenic disease, asthma is the most instructive, partly because the investigations into its genetic background have been carried out on a longer time scale and on a much greater scope than in COPD. This chapter will focus on the genetics of asthma because this best illustrates the importance of interactions between genes and environment with respect to genetics and respiratory disease.

CURRENT KNOWLEDGE OF GENETIC INFLUENCES ON RESPIRATORY DISEASE

Since the first studies of the genetics of asthma that utilized DNA analysis started nearly 20 years ago, steady progress has been made in understanding the genetics of asthma and more recently COPD. During this period, several findings with respect to asthma have become well established (Box 56-1). To summarize Box 56-1, after 20 years of research into the genetics of asthma, studies have established that asthma is a polygenic disease, with no major susceptibility genes discovered to date, and also thus far asthma genetics studies have made no major contribution to the understanding of the mechanisms of asthma. This situation is a long way from the optimistic predictions made when these studies started. There are several reasons for the slow progress; perhaps the most important of these is the very strong relation between asthma, genes, and environment. The important role of the environment in this triad has been clarified recently, because without an environmental influence, a genetic susceptibility will not be present.[1] A further factor complicating analyses of gene by environment interactions is the paradoxical nature of some of the relationships, with a given allele showing an association with a low level of an environmental load in one region or population, but with the other allele in another population.[2] Another complex relation between an allele and an outcome involves age. For the association between the CD14 C-159T genotype, atopy, and age, one allele was a susceptibility allele for atopy in children but only within a particular age range.[3]

CURRENT KNOWLEDGE OF ENVIRONMENTAL INFLUENCES ON RESPIRATORY DISEASE

Before considering gene by environment interactions, the current state of knowledge of environmental influences on asthma should be taken into account. This subject has been summarized in Chapter 2. Many environmental factors are now known to significantly affect risk factors for the development of asthma. These include: the protective effects of exposure to animals, including farm animals, cats, and dogs,[4,5] respiratory infections in early life;[6] and day care in infancy.[7]

BOX 56-1 Major Findings of Asthma Genetics Studies to Date

Many genes have variations that contribute to the susceptibility to asthma.
Many other genes have variations that affect the severity of asthma.
No single gene provides a substantial contribution to genetic susceptibility or severity, and each of the known genes provides less than 10% of a population's asthma susceptibility.
No genotypes have been found that are consistently related to an asthma phenotype in all populations studied.
Most genes and genotypes for which there is evidence of involvement in asthma were studied because their known function suggested they would be candidate genes for asthma.
In genome-wide screening studies, only a few new genes with a recognized involvement in asthma genetics have been found to date.
Several genotypes have been well substantiated in a broad range of populations and are undoubtedly important in increasing susceptibility.
Asthma genetics studies done to date have led to some important gains in knowledge of asthma but no major advances into its etiology.

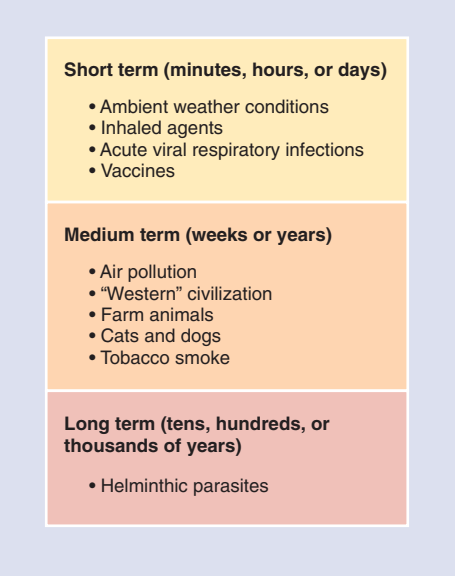

Figure 56-1 Gene by environment interactions. Evidence has been reported for the following short-, medium- and long-term interactions between genes and environment

They also include the increased risk of asthma conferred by tobacco products.[8]

However, despite this valuable body of knowledge, the most important environmental influences are still unknown. This is well demonstrated by the complete lack of a plausible hypothesis for the environmental factors responsible for the increase in asthma seen in the 1980s and 1990s and also perhaps for the decrease in asthma rates and severity seen since the turn of the millennium.[9-11] Part of the decrease may be due to better treatment,[11] but this would appear unlikely to be the major cause of the decrease in some locations, as in these the use of asthma medications decreased at the same time as the decrease in asthma prevalence.[9] The powerful influence of the environment is also shown by the substantial differences in wheezing rates in children between the developing and developed world.[12] A further excellent example of highly differing environments acting to affect asthma-related phenotypes in populations with substantially the same ethnic background is the Karelian study[13] in which children on the Finnish side of the border had an atopy prevalence that was four times higher than that of children on the Russian side. To summarize the effects of environment on asthma susceptibility, several risk factors have been identified, but the most important factors are still unknown.

DIFFICULTIES IMPOSED BY THE POOR CURRENT STATE OF KNOWLEDGE OF ENVIRONMENTAL INFLUENCES ON ASTHMA

This profound lack of knowledge on the most critical and powerful environmental factors has almost certainly impaired the ability of researchers to gain good insight into gene by environment interactions. Indeed, the broad lack of reproducibility of findings between different populations for asthma genetics studies is plausibly related to variations in these factors between different populations. A lack of appreciation of this issue was evident in early asthma genetics studies in which the absence of a significant relation between a linkage site or genotype and an asthma-related phenotype was held up as evidence that the site or genotype had "failed" to influence asthma,[14] and this view persists in some current studies.[15] An alternative, and in many cases more plausible, explanation is that the absence of a relation between a genotype and an asthma phenotype is due to the absence of the necessary environmental factor. Thus, the presence of powerful, unknown, and highly variable environmental influences on asthma susceptibility may be behind the lack of reproducibility of gene by environment findings. An opposing view that there are many type one statistical errors in studies reporting positive associations between genotype and asthma phenotype is also, however, highly likely to be true, as is the likelihood that many negative studies have type two statistical errors.

GENE-ENVIRONMENT INTERACTIONS—CURRENT KNOWLEDGE

Despite these major unsolved methodological issues, there is now good evidence for specific polymorphisms and haplotypes affecting asthma susceptibility, and the rest of this chapter will concentrate on this rapidly evolving area of research. In describing current knowledge on this issue, three areas will be discussed. These are the short-, medium-, and long-term interactions between genetics and environment (Fig. 56-1). In this context, *short-term* is the immediate or acute effects of an environmental exposure, *medium-term* refers to exposures that take place over days, weeks, or years, and *long-term* refers to environmental influences that affect

populations over tens, hundreds, thousands, or tens of thousands of years. In Chapter 2, the need to consider environmental influences as more than simply the external physical environment was argued. In the following sections, this theme is continued and environment is considered as any influence outside those intrinsic to the individual. Thus, environment in this context includes the physical environment, substances present in food and fluid, inhaled substances, proximity to other life forms, infectious agents, and social and household factors.

Short-Term Exposures to Environmental Influences

ATMOSPHERIC CONDITIONS

Short-term changes in climatic conditions or air pollutants have been associated with increased presentations of asthmatics to acute medical care and are likely to be under genetic influence. An association between respiratory symptoms, ozone levels, and glutathione-S-transferase (GST) M null and GSTP1 Val/Val genotypes has been reported from Mexico.[16]

Airway Responsiveness

Acute changes in airway caliber have been associated with factors related to the physical environment including dry or cold air, but have also been associated with provocative agents such as methacholine and histamine. Polymorphisms in several genes have been shown to be associated with the latter, including the genes in the chromosome 5q cytokine region,[17] and the genes for interleukin-13 (IL-13),[18] IL-4,[19] tumor necrosis factor alpha (TNF-α),[20] the β2 adrenoreceptor,[21] and CD14 in mid-childhood but not adulthood.[3] Allergen inhalation challenge has been associated with several polymorphisms, but almost all of these studies have been in mice.

Acute Respiratory Virus Infections

The most common and important cause of asthma exacerbations is acute viral respiratory infection. Over recent years, several studies have shown that the majority of children presenting with acute asthma have viral antigen present in their airway secretions and the most common viral infective agent is rhinovirus (RV).[22] Respiratory syncytial virus (RSV) is also found in this situation, but much less frequently. Recent studies have also shown that RV is more commonly associated with bronchiolitis than RSV in cases diagnosed in the community,[23] whereas the reverse is true for infants admitted to hospital with bronchiolitis. RV was also commonly associated with lower respiratory symptoms in young children.[22]

Understanding the genetic susceptibility to acute viral infection and its link to asthma would be key to providing important new information into mechanisms involved in asthma exacerbations, but very few studies have been reported in this area. One study has shown that the severity of an acute asthma episode was related to presence of the C allele of CD14 C-159T and the A allele of Clara cell 16 (CC16) A38G.[24] This study showed that a potentially important basic mechanism that predisposes to the development of asthma is the failure of an increase in soluble CD14 that is seen in those homozygous for the C allele, whereas those with one or more T alleles had significant increases in CD14 levels and less severe asthma (Fig. 56-2).[24] From the same study, a preliminary analysis has not found any genetic variations in innate immunity genes that could explain an increased susceptibility to acute viral infections in asthmatics.[25] Further genetic studies in this area are likely to be highly productive because a defective Th1 response has been implicated as an underlying feature of increased susceptibility of asthmatics to acute viral respiratory infections.[26-28]

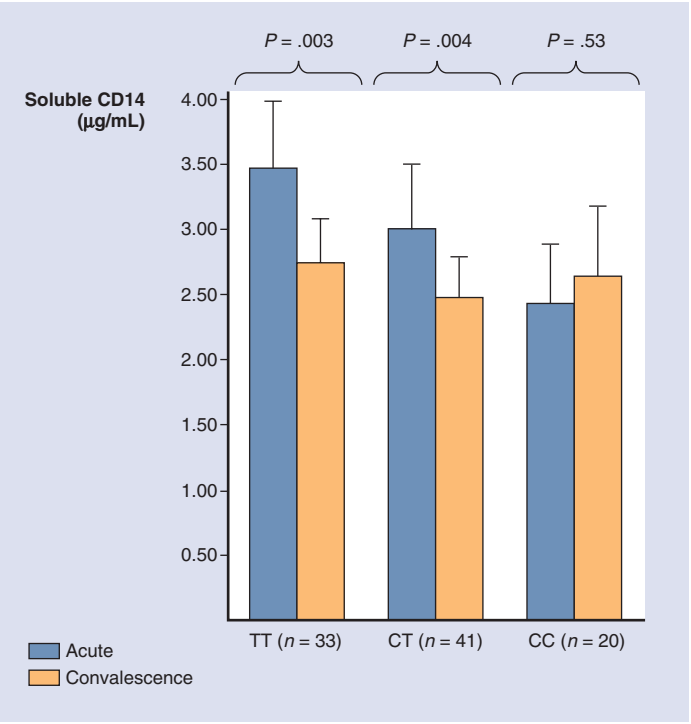

Figure 56-2 Relation between plasma levels of soluble CD14 and genotypes of CD14 C-159T. Subjects homozygous for the C allele failed to increase CD14 levels during acute asthma and were more likely to have severe asthma. (Redrawn from Martin AC, Laing IA, Khoo SK, et al: Acute asthma in children: Relationships among CD14 and CC16 genotypes, plasma levels, and severity. Am J Respir Crit Care Med 173[6]:617-622, 2006.)

VACCINES

The responses of young infants to vaccines are of interest because these represent the immune system's response to a discrete, precise, controlled dose of either an antigen or an infective agent. A vaccine, therefore, can be seen as well-characterized environmental exposure that offers strong insight into an individual's response to the natural environment. With respect to infants at risk of atopy, studies some years ago showed that there were significant differences in the way that atopic and non-atopic infants responded to regular vaccines. Examining young children's responses to tetanus toxoid and diphtheria antigens illustrates this point.

Both Th1 and Th2 responses are produced by tetanus vaccination. Young children with a family history of atopy have delayed development of Th1 responses and a predominance of Th2 responses.[29] Children with Th2 predominance exhibit a slower development of protective levels of response against the infective pathogens targeted by the vaccine.[30] Indeed, vaccine responses early in life appear to be impaired

in children with a genetic bias toward Th2 responses. At one year of age, a higher total serum IgE was associated with lower concentrations of diphtheria-specific IgG, and at 2 years of age, an inverse correlation was noted between total serum IgE levels and cellular immunity to tetanus toxoid as assessed by lymphoproliferation.[31] Thus, Th1 and Th2 lymphocyte responses are intimately involved with the responses to vaccines in early life and evidence suggests that increased Th2 responses may impair or delay the response to vaccines. Variations in genes involved in determining the rate of maturation of Th1/Th2 responses, the deviation of these responses, or the level of Th1 and Th2 responses themselves may influence responses to vaccines.

Given this situation, examining vaccine responses with respect to Th1 or Th2 gene polymorphisms would be of interest. Based on the data just mentioned, one would expect to see that alleles associated with either increased Th2 or perhaps decreased Th1 responses would be associated with reduced vaccine antibody production and reduced cytokine responses following stimulation of T cells by the vaccine antigen. This does appear to be true and recent studies have shown associations between decreases in specific IgG antibody production for each antigen of the 7-valent pneumococcal vaccine and the pro-Th2 response allele for CD14,[32] IL-4, IL-4 receptor alpha chain (Ralpha) and IL-13 (Fig. 56-3).[33] A further study has shown that the "pro-Th2" alleles in IL-4, IL-4 Ralpha, and IL-13 are also associated with decreases in specific IgG against tetanus toxoid and diphtheria vaccine antigen, but only in infants with at least one parent who was a smoker.[34] In this study, pro-Th2 alleles were also associated with altered cellular responses because PBMC stimulated with tetanus toxoid showed reduced cytokine responses for interferon-gamma and IL-10 and IL-13 for individuals with at least one R allele for IL-4 Ralpha Q551R and again, only in individuals exposed to parental smoking.[34] These findings are striking because genes related more to antibody production are likely to be important in vaccine responses to both killed vaccines and live attenuated vaccines, but genes that contribute to cell-mediated immunity are more likely to be important in responses to live viral vaccines.[35]

These vaccine response genetic studies have broad implications to gene by environment interactions, as they suggest that there may be a basic problem with both specific IgG and cellular responses to foreign antigens that is independent of the IgE system of antibodies. Taken further, they also suggest that part of the problem with asthma might be a relative impairment of the immune system toward hostile environmental threats. Given that acute asthma is triggered most frequently by viral respiratory infections rather than allergic responses, the possibility is raised that atopy may be of much less importance in asthmatics than the accompanying impairment of the immune system toward respiratory viral infections. Clearly, further studies are needed to determine the importance of these aberrant immune responses.

Medium-Term Exposures to Environmental Influences

AIR POLLUTION

Medium-term exposure to air pollution variables has been shown to affect individuals with particular genotypes more than others. In a study of Taiwanese children from three districts with different air pollution levels in southern Taiwan, those homozygous for GSTP1 Ile-105 had a weakly significant association with asthma.[36] However, when air pollution was accounted for, a significant gene-environmental interac-

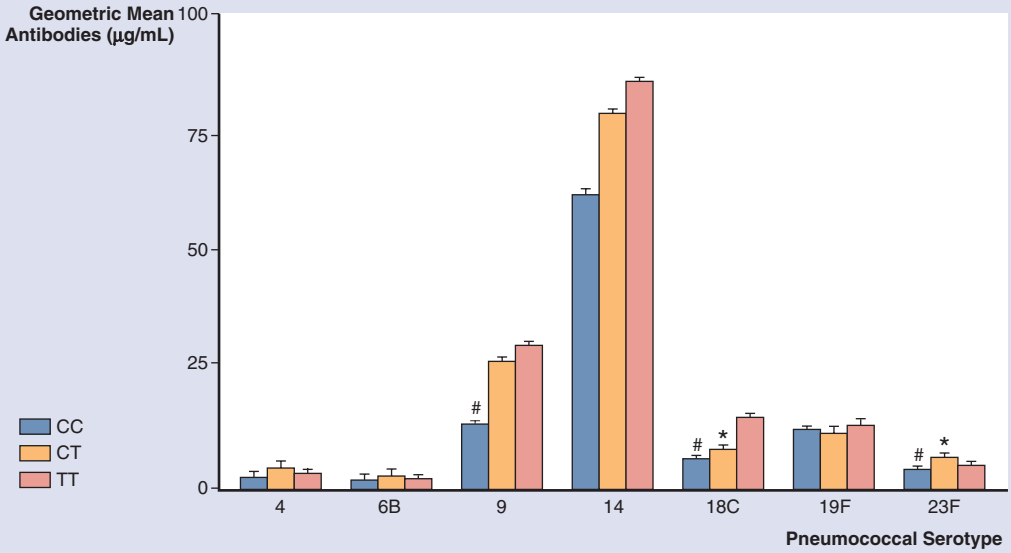

Figure 56-3 Antipneumococcal antibodies after pneumococcal vaccination and CD14 C-159T. Geometric mean (error bars = standard errors) IgG titers against seven pneumococcal serotypes versus CC, CT, and TT. (Redrawn from Wiertsema SP, Khoo SK, Baynam G, et al: Association of CD14 promoter polymorphism with otitis media and pneumococcal vaccine responses. Clin Vaccine Immunol 13[8]:892-897, 2006.)

tion was apparent, with Ile-105 homozygotes in the high air pollution district having an adjusted odds ratio of 5.52, 95% confidence interval (CI) = 1.64 to 21.25 for asthma.[36] This association of GSTP1 is not unexpected because this enzyme is important in the detoxification of products of oxidative stress. The same enzyme has also been linked to the development of lung cancer.[37]

"WESTERN SOCIETY"

As indicated earlier, knowledge of the most critical and powerful environmental factors that act within "Western society" is lacking. The existence of a broad range of environmental exposures that are included in this general term is supported by very strong evidence. In the ISAAC study, with few exceptions asthmatic symptoms are most common in the most affluent Western countries and least common in developing countries.[12] Asthma-related phenotypes are also more common in Russian Karelia compared with Finnish Karelia.[13] In developing countries that are making rapid economic progress, asthma is increasing in prevalence fastest in the most affluent areas. For example in India, Bangalore has made remarkable economic advances in recent years, but has at the same time seen rates for asthma in children increase faster than in the rest of India.[38] In general, exposure to a Western environment results in high rates of atopic sensitization, allergic diseases, and asthma. Several theories have been put forward to explain this situation, the "hygiene hypothesis" being the best known of these[39,40] and one of the most controversial.[41] This hypothesis contends that Western society has experienced a marked reduction in exposure to infectious and potentially noxious agents. However, there are many contradictions to this theory, the most striking being the large number of populations in developing countries, especially in South America, with high rates of asthma despite exceedingly poor social circumstances and endemic parasitic disease.[42]

The majority of the genome-wide screens done to detect asthma genes have been performed in Western countries. Remarkably, not many of the linkage sites detected in these studies have been replicated in more than a few of these studies.[43] Sites that have been most reproducible include 5q31-33, 6p21, and 12q13–q24.[44] In the absence of any better concept, the best and, unfortunately, the least remarkable explanation for these findings is that the environmental interaction is with "Western society" and the variability in the results from these studies is due to variability in the environmental factors that contribute to Western society. From an environmental point of view, this is a disappointing summary of how much progress has been made with the issue of gene by environment interactions after nearly 2 decades of studies using the best technologies available.

A recent summary of asthma genotypes has noted that 118 genes have shown associations with asthma-related phenotypes, 79 of which have had findings replicated in two or more publications and 10 of which have had findings replicated in at least 10 reports.[44] Again, for the majority of this large number of reports, the environmental factors responsible for producing the genetic association were not identified.

A complicating factor in gene by environment is the problem that a given allele can be associated with a particular asthma-related phenotype in one environment, but the opposite allele can be associated with the same phenotype in another environment.[1] Another difficulty is that some genotypes are related to phenotype in an age-related manner. For example, in a longitudinal data set of nonselected children followed frequently from age 8 to 25 years of age, the C allele of CD14 C-159T was associated with the development of atopy in mid-childhood, but this effect disappeared completely by 25 years of age.[3]

EXPOSURE TO FARM ANIMALS

For some years, the relation between proximity to farm animals and a protective effect against asthma in children has been known. This relation appears to be particularly strong for children raised on farms in which the animals lived under the same roof as the humans.[13,45] Lipopolysaccharide (LPS) has been implicated as the principal causative agent in this relation.[5] An in vitro study of PBMC taken from Swedish farm children has reported an association between PBMC responses to LPS and a polymorphism in Toll-like receptor 4 (TLR4).[46]

A few studies have been able to isolate specific genes likely to be involved in vivo. The first of these studies was an investigation into TLR2 polymorphisms in children of farmers; those with a TLR2-16934T allele compared with children with TLR2-16934AA were less likely to have a diagnosis of asthma (3% versus 13%, respectively; $P = .012$), current asthma symptoms, atopic sensitization, and current hay fever symptoms.[45] The association between asthma and TLR2 C-16934T in this population was independent of atopy. A similar protective relationship between farm exposure and the development of allergy has been shown for those with CD14-159TT.[47] A polymorphism in the gene for caspase recruitment domain protein (CARD) has also been reported to affect the relation between farm exposure and allergy, with a strong protective effect being found for children homozygous for the CARD4-21596T compared with those with a CARD4-21596C allele.[48]

EXPOSURE TO CATS AND DOGS

An interesting paradox is the observation that allergies to cats and dogs are much more common in allergic asthmatics, but that exposure to these animals early in life is associated with protection from the development of asthma in those predisposed to atopy. Several studies have shown this. For example in a study from Tucson, children exposed from early life to a dog had less wheeze, although not less atopy.[49] This appears to be true in otherwise very different environments, as the presence of a dog in Finland (OR, 0.57; 95% CI, 0.35 to 0.95) or a cat in Russia (OR [odds ratio], 0.43; 95% CI, 0.24 to 0.80) in the adjacent Karelian areas of these two countries was associated with protection from the development of atopy.[13] These two Karelian regions are very similar with respect to the natural environment, but very different with respect to the socioeconomic environment.

The genotypes that might be involved in the mechanism of this childhood cat exposure–related tolerance include IL-1A and IL-10 polymorphisms.[4] IL-13 may also be involved, as those homozygous for Gln form of the R130Q polymorphism in the IL-13 gene had higher levels of specific IgE to dog ($P = .003$).[50] Similar findings have been made for RANTES G-401A with the A allele being significantly associ-

ated with IgE sensitization to cat (OR 2.35; 95% CI 1.15 to 4.77).[51] However, finding genotypes associated with specific skin responses to cat, dog, or other allergens, although interesting, is not necessarily important. Rather, the findings may be nonspecific in that a genotype would need to be specifically associated with reduced disease prevalence or severity in those exposed to either cats or dogs, compared with individuals who have not been exposed, to be seen as a genotype interacting with an environmental factor.

EXPOSURE TO TOBACCO SMOKE

A large number of studies over the last 20 to 30 years have reported associations between parental smoking and respiratory disease in children.[8,52,53] More recently, genetic variants have been associated with tobacco-related effects on respiratory status or disease. One of the first of these studies was an investigation into the effects of a glutathione-S-transferase (GSTM1) genotype, tobacco product exposure during pregnancy, and environmental tobacco smoke (ETS) exposure in early life on asthma and wheezing in 2950 children aged 6 to 12 years in 12 communities in Southern California.[54] The adverse effects of in utero exposure with respect to the development of asthma and wheezing were substantially determined by the presence of the GSTM1 null genotype. Subjects with this genotype and in utero exposure had an increased prevalence of several asthma-related phenotypes including early-onset asthma, asthma with current symptoms, persistent asthma, wheezing with exercise, or requiring medication and emergency room visits in the past year (OR 3.7, 95% CI 1.9 to 7.3). These associations were not present in the group of children exposed to smoking in utero but with the GSTM1^{+} genotype.

These striking findings have been confirmed in several other studies. In more than 3000 German school children, associations were sought between GSTM1 and GSTT1 genotypes and asthma with respect to current and in utero ETS exposure.[55] Children with GSTM1 null allele exposed to current ETS had a greatly increased risk for current asthma (OR 5.5, 95% CI 1.6 to 18.6) as well as wheeze ever, current wheezing, and shortness of breath compared with GSTM1-positive individuals not exposed to ETS. In utero tobacco product exposure in children deficient in GSTT1 was associated with reduced lung function compared with GSTT1-positive children not exposed to ETS.[55] A further study supporting the importance of the GST genes in preventing harm from tobacco smoke used a placebo-controlled, crossover study designed to demonstrate that individuals with ETS exposure and GSTM1-null or GSTP1 Ile105 showed larger responses to nasal allergens, but also that IgE levels were greatest in subjects with both the GSTM1-null and GSTP1 Ile homozygotes.[56]

Additional evidence linking genetics and an adverse effect of parental smoking comes from a genome-wide screening study in 200 families in which a site on chromosome 5q was linked to bronchial hyper-responsiveness for children with ETS exposure.[17] This linkage was not present for children not exposed to ETS (Fig. 56-4).

The foregoing results related to the GST polymorphisms, and the data previously presented on the relation between vaccine responses, Th2 response alleles, and parental smoking provide evidence that tobacco smoke is the most important known environmental factor in gene by environment studies in respiratory disease in children.

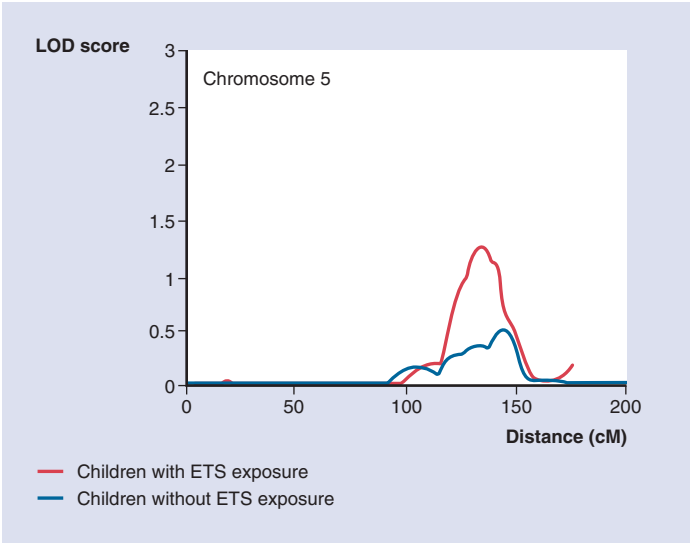

Figure 56-4 Evidence linking genetics and parental smoking from a genome-wide screening study in 200 families with significant LOD score for a site on chromosome 5q showing linkage to bronchial hyperresponsiveness for children with ETS exposure (*red line*). This linkage was not present for children not exposed to ETS (*blue line*). LOD, logarithm of the odds. (Redrawn from Meyers DA, Postma DS, Stine OC, et al: Genome screen for asthma and bronchial hyperresponsiveness: Interactions with passive smoke exposure. J Allergy Clin Immunol 2005;115[6]:1169-1175, 2005.)

Long-Term Exposures to Environmental Influences

Genes and environment also interact over a very long period via Darwinian selection. Although investigations into the extent of this interaction with respect to allergy and asthma are still few, there is now strong evidence suggesting that current function of the immune system has been determined by environmental factors.[57,58] Given that various regions on the planet have hostile infective agents that require robust Th2 responses for defense, populations with long-term ancestry in such regions could be expected to show selection in favor of alleles that promote Th2 responses. The available data suggest that this is the case, as pro-Th2 alleles are consistently more frequent in populations that originate from equatorial regions compared with those from regions of higher latitude.[42] Current evidence supports an important role for strong Th2-biased responses in defense against helminthic parasites and that these parasites are more prevalent in hot, moist conditions.[42] The lower frequency of pro-Th2 alleles in populations with long-term ancestry in temperate or cold climates could be due to a small but significant decline in competitiveness in individuals with excessive Th2 responses. Having over-reactive Th2 responses could lead to allergic diseases, asthma,[42,59] and both an increase in mortality and a decrease in general competitiveness for survival or reproduction. However, there is no direct evidence to suggest why pro-Th2 alleles are less frequent in populations away from the tropics.

The evolutionary gene/environment interactions that have resulted in the current differences in pro-Th2 allele frequen-

Table 56-1
Genes with Variations Associated with Asthma-Related Phenotypes

Gene	Chromosomal Location	Positive Studies*	Total Number of Studies
GSTM1	1p13	6	10
IL10	1q32	8	12
CTLA4	2q33	7	9
CD14	5q31	16	24
IL4	5q23	19	34
IL13	5q23	18	21
ADRβ2	5q32-24	33	44
LTC4S	5q35	7	16
HLA-DQB1	6p21	12	18
HLA-DRB1	6q21	34	40
TNFα	6q21	17	30
CC16	11q12	7	12
FCER1β	11q12	18	30
GSTP1	11q13	9	13
STAT6	12q13	10	13
NOS1	12q24	7	8
IL4Rα	16q12	24	38
RANTES	17q21	7	10
TBXA2R	19q13	6	6
TGFβ1	19q13	8	11
ADAM33	20p13	11	13

*Genes that are listed have been reported to be associated with an asthma-related phenotype in at least six publications.
From Koppelman GH: Gene by environment interaction in asthma. Curr Allergy Asthma Rep 6(2):103-111, 2006.

cies are of more than anthropologic interest because they have direct consequences toward current disease patterns.[60,61] For example, African Americans originate substantially from tropical west Africa and, for genes for which data are available, pro-Th2 alleles have higher frequencies in these populations than in European-Americans.[57] In the United States, when environmental differences between African Americans and European Americans are controlled for, African Americans also have a higher prevalence of allergy and asthma.[58] Approximately 2 billion people have tropical ancestry up to current times and these people may all be at risk of much higher rates of asthma and allergy than those with their most recent ancestry from more temperate climates (Box 56-2). People with tropical ancestry may also be at risk of infectious diseases due to inadequate responses to immunization.

BOX 56-2 Potential Consequences of Long-Term Exposure to a Tropical Climate

- Increases in frequency of pro-Th2 response alleles in genes affecting immunologic function
- Increased susceptibility to develop allergies and asthma
- Impaired ability to limit airway inflammation from acute respiratory viral infections
- Impaired humoral and cellular responses to vaccines

CONCLUSION

In conclusion, after nearly 20 years of research, much new information has been obtained on the genetics of respiratory disease, and on asthma in particular. This information has shown that there are a great number of genes associated with asthma, some of which have shown reproducible associations with asthma phenotypes (Table 56-1), but none of these on their own have been found to exert a strong influence. More careful analyses have shown that several immunologic and inflammatory pathways have many genetic variations that contribute to asthma susceptibility. Ethnic differences in the frequency of these variations have probably been caused by geoclimatic influences and these differences may be responsible for the current differences in respiratory disease susceptibility that have been observed between different ethnic groups. A great deal more research is needed before the relationships between genes, environment, and respiratory disease can be properly understood.

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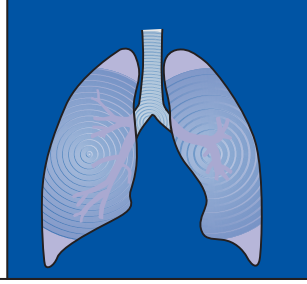

CHAPTER 57 Disease Mechanisms and Cell Biology

Peter D. Sly, Patrick G. Holt, Renato Stein, and Fernando D. Martinez

TEACHING POINTS

- Asthma is a developmental disease in which the normal development of the respiratory and immune systems is altered by the impacts of environmental exposures acting on underlying genetic predispositions.
- The developmental stage of environmental exposures is an important determinant of their effects.
- Slow maturation of the immune system after birth is a major risk factor for both viral lower respiratory infections in early life and for allergic sensitization.
- While atopy is a significant risk factor for the development of persistent asthma, not all asthmatic children are atopic and the true relation between asthma and atopy is poorly understood.

DEVELOPMENT OF ASTHMA

Asthma is essentially a developmental disease, in which the normal development of the respiratory and immune systems is altered by the impacts of environmental exposures acting on underlying genetic predispositions (see Chapter 56 for further details). When considered from this point of view, it makes sense to briefly review the basics of normal respiratory and immune system development and then consider how alterations of these by genetic and environmental factors result in the development of asthma.

Normal Development of the Respiratory System

Although the lungs at birth are immature, the basic structure is formed in utero, which means that normal lung growth is susceptible to alteration by adverse exposures before birth. Knowledge of the phases of normal development of the lung (Fig. 57-1) allows an understanding of how the timing of adverse environmental exposures produces adverse effects on lung structure. Airway development is essentially complete before birth. Airway branching is complete to the terminal bronchioles by 16 weeks' gestation and the pulmonary vasculature develops along with the airways. Airway smooth muscle development begins around 8 to 10 weeks' gestation and has extended to respiratory bronchioles by 26 weeks' gestation. Cartilage development is essentially complete by 28 weeks. Alveolar development begins around 24 weeks' gestation and at birth approximately 30% to 50% of the final complement of alveoli is present. Lamellar bodies, the structures responsible for secreting and storing surfactant, appear within type II alveolar epithelial cells by 24 weeks' gestation.

After birth, alveolarization continues rapidly for the first 18 to 24 months. Although the timing of cessation of alveolar development is not known with certainty and may continue until 5 to 8 years of age, the rate of alveolar formation is most rapid in early postnatal life. The pulmonary microvasculature develops mostly during this secondary phase of alveolarization. Lung volume increases along with somatic growth, with the lung volume approximately doubling from birth to 18 months, doubling again by 5 years of age, and doubling again by adult life. The lungs continue to grow longer in boys, continuing into the early 20s, whereas lung growth appears to stop in the late teen years in girls.[1,2] Boys are thought to have relatively smaller airways for the size of their lungs than girls in early life,[3] and this is thought to contribute to the increased prevalence of wheezing in boys during infancy and the preschool years.[4] Lungs grow along trajectories set in early life, similar to percentiles for somatic growth.[1] This means that adverse influences on lung growth in early life, such as maternal smoking during pregnancy (see later), have lifelong consequences.

Normal Development of the Immune System

The immune system has two major arms, the innate immune system and the adaptive immune system. The innate immune system in the lungs represents the first line of defense against invading organisms, consisting of nonspecific responses triggered by recognition of conserved molecular patterns carried on the surface of microorganisms (pathogen-associated molecular patterns or PAMPs). This response is generated by macrophages resident in the airways, which secrete cytokines and chemokines that recruit inflammatory cells to the lungs. The innate immune system relies on a limited number of pattern recognition receptors (PRRs) to identify PAMPs. Secreted PRRs, such as CD14 or LPS-binding protein, bind to microbes and facilitate their destruction by phagocytosis or the complement system. Toll-like receptors (TLRs) induce antimicrobial genes and inflammatory cytokines within a variety of cells while activating dendritic cells (DCs), the major professional antigen presenting cells in the airways, to initiate adaptive immune responses. Mesenchymal cells, in particular airway epithelial cells, can also utilize some of these innate immune mechanisms, including TLR-mediated cytokine secretion, to signal the presence of invading microorganisms.

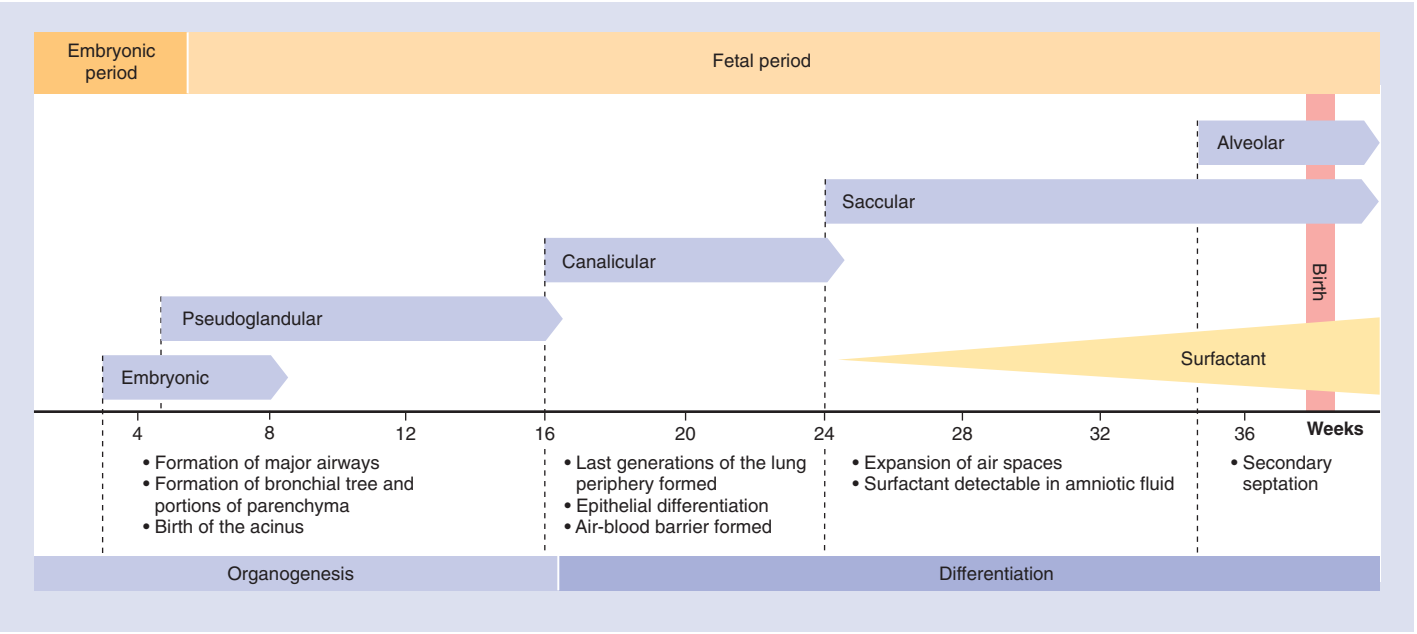

Figure 57-1 Schematic representation of the stages of lung development. These periods outline periods of vulnerability of different components of the lungs to environmental exposures.

The adaptive immune system adds specificity to host defense responses by recognizing specific antigens and producing both a humoral and cell-mediated response involving activation B and T cells. A fundamental characteristic of the adaptive immune system is the development of immunologic memory, in which a rapid response is mounted on subsequent reinfection with individual pathogens. Although the strengths of such a mechanism in providing resistance to infection is important for survival in the face of infectious diseases, immunologic memory is also the basis for immunopathology in allergic disease.

Both the innate and adaptive immune systems undergo considerable development in utero but both are immature at birth.[5] Studies of the normal development of T cells have shown that circulating T cells can be demonstrated by 15 weeks' gestation and that these are capable of proliferating in response to mitogen stimulation in vitro by 17 weeks' gestation. Surface markers characteristic of T cells (i.e., CD3, CD4, and CD8, have been demonstrated by 18 weeks' gestation) as has the surface expression of the major histocompatibility complex class II. T cell responses to antigen have been reported, using ex-vivo stimulation protocols as early as 22 weeks' gestation; however, as discussed later, considerable doubt exists over the specificity of these responses.[6] Fetal and placental tissues secrete cytokines in utero and measuring these in cord blood can give an indication of the maturational state of the fetal immune system.[7]

Considerable maturation of both the innate and adaptive immune systems occurs after birth. although a thorough review of this topic is beyond the scope of this chapter and the interested reader is directed to a recent review by Holt and colleagues,[8] a brief overview is warranted. As reviewed by Holt and coworkers,[8] monocytes circulating in neonates respond less well to a variety of bacterial and viral signals than do adult monocytes. Dendritic cell function is immature at birth in several important ways.[9-15] Neonatal DCs have reduced ability to present antigen[8] and reduced ability to induce T cell differentiation.[9-11] Their ability to secrete bioactive interleukin (IL)-12, a key cytokine for inducing T cells to differentiate into T-helper (Th)-1 cells, is deficient at birth and matures slowly through childhood.[8] DCs also show a reduced ability to secrete type I interferons, an important part of the innate antiviral response.

Circulating T cell numbers are increased in infancy relative to later life[16] but many of these show characteristics of being functionally immature cells known as *recent thymic emigrants* (RTEs), including the expression of the surface markers CD1[17] and CD38,[18] coexpression of T cell markers CD4 and CD8,[19,20] whereas very few express classic activation markers, such as CD25, CD69, or CD154.[19] T cells from neonates and infants appear to be incapable of sustaining responses to stimuli in vitro. Although initial rapid proliferative responses are seen[21,22] and are associated with cytokine production, these responses are not maintained and most appear to undergo apoptosis.[6,18] An inability to generate true memory responses has also been reported[23]—further questioning the specificity of allergen-induced T cell responses in early life.

The T cell responses in early life are characterized by the production of Th-2 cytokines, which appears to be related to an active suppression of secretion of Th-1 cytokines in utero and an inability of neonatal DCs to induce Th-1 differentiation in early life.[24-27] The ability to produce a wide variety of Th-1 cytokines is reduced in early life and maturation is not complete until late adolescence (Fig. 57-2).

Postnatal maturation of the immune system is driven by environmental exposures, especially to microbial products.[28-33] Postnatal colonization of the gut and skin with bacteria is thought to provide potent maturational signals. Other maturational signals are thought to be provided by exposure to components of microbial cell walls, such as lipopolysaccharide (LPS) from gram-negative organisms, lipoteichoic

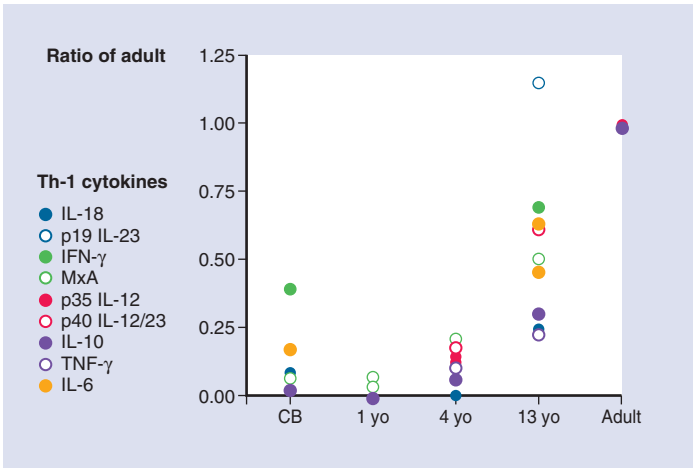

Figure 57-2 Maturation profile of a number of markers of Th-1 cytokine capacity. Data are derived from a variety of studies in which peripheral blood mononuclear cells were stimulated ex vivo with relevant stimuli. Data from cells harvested from children at various ages are shown and expressed as a ratio of the cytokine production capacity of cells harvested from adults and simulated under identical circumstances.

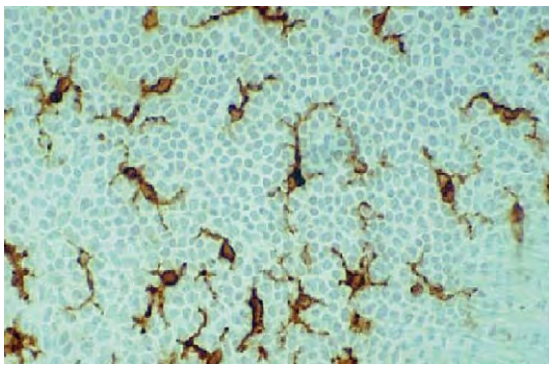

Figure 57-3 Transverse section of tracheal epithelium of an adult rat. The network of dendritic cells can be seen as the dark staining.

acids from gram-positive organisms, glucans from fungi, and many others. These maturational signals result in an increased expression of MHC class II on DC and an increased ability of T cells to produce Th-1 cytokines with age.

Mechanisms Underlying the Development of Allergic Sensitization

When a protein antigen is encountered at a mucosal surface, such as the airway epithelium, for the first time, a series of events is initiated that result in the development of either immunologic memory or tolerance to that antigen. In the lungs, respiratory tract dendritic cells (RTDCs) form a network within the epithelium (Fig. 57-3) with dendrites protruding between epithelial cells like snorkels that "sample" the luminal environment. Protein antigens are taken up by the RTDCs through these snorkels by endocytosis and are processed. The RTDCs then undergo a transformation from cells specializing in uptake of antigen to cells specializing in antigen presentation, and at this stage they leave the lungs, trafficking to the regional lymph nodes via the lymphatic system. On the first occasion that protein antigens are encountered they are presented to naïve T cells, together with maturational signals from the RTDCs that determine how the T cells differentiate. If the protein antigen is completely inert and contains no motifs recognizable by PRRs, and the RTDC containing the protein has not recently encountered any microbially related inflammatory signal and thus is (functionally) in a baseline "resting" state, the RTDCs will trigger the induction of a state of immunologic unresponsiveness to that program by stimulating the differentiation of populations of T-regulatory cells. If however the RTDCs have been exposed to an environmental signal that alerts their PRR system (e.g., via TLRs stimulation), they will provide a strong IL-12 signal in conjunction with the processed antigen, the recipient T cells will differentiate as Th-1 cells and produce Th-1 cytokines. Some of the progeny of these activated Th-cells differentiate further into long-lived "memory" cells. In the absence of a strong IL-12 signal or in the presence of an IL-10 signal (which is the default signal delivered by resting DCs), the T cells will be more likely to differentiate into Th-2 cells and produce Th-2 cytokines, such as IL-4 and IL-5 and will give rise to Th-2 memory cells. Interestingly, an initial Th-2 response is usually observed during the early stages of tolerance induction, including in non-atopic human infants,[23] indicating that Th-2 memory programming is potentially reversible.

When the same protein antigen is encountered on subsequent occasions and presented to T cells in individuals who did not develop tolerance at first exposure, a rapid expansion of the antigen-specific T-memory cells occurs, together with the rapid production of cytokines. Antigen is also presented to B cells, which triggers the production of antibodies directed against the antigen. B cells require "T-cell help" for the efficient production of antibody. The default response of B cells is to produce IgG antibodies, especially IgG_1 subclass antibodies; however, in the presence of IL-4, class switching can occur—resulting in the production of IgG_4 and IgE antibodies.

During fetal life active suppression of Th-1 cytokine production leads to Th-2 biased T cell responses.[34,35] This Th-2 bias persists into early postnatal life and, in those who do not develop allergic sensitization, switches to a low-level Th-1 bias as the immune system matures under the influence of environmental exposures (as earlier). In those who develop allergic sensitization to protein antigens from the environment during this period, the Th-2 bias remains imprinted in specific areas of their immune response repertoire, into later life. Viewed in this light, allergic sensitization can be considered as a maladaptive response to exposure to protein antigens, generally known as *allergens*.

Genetic predisposition is recognized as an important component of risk for development of allergic sensitization (see Chapter 56). This predisposition is manifest in the observation that allergies run in families. Children at high risk of developing allergies, based on a strong family history of allergy, show sluggish postnatal immune maturation, as evidenced by decreased T cell proliferation to stimulation in vitro[36] and decreased ability to secrete cytokines, especially Th-1 cytokines.[37] In addition, sluggish postnatal immune system maturation is a major risk factor for the development of allergic sensitization and atopic asthma in later life.[8]

Impact of Intrauterine Exposures on Respiratory and Immune System Development and the Risk of Asthma

The intrauterine environment is the first environment a child is exposed to and adverse exposures have the potential to alter the development of the respiratory and immune systems. The most well-studied adverse intrauterine exposure is maternal smoking, although there is increasing interest in maternal exposure to other toxic substances, including heavy metals, pesticides, and persistent toxic substances in our environment.

Maternal smoking during pregnancy results in the direct exposure of the developing fetus to nicotine and carbon monoxide (CO). These components of cigarettes are thought to be responsible for the adverse effects of maternal smoking on the fetus. Nicotine is concentrated in the fetal circulation, reaching concentrations many times higher than present in the maternal circulation. Nicotine and CO result in constriction of the uteroplacental circulation, compromising oxygen delivery to the fetus. The adverse consequences of maternal smoking on fetal development include: alteration in airway growth resulting in lower lung function at birth[38]; increased deposition of collagen in both large and small airways[39]; decreased immune maturation demonstrated by lower levels of cytokines in cord blood[7]; and lower birth weight and abnormal control of breathing with blunted ventilatory responses to hypoxia.[40] Maternal smoking during pregnancy is a major risk factor for wheeze in infancy and is an independent risk factor for asthma in childhood.[7]

Maternal smoking during pregnancy also increases the risk of asthma in grandchildren born to mothers exposed to maternal smoking during pregnancy through epigenetic mechanisms.[41] When the maternal grandmother smoked but the mother did not, the risk of developing asthma was 80% higher in children (odds ratio 1.8, 95% CI 1.0 to 3.3). This risk increased to 2.6-fold (odds ratio 2.6, 95% CI 1.6 to 4.5) if the mother also smoked during pregnancy. This can be explained by an effect of the tobacco smoke products on ova development in fetal girls; this effect takes place in utero and is an example of an epigenetic phenomenon that increases the risk of asthma.

Impact of Postnatal Exposures on Respiratory System Development and the Risk of Asthma

As discussed earlier lungs grow along trajectories. However, exposure to inflammatory or irritant stimuli can retard lung growth. Lung function can also be damaged by postnatal exposures, such as environmental tobacco smoke or viral infections, in early life. Inflammatory stimuli from environmental exposures (e.g., to allergens, air toxics, or pollutants) could also limit lung growth. Woodcock and colleagues[42] used a strict environmental control regimen to reduce house dust mite (HDM) allergens to very low levels. They demonstrated that children in the clean environment had better lung function at 3 years of age than children in a control group. Lung function was not different between the groups at 4 weeks of age, showing that this was a postnatal effect.

Studies performed in rhesus monkeys[43] reared in controlled laboratory conditions show that postnatal exposures to the irritant stimuli O_3 and house dust mite allergen can alter airway growth. Infant monkeys were exposed to filtered air, house dust mite aerosol (HDMA), O_3 or HDMA + O_3 over a 6-month period. One half of the monkeys were previously sensitized to HDM. O_3 exposure had little effect on airway structure or on airway resistance. Similarly, in sensitized monkeys, exposure to HDMA or O_3 alone had minimal effects, whereas repeated exposures to HMDA and O_3, either sequentially or simultaneously, resulted in exaggerated structural and functional changes in airways. Although these data support the concepts presented, no detailed assessments of lung growth have been undertaken and the effects of early life viral infections have not been studied by direct measurement.

Air pollution, both outdoor and indoor, has been identified as a potential risk factor for both the initiation/induction and the exacerbation of asthma. One potential mechanism is through the induction of pulmonary inflammation, with the resultant effects on postnatal lung growth. Pollutants or irritants that may induce pulmonary inflammation include: combustion-related products formed by the burning of organic fuels, including nitrogen dioxide, particulate matter, and diesel exhaust particulates; bioaerosols including molds, allergens, and bacterial products (e.g., LPS), and air toxins including formaldehyde and other volatile organic compounds.

Recurrent viral lower respiratory infections (LRIs) may also alter lung growth. Although no definitive data exist demonstrating the adverse effects of recurrent viral infections on lung growth, this concept is not fanciful. Recurrent LRIs in early life are a major risk factor for the subsequent development of asthma.[44-47]

Virus-Induced Wheezing during Childhood

Wheezing with viral infections is a very common occurrence during childhood. One fifth of all children have at least one episode of LRI with wheezing (wLRI) in the first year of life, and up to 70% of these cases are associated with documented viral infections.[48] Up to 30% of all children have one or more episodes of wheezing during LRIs.[49] Such episodes are mainly caused by rhinoviruses (RV), respiratory syncytial virus (RSV), parainfluenza viruses and—to a lesser extent—adenoviruses, human meta-pneumovirus, and influenza virus.[50,51] In older children RVs are most commonly associated with triggering episodes of asthma.[52-54] Certain factors are common to all forms of virus-associated childhood wheezing. In general, male children tend to develop wheezing more commonly than female children,[3,50] as do children of lower socioeconomic status and of less educated and younger mothers.[55,56] Children who spend several hours each day in settings where several other children are taken care of also tend to develop more wheezing illnesses than other children.[44,57] Therefore, both factors that increase the likelihood of becoming infected with viruses and factors associated with the nature of the response to the virus tend to increase the likelihood of wheezing.

Whereas much of the epidemiologic data have focused on the relation between RSV infection in early life and asthma (see later), wLRI associated with RV also increases the risk of asthma in later childhood. The number and viral associations with LRI in the first year of life have been studied in a cohort of children at high risk of developing asthma in Perth,

Australia[50] and the asthma outcomes were assessed when the children were 5 years old. RV was responsible for more wLRI (46%) than RSV (16%). In addition, RV-associated wLRIs were significant risk factors for both current asthma (odds ratio 2.8 [95% CI 1.2 to 6.6], $P = 0.02$) at age 5 and persistent wheeze (2.8 [1.2 to 6.6], $P = 0.02$) throughout early childhood. The risk factors for current asthma and persistent wheeze for RSV-associated wLRI were 2.7 (0.7 to 9.6), $P = 0.10$ and 3.5 (1.1 to 12.1), $P = 0.04$, respectively. RV and RSV are very different viruses and use different mechanisms to infect epithelial cells. These data raise the possibility that host-response factors rather than virus-specific factors are responsible for the asthma risk associated with LRI in early life.

Recent data suggest that asthmatics have a decreased ability to make type 1 interferons, in particular IFN-β and IFN-λ.[58,59] These cytokines form a vital part of the host antiviral response and aid viral clearance. It is not known whether this is a congenital or an acquired defect or what the mechanisms underlying the defect may be. However, it does raise the possibility that a primary defect in antiviral immunity may play a part in the initiation of asthma. Studies in early life, especially in the first year of life, will be needed to clarify this.

Mechanisms of Virus-Induced Airway Obstruction

Considerable advances have been made in recent years in our understanding of the alterations that may be associated with bronchial obstruction during viral infections in childhood. Two main areas of knowledge have been extensively explored: the possibility that intrinsic characteristics of the lungs may enhance airway obstruction during viral infections and the possibility that altered immune reactions to the virus may enhance bronchial obstruction in certain children.

It is now apparent that infants and young children whose airway function is in the lower percentiles of the population distribution at birth are at increased risk of developing wheezing during lower respiratory tract illnesses.[60,61] If not associated with other risk factors for asthma, this condition is transitory and not characterized by persistence of symptoms beyond the preschool years. For this reason, it has been called *transient early wheezing*.[49] RSV-wLRI in these children is not associated with an increased incidence of atopy in later life.[62-64]

Children hospitalized with bronchiolitis show persistent reductions in lung function[62] lasting into later life.[63] Several studies have found that these children had lower flows, increased inspiratory or expiratory resistance, or increased gas volume months or years after the initial event.[62-64] Several studies have demonstrated that children who will go on to wheeze during the first 3 years of life have diminished levels of lung function that precede the development of the wheezing illnesses.[60,61,65] It has thus been suggested that these lower levels of lung function are a predisposing factor for airway obstruction during viral infections. The nature of the alteration in airway dynamics present in these "transient infant wheezers" is not known. It is possible that diminished airway function may be associated with narrower airway diameter for a given airway generation.[61] The internal diameter of an intrapulmonary airway is determined by the balance between pressures that tend to keep it open (airway resistive pressure, elastic recoil pressure of the airway, and alveolar pressure) and the transmural pressure, which tends to compress the airway during expiration,[66] and elastic recoil pressure of the lung, which tethers the airway.[66]

Because of developmental immaturity, the infant's lung is stiff and has a low content of elastin and collagen.[67] Also, the chest wall is quite compliant during the first years of life.[68,69] The stiff lung and decreased chest wall stiffness combine to set the elastic equilibrium point of the infant's lung at a lower relative volume than that of the adult.[70] The elastic equilibrium volume may be very close to, or even below, the closing volume of the infant's airways, making the infant particularly vulnerable to airway closure during tidal breathing.[71] Genetic factors or environmental exposures such as maternal smoking during pregnancy[38,72] may further decrease elastic recoil pressure of the lung and resting airway diameter. In children with any of these alterations, mucus deposition and airway edema occurring during viral infections may cause sufficient narrowing to allow the airways to reach a critical diameter. This may predispose these children to airway obstruction and wheezing. Interestingly, although these children tend to outgrow their symptoms with age, their mean levels of lung function remain lower than those of children without any history of wheezing.[63]

Synergism between Allergic Sensitization and Virus-Induced Wheeze in the Initiation of Asthma

Although allergic sensitization is a major risk factor for asthma the relation between allergic sensitization and asthma is not invariably close. A community-based longitudinal birth cohort study in Perth, Australia, has shown that approximately 40% of 6-year-old children were sensitized to inhalant allergens; however, only one half of these children had current asthma.[44-47] This target-organ selectivity is poorly understood. Atopic sensitization to one or more inhalants during the preschool years doubled the risk for current asthma in these children at age 6 years. However, if this was accompanied by severe (wheezing) LRI during infancy, odds ratios for persistent asthma rose to more than 9 (Fig. 57-4). This synergistic interaction between allergic sensitization and viral infections in early life depends critically on when the sensitization occurs. Data from a high-risk birth cohort study in Perth, Australia have shown that viral LRIs are only a risk factor for asthma at 5 years of age if the children were sensitized to aeroallergens at or before 2 years old and not in those sensitized between 2 and 5 years of age.[73]

These findings form the basis for the "dual hit" model for asthma etiology proposed by Holt and Sly (Fig. 57-5).[8] While the early acquisition of allergic sensitization is a risk factor for the subsequent development of asthma, a second "hit," sensitization that is associated with pulmonary inflammation, is required for the development of persistent asthma. Theoretically, other inflammatory stimuli (e.g., exposure to air toxics, combustion-related products, and vehicle exhaust emissions), could also provide the second hit.[74-78] The key target of the second hit is postnatal growth and development of the lungs.[8] The important aspects of these processes are

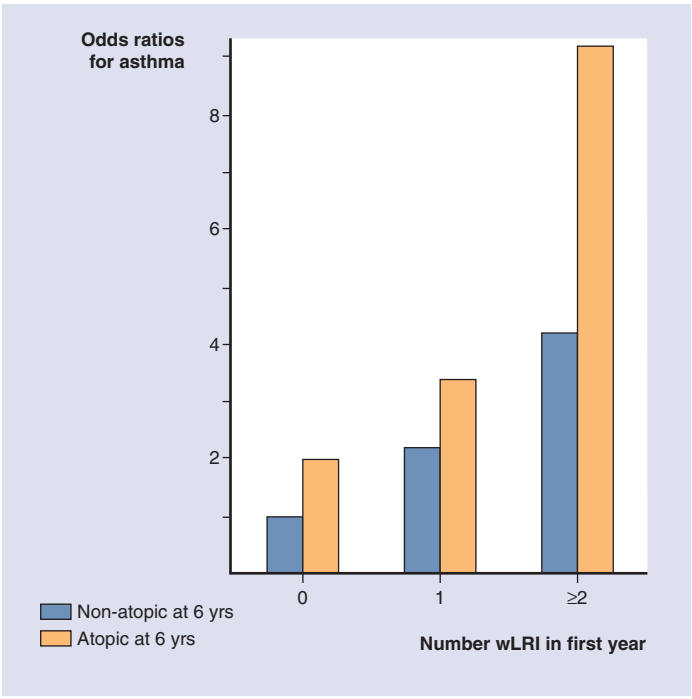

Figure 57-4 Synergistic interaction between atopy, defined as having a positive skin-prick test to at least one aeroallergen at the age of 6 years and the number of wheeze-associated lower respiratory illness (wLRI) in the first year of life and the risk for current asthma at the age of 6 years.

that (1) infancy is a period of intensive growth and differentiation of lung and airways tissue, and (2) lung function "tracks" from early childhood into later life.

In this context, it is important to point out the potential dual role that airway inflammation may play. On one hand, airway inflammation related to viral LRI results in symptoms that we recognize as asthma. On the other hand, airway inflammation has been thought to underlie structural changes in the airway wall, including deposition of collagen beneath the basement membrane, increase in smooth muscle bulk, and inflammatory infiltrates in the airway wall. A lung function deficit is seen in children with persistent asthma and is seen in the earliest measurements available in longitudinal studies.[79] The failure of recent studies postulating that using inhaled corticosteroid to show true disease-modifying action, in spite of achieving good symptom control, questions the long-held belief that airway inflammation results in both asthma symptoms and airway remodeling. As postulated by Martinez,[79] it is possible that asthma symptoms and airway remodeling result from different mechanisms and that the relation between altered lung growth and asthma is both complex and not "steroid responsive."

ESTABLISHED OR PERSISTENT ASTHMA

In the earlier sections in this chapter we have been discussing risk factors for the development of asthma. We will now turn

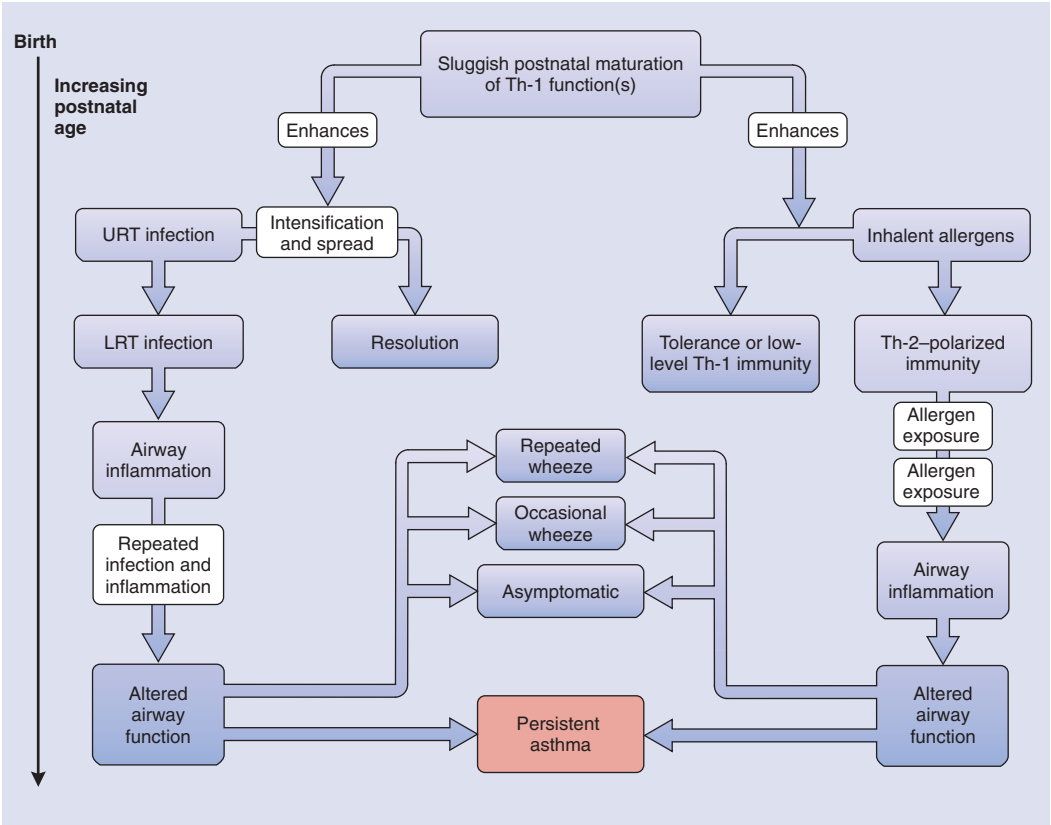

Figure 57-5 Schematic representation of the "dual-hit" model for the development of persistent asthma. The model proposes a common genetic susceptibility resulting in sluggish postnatal maturation of Th-1 function that results in both an increased risk of lower respiratory tract infections (LRTI) in early life and an increased risk of allergic sensitization. A child traveling down either the pathway of repeated LRTI or allergic sensitization alone has an increased risk of wheeze. The increased risk of persistent asthma is conveyed to children who travel down both pathways simultaneously.

to discussing mechanisms underlying persistent asthma. The bulk of the epidemiologic literature indicates that the type of asthma that is most likely to persist into adult life is the type associated with allergic sensitization, known as atopic asthma, and this chapter will concentrate on this. For a discussion on other types of wheezing, the interested reader is directed to other chapters in this book and to an excellent review.[4]

Non-atopic Asthma

Although there is a strong association between atopy and persistent asthma, especially in older children, a significant proportion of asthmatic children are non-atopic. In a longitudinal cohort study conducted in Perth, Australia, atopy was a strong predictor of persistence of asthma from 6 years of age to 14 years of age. However, only approximately one half of the asthmatic children at age 6 years were atopic[44] and only two thirds were atopic at age 14 years (unpublished observations). The association between atopy and childhood asthma is even less strong in low-income developing countries, where lower respiratory infections in early life are major risk factors for persistent asthma in later childhood.[80]

The mechanism(s) underlying non-atopic asthma are not well understood. As outlined earlier, viral lower respiratory infections can result in airway inflammation and heightened bronchial responsiveness. Animal studies in which activated T cells are adoptively transferred into naïve animals can increase airway responsiveness in the total absence of IgE antibodies[81]; however, the direct relevance of these studies to asthma in children is not known. Recent data point to some differences but also similarities in the inflammatory factors driving atopic and non-atopic asthma. In one small cohort, the T-cell responses to stimulation with the mitogen PHA were seen to differ in atopic subjects and non-atopic subjects with bronchial hyperresponsiveness (BHR). Asthma and BHR in atopic children were most strongly related to peripheral blood eosinophil counts and to TH-2 cytokine responses, whereas the strongest relation seen in the non-atopic children was with the regulatory cytokine IL-10 made by stimulated T cells.[82]

In a larger cohort of teenaged children the peripheral blood eosinophil count was strongly associated in both atopic and non-atopic children. This effect was particularly strong in non-atopic girls (unpublished observations). Eosinophils are generally thought of as being part of an atopic inflammatory response and are responsive to secretion of the TH-2 cytokine IL-5. However, eosinophils also have surface receptors for estrogen and are increased in the peripheral blood of girls during the mid-stage of the menstrual cycle. These data show the mechanistic complexity underlying asthma; we are a long way from understanding the true link between asthma and atopy in children.

Airway Inflammation

Our understanding of the characteristics of airway inflammation in chronic asthma has been considerably enhanced by the availability of bronchoalveolar lavage (BAL) and bronchial biopsies. Although the majority of these data have come from studies in adults, they are instructive. We do not know when the chronic changes seen in adult asthma begin, and considerable doubt exists as to whether these same changes are present early in the course of childhood asthma in those who are destined to develop persistent asthma. Few studies directly addressing this issue have been performed in children. Indeed, bronchial biopsies from children with asthma do not invariably show the eosinophilic inflammation characteristic of adult asthma.[83] In addition, the reservations about the link between chronic airway inflammation and airway remodeling and abnormal lung growth in children raised by Martinez[79] (see earlier) should be noted.

Various studies in adults have consistently shown the presence of increased numbers of ciliated epithelial cells often in clumps, mast cells, and eosinophils,[84-86] whereas others have revealed increase in lymphocytes[87,88] and epithelial cells[89,90] in the BAL of asthmatic patients. More recently, sputum analyses have shown that a noneosinophilic type of asthma may be present in adults[91-93] in which the predominant cell type is neutrophils. In mild asthmatics, numbers of T lymphocytes (CD3+) and their subclasses (CD4+ helper, CD8+ suppressor/cytotoxic) are not increased, although using activation markers there is accumulating evidence of T cell activation. Macrophage and neutrophil function are also enhanced; even in mild disease, macrophages have been shown to respond to allergen by generating cytokines such as IL-8 and IL-1β, and this may reflect an important change in the phenotype of these cells in asthmatics. Both mast cells and eosinophils are also present in airway secretions. A variety of different mediators from many cell types have been described, but some of the most important are: histamine, prostaglandin D_2 (and other prostanoids), 15-hydroxyeicosatetraenoic acid (15-HETE), leukotrienes B_4, C_4, D_4, and E_4, lysosomal enzymes, and a number of basic proteins from the eosinophil. Many of these mediators originate from activated mast cells and eosinophils, but platelets, macrophages, and monocytes also contribute to the autacoid pool.

Some aspects of the inflammatory response in asthma can be modeled by the early and late asthmatic reactions (EARs, LARs) to inhaled allergen challenge (Fig. 57-6).[94] After bronchial provocation with an allergen to which the subject is sensitized, a rapid bronchoconstriction usually occurs, which lasts for about 1 hour (EAR). This is often followed by a more prolonged phase of airway narrowing (LAR) that starts 2 to 3 hours after exposure, reaches a maximal airway response by 4 to 8 hours, and resolves in 12 to 24 hours. Similar patterns are seen in young children with atopic asthma.[95] LAR occurs in parallel with an increase in airway responsiveness to bronchoconstrictor agents, such as methacholine and histamine, and this heightened responsiveness may persist for days after the LAR has resolved.

The EAR is mostly characterized by activation and degranulation of the mast cell with release of mediators, although the direct evidence for this in humans is scant. After inhalation of challenging allergens there is rapid airway narrowing, presumably due to airway smooth muscle contraction following the release, among others, of the lipid-derived mediators prostaglandin PGD_2, $9\alpha11\beta P\text{-}PGF_2$, thromboxane, leukotriene LTC_4 and 15-HETE, and kinins,[96] as well as proteases, lysosomal hydrolases, and proteoglycans that will, in a later phase, act on tissue damage and repair.

The LAR expresses itself in the airways with an important edema component, and BAL fluid during this phase contains

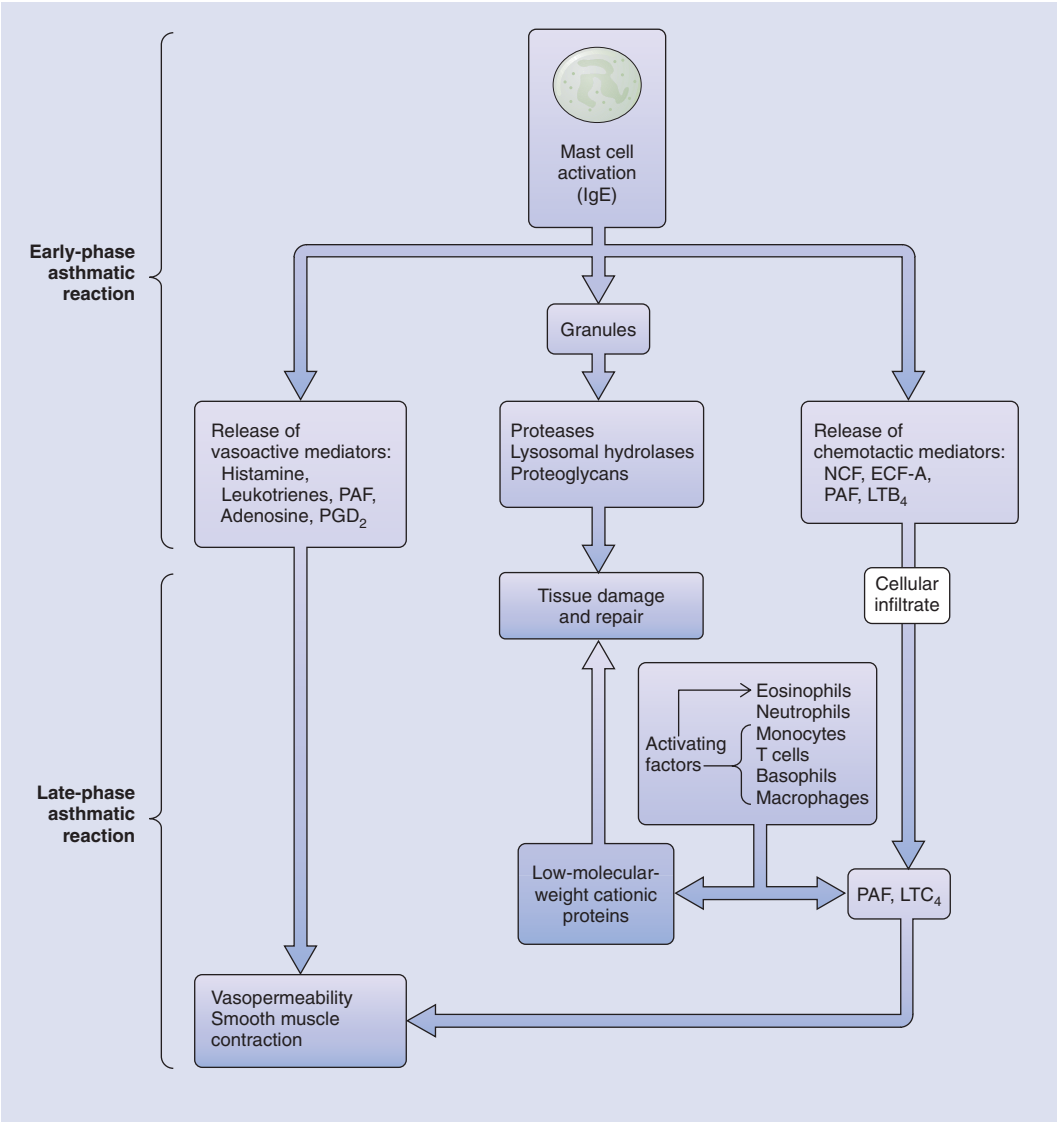

Figure 57-6 Early- and late-phase asthmatic reaction (EAR, LAR) model. ECF-A, eosinophilic chemotactic factor of anaphylaxis; PAF, platelet-activating factor; LT, leukotriene; PG, prostaglandin. (From Malo JL, Cartier A: Late asthmatic reactions. In Weiss EB, Stein M [eds]: Bronchial Asthma: Mechanisms and Therapeutics, 3rd ed. Boston, Little, Brown, 1993, p 140.)

increased numbers of eosinophils.[97] Some studies have shown increased numbers of neutrophils and lymphocytes after antigen challenge; these changes were not seen in subjects with an EAR only.[96] Patients who demonstrate both EAR and LAR show increased levels of eosinophil-derived major basic protein (MBP) and neurotoxin (EDN), but LTC_4 is seen only in patients who have a LAR. The second inflammatory "wave" represented by LAR may be important in asthma, because it may lead to proliferative and repair responses, including the targeted destruction of the bronchial epithelium, the expansion and activation of fibroblasts, hypertrophy and hyperplasia of the smooth muscle, and proliferation of neuropeptide-containing nerves.

It is clear from the preceding description that many inflammatory mediators and cells are involved in the disease process in chronic asthma. The model of EAR and LAR has been very useful in expanding an understanding of the immunopathology of hyperreactive airways. However, consensus has been reached today that there is overlap between the two responses. Interaction among cells and mediators in the airway inflammatory response could be responsible for airway bronchial hyper-responsiveness.

The relation between allergic sensitization and atopic asthma is not a simple one. Many epidemiologic studies consider atopy to be a binary variable, based on a positive skin prick test to inhalant allergens. However, recent data suggest that the degree of allergic sensitization is important. Joseph-Bowen and coworkers[98] derived a composite index based on the wheal sizes of inhalant allergens. They reported that serum levels of ECP were higher in those with more severe atopy and that more severe atopy was related to more severe asthma in 6-year-old children.[98] In addition, Douglas and colleagues[95] have demonstrated that a wheal size of >4.5 mm is highly predictive of a positive response (both EAR and LAR) to inhalational allergen challenge in young children.

Inflammatory Mediators in Atopic Asthma

Histamine is probably one of the most widely studied inflammatory mediators in asthma. A rise in plasma histamine concentrations is seen minutes after allergen inhalation,[99-101] and the subsequent increase in urinary *N*-methylhistamine[102] indicates that histamine is responsible at least in part for the early asthmatic response. Mast cells are the main source of this mediator,[90] as demonstrated by the increased levels of histamine seen in BAL from stable asthmatics, together with increased mast-cell activation.

Three types of histamine receptors are known to be present in the airway:[103] H_1, H_2, and H_3. H_1 receptors mediate histamine-induced bronchospasm in asthmatics as well as in normal subjects in higher concentrations. Histamine also elicits activation of sensory reflexes, vasoconstriction, and vasodilation of bronchial vessels through H_1 receptors.[103] H_2 receptors mediate mucus secretion and vasodilation, whereas H_3 receptors are responsible for the regulation of cholinergic and sensory nerve function. Most histamine receptors also mediate feedback inhibitory mechanisms for histamine secretion by mast cells.

Although there is evidence indicating that histamine contributes to the EAR, a direct role for histamine in the LAR has not been well established.[104] Antihistamines have not proved to be very effective in the treatment of asthma.[105] Despite the improvement in symptom scores and airway caliber measurements, studies involving continuous treatment for 2 to 7 weeks with antihistamines have not shown any significant change in airway responsiveness when assessed by methacholine inhalation challenge.[106,107] This suggests a limited role for histamine in the chronic inflammation present in asthma.

Prostaglandins or prostanoids are one of a group of local mediators believed to play a role in the asthmatic inflammatory process. After immunologic or nonimmunologic stimulation, cytosolic phospholipase A_2 (PLA_2) is activated, causing cleavage of arachidonic acid from the cell membrane phospholipid. Arachidonic acid is then metabolized in either of two pathways: the cyclooxygenase pathway, leading to the formation of prostaglandins, thromboxane, and prostacyclin, and the 5-lipoxygenase enzyme system pathway, to form leukotrienes. To become active, this PLA_2 enzyme requires the action of another protein called 5-lipoxygenase activating protein (FLAP).[108]

Alveolar macrophages also generate various prostaglandins (PG_2, PGE_2, and PGF_2-B_5) and thromboxanes. In humans, prostanoids (except those of the E series) contract airway muscle.[109,110] PGF_2-B_5 causes increased airway secretions with the production of glycoproteins.[110] Prostaglandins cause contraction of airway smooth muscle by activating the thromboxane receptor. The role of thromboxane and prostaglandins in chronic asthma is not well understood.

Leukotrienes (LT) are biologically active fatty acids derived from the oxidative metabolism of arachidonic acid.[111] Several forms exist: LTA_4, which is formed and then rapidly converted to LTB_4; and the cysteinyl LTs, LTC_4, LTD_4, and LTE_4, which are potent constrictors of human airways. LTs can be produced by mast cells (cLT and LTB_4), eosinophils (cLT), and neutrophils (LTB_4). Epithelial cells and macrophages have also been shown to produce leukotrienes. Immunoreactive LTC_4 has been recovered from the plasma of children with severe asthma; the amounts recovered are significantly greater than those recovered from the plasma of normal children.[112] In addition, treatment of asthma is associated with a decrease in the amount of immunoreactive LTC_4 recovered from plasma. LTC_4 is detectable in significant amounts in the BAL fluid of patients with chronic stable asthma in the absence of a specific challenge.[113] Both LTD_4 and LTE_4 have been reported to increase airway hyperresponsiveness[105,114] and may play an important role in asthma. LTB_4 is a potent chemokine: it acts at accumulating and activating inflammatory cells (mostly neutrophils and eosinophils).[115] Although it has been found in BAL of asthmatic subjects,[101] the role of LTB_4 in asthma remains unclear. LTC_4, LTD_4, and LTE_4 bind to the same receptor (LT_1) on the bronchial smooth muscle. Most leukotriene antagonist drugs that have been developed block this receptor.[116] The relatively poor clinical response of children with moderate to severe asthma to leukotriene receptor antagonists raises questions about the true role of these mediators in chronic asthma.

Platelet-activating factor (PAF), like prostaglandins and leukotrienes, is formed by the action of phospholipase A_2 on membrane phospholipids and may be produced by several of the inflammatory cells implicated in asthma (i.e., macrophages, eosinophils, and neutrophils). Inhaled PAF causes bronchoconstriction and a small increase in airway hyperreactivity[117] in normal subjects. Once PAF is rapidly inactivated in vivo, it apparently triggers a chain of inflammatory events that lead to increased bronchial responsiveness. Release of PAF is apparently associated with increased accumulation of eosinophils in the lungs[118] and skin of atopic subjects.[119] PAF makes eosinophils adhere more easily to endothelial surfaces, a property that may be involved in the recruitment of eosinophils into tissues.[120] Because eosinophils are a source of PAF, they can attract more eosinophils and perpetuate an inflammatory reaction. PAF stimulates eosinophils to release basic proteins, which are known to cause tissue damage. PAF also causes an increased expression of low-affinity IgE receptors on monocytes.[121] In addition, PAF induces microvascular leakage[122] and increases airway secretions and epithelial permeability.

Bradykinin is derived from kininogens in the plasma by the action of kininogenases (including kallikrein and tryptase from mast cells). Inhaled bradykinin causes bronchoconstriction in asthmatics but not in normal subjects[123,124] inducing a sensation of dyspnea and coughing spells similar to those observed during asthmatic attack. This supports the idea that bradykinin acts as an activator of sensory nerves in the airways.[125] Mucus hypersecretion and airway edema are main features of asthma. Bradykinins could contribute to both these phenomena by dilating blood vessels, increasing vascular permeability, and stimulating ion transport. Kinins can also activate inflammatory cells and amplify the release or production of other putative mediators in asthma, notably histamine, lipid-derived mediators, and neuropeptides.[126] Bradykinin may also contribute to bronchial obstruction by mechanisms other than spasmogenesis. Bradykinin increases mucus production[127] and elicits airway edema with microvascular leakage.[128] The presence of kinins, tissue kallikrein, and kininogen in the airways at the time of either provoked

or naturally occurring asthmatic attacks has been documented.[129] Bronchial responses to bradykinin are strongly correlated with airway eosinophilic inflammation,[130] perhaps explained by damage to the airway epithelium.[131,132] Eosinophils may damage the airway epithelium, thus impairing the production of two major bronchial peptides, neutral endopeptidase (NEP) and kinase II.[133] These peptides are mainly produced by the airway epithelium, and they degrade bradykinin, thus limiting its bronchoconstrictive effects.[129,132-134] Prostaglandin E_2 is also released by the airway epithelium, and it has a strong bronchodilating effect that also balances the effect of bradykinin.[134]

Many inflammatory cells produce **oxygen-derived free radicals** such as superoxide anions which may contribute to epithelial damage.[135] These free radicals induce an oxidative stress response in the airways that appears to play an important role in the pathogenesis of asthma. Increased levels of hydrogen peroxide and nitric oxide have been reported in the exhaled breath of asthmatic patients.[136] Air pollutants have the ability to drive free radical reactions, inducing oxidative stress in the lung when endogenous antioxidant defenses are overwhelmed.[136,137] The resultant inflammatory response appears to be particularly strong among susceptible individuals, including asthmatics. "Gene + environment" interaction seems to be important in determining the increased asthma risk in children exposed to traffic-related pollutants.[138,139] Children with a genetic deficiency in their ability to neutralize oxygen-free radicals are more likely to have low lung function, respiratory symptoms, and asthma.

Oxygen radicals react with polyunsaturated fatty acid residues in phospholipids, resulting in the production of reactive aldehydes. The most abundant of these, malondialdehyde (MDA),[140] has been used as a biomarker of pulmonary oxidative stress in occupational settings.[141-143] As part of an inflammatory response in the airways, activated neutrophils, eosinophils, monocytes, mast cells, and alveolar macrophages release free radicals, which in turn provoke bronchoconstriction and changes in receptor function, which could influence airway reactivity.[144] Superoxide anion generation by eosinophils appears to be an important factor in both host defense and inflammation, and the presence of an eosinophil infiltrate in the airway of asthmatic patients can provide a potent mechanism for tissue damage.

Cytokines such as IL-5, GM-CSF, and IL-3, which are able to prolong eosinophil survival in vitro, are found in a biologically active state in the circulation of asthmatic subjects.[145] Overtly atopic and apparently non-atopic patients with asthma have been shown to have different cytokine production patterns.[145-147] Table 57-1 summarizes the functions and cell origin(s) of some of the most important cytokines involved in the airway inflammation in asthmatic subjects.

Chemokines with specific leukocyte-selective chemotactic activity are also increased in asthmatics. IL-8 is a CXC chemokine and is a chemotactic factor for neutrophils and T lymphocytes, and under some conditions for eosinophils. Other members of the CXC subfamily are MGSA/Gro-α, CTAP-III, and NAP-2, and they have similar chemotactic activities. The CC subfamily has proteins that are chemotactic for monocytes, but not neutrophils. One such cytokine is RANTES, which has been shown to be a chemoattractant for memory T cells.[146] RANTES also stimulates the migration of eosinophils across IL-1–stimulated endothelium.[147] This suggests that RANTES has an important role as a selective chemoattractant pathway for eosinophils and memory T cells in asthma.

Inflammatory Cells in the Asthmatic Airways

EOSINOPHILS

The importance of eosinophils in the pathogenesis of asthma is related to its central role in the airway inflammatory process.[148,149] To stress this role, some authors have described asthma as "chronic eosinophilic bronchitis," a concept that perhaps underestimates the importance of the contribution of many other, interconnected cells in the development and persistence of asthma. An increase in eosinophil counts is found in sputum,[150] BAL fluid,[151,152] airway epithelium and submucosa,[153,154] and commonly in blood[155] of asthmatic subjects. Although both lymphocytes and eosinophils often infiltrate the airway mucosa of asthmatics, eosinophils seem to play a major role. Eosinophils are now believed to be the cells responsible for the development of many features of asthma, such as damage and desquamation of the respiratory epithelium,[156] allergen-induced LAR,[157] and airway hyper-responsiveness.[90]

Eosinophils are derived from bone marrow precursors. After allergen challenge, eosinophils appear in BAL fluid during the LAR,[151] and this is associated with a decrease in peripheral eosinophil counts and with the appearance of eosinophil progenitors in the circulation.[157] This signal for eosinophil recruitment probably originates in the inflamed airway. The recruitment initially involves adhesion of eosinophils to vascular endothelial cells in the airway circulation, their migration into the submucosa, and their subsequent activation.

This process involves interactions between specific adhesion molecules expressed in the endothelium and their complementary ligands expressed in the leukocytes. These adhesion molecules are classified into families of related molecules: one of these families is that of the selectins.[158] E-selectin is present in cell surface glycoproteins and glycolipids of many leukocytes, including eosinophils, neutrophils, monocytes, and some lymphocytes; P-selectin[159] responds to the stimuli of histamine; L-selectin[160] is present in lymphocytes and also in eosinophils and neutrophils. There are two other large families: the immunoglobulin gene superfamily[161] and the integrins. ICAM-1 (intercellular adhesion molecule-1)[162] belongs to the immunoglobulin gene superfamily and is expressed in the vascular endothelium. It binds to two integrins that are expressed in many types of leukocytes. VCAM-1 (vascular cell adhesion molecule-1)[163] is also a member of the same family and mediates leukocyte adhesion via an integrin present on eosinophils, monocytes, and basophils. The selectins mediate central contact between the eosinophils and the endothelium, whereas the integrins and their ligands ensure a stable adhesion, following which the eosinophils transmigrate into the submucosa.

IL-1 and TNF-α increase the expression of ICAM-1 and VCAM-1, whereas IL-4 is selective for VCAM-1 and IFN-γ for ICAM-1.[164,165] Although both ICAM-1 and E-selectin appear to be involved in the process of eosinophil adhesion, the specific upregulation of VCAM-1 by IL-4 may play a

Table 57-1
Cytokines and Their Role in Airway Inflammation Reaction in Asthmatics

Cytokine	Cell Source	Functions
Interleukin-2 (IL-2)	T cells	T cell growth factor Eosinophil chemoattractant
Interleukin-3 (IL-3)	T cells Mast cells Eosinophils	Granulocyte (eosinophil and neutrophil) differentation activation in vitro survival enhancement primary chemotaxis (eosinophil)
Interleukin-4 (IL-4)	T cells Mast cells	Essential for IgE synthesis (isotype switch of B cells) Inhibition of IFN-γ-mediated responses T cell growth factor Inhibits macrophage-activated inflammatory cytokines Survival enhancement (eosinophils)
Interleukin-5 (IL-5)	T cells Mast cells Eosinophils	Eosinophil differentiation and maturation activation transmigration endothelial adhesion chemotaxis (eosinophilis) survival enhancement Basophil differentiation priming Cofactor for IgE synthesis
Interleukin-1 (IL-1a and b) Tumor necrosis factor (TNF-α) Interleukin-6 (IL-6)	Many cell types	Increased endothelial adhesion molecule expression T cell activation costimuli Macrophage activators Eosinophil activators
Granulocyte/macrophage colony-stimulating factor (GM-CSF)	T cells Mast cells Macrophages Epithelial cells Eosinophils	Granulocyte (eosinophil and neutrophil) differentation activation in vitro survival chemotaxis (eosinphils)
Interferon-γ (IFN-γ)	T cells	Inhibition IgE isotype switch Inhibition of Th-2 cell growth Eosinphil activation (late acting) Macrophage activation
Interleukin-8 (IL-8)	Monocytes T cells Fibroblasts	Neutrophil and T cell chemoattractant Neutrophil activator Inhibition of IgE synthesis Primes for eosinphil chemotaxis
RANTES	T cells Platelets	Memory T cell and eosinophil chemoattractant
Interleukin-10: human (IL-10)	T cells Monocytes Macrophages	Inhibition of Th-2 and Th-1 cytokine production Inhibition of macrophage-activated inflammatory cytokines Inhibition of eosinphil survival Inhibition of IgE synthesis
Interleukin-12 (IL-12)	T cells	Natural killer cell, T cell growth Inhibition of IgE synthesis
Interleukin-13 (IL-13)	T cells Mast cells	Induces isotype B cell switch to IgE Inhibition of macrophage-activated inflammatory cytokines
Platelet-derived growth factor b (PGDF-b)	Monocytes Macrophages	Fibrosis Th-2 cytokine inhibition
Transforming growth factor b (TGF-b)	Monocytes Macrophages	Fibrosis Th-2 cytokine inhibition

Modified from Robinson DS, Durham SR, Kay AB: Cytokines. 3. Cytokines in asthma. *Thorax* 48(8):845-853, 1993.

crucial role in this process. The role of individual cytokines and mediators in coordinating these responses is not yet fully understood. Eosinophils can respond to cytokines but are also able to produce cytokines themselves.[166,167] Attention has also been focused on the production of growth factors by eosinophils. TGF-α mRNA has been detected in eosinophils of patients with high eosinophil counts.[168] If these findings are confirmed in bronchial tissue from asthmatics, they would suggest that TGF-α and also TGF-β may be important in the epithelial regeneration, myofibroblast proliferation, and subepithelial collagen deposition that are characteristic of chronic asthma.

Eosinophils can be activated in a number of different ways, including by allergen exposure, PAF, and cytokines such as GM-CSF and IL-5. Eosinophils release a variety of mediators, including LTC_4, PAF, 15-HETE, and oxygen-derived free radicals. Eosinophils also release four basic proteins that are toxic to the airway epithelium: MBP, eosinophil cationic protein (ECP), eosinophil-derived neurotoxin, and eosinophil peroxidise.[149,169] These basic proteins are involved in such

actions as bronchoconstriction, mucus hypersecretion, increased vascular permeability, and epithelial desquamation, causing damage to the respiratory epithelium, which ultimately leads to the clinical features of asthma.

A number of tissue leukocyte-induced eosinophil surface proteins act to regulate airway eosinophilic inflammation. ICAM-1 was demonstrated on the surface of eosinophils in sputum. Blood eosinophils also show ICAM-1 after incubation with TNF-α and eosinophil survival factors. By these and other pathways, the eosinophil is able to maintain eosinophil-lymphocyte and eosinophil-eosinophil interactions to directly influence its own accumulation and activity and that of other inflammatory cells.[170] The same cytokines that are responsible for eosinophil production also have an important role in the priming of eosinophils.

MAST CELLS

Mast cells are widely distributed in the body and are part of its defense against harmful agents. They can also be found in the connective tissue of the lamina propria in the airways.[171] Mast cells can also be found in association with airway smooth muscle cells in the airways of adult asthmatics in greater numbers than seen in patients with eosinophilic bronchitis or nonasthmatic controls,[172] suggesting that these cells are involved in the airway dysfunction characteristic of chronic asthma. Whether similar infiltration occurs in asthmatic children is not known.

Mast cells release a variety of preformed and newly synthesized mediators that could be responsible for many of the clinical expressions of asthma.[90] Moreover, mast cells are one of the only cell types carrying the high-affinity receptor for IgE (FcGRI), suggesting that this cell plays an important role in signaling the presence of antigen in its vicinity. An important feature in asthmatic patients is the presence, density, and degranulation of mast cells within the epithelium. Once activated, mast cells release a number of mediators. Histamine, neutral proteases, and proteoglycans are preformed and stored in granules, whereas the lipid mediators, PGD_2, LTC_4, and PAF, are all newly synthesized. As discussed earlier, histamine is a bronchoconstrictor that may also mediate vasodilation, increase vascular permeability, and increase mucus secretion. PGD_2 is a potent bronchoconstrictor; LTC_4 and its metabolites also contract smooth muscle and increase vascular permeability.

Mast cells synthesize and release cytokines.[173] Murine cell lines when activated have been shown to secrete a large number of cytokines: GM-CSF,[174,175] IL-3,[175] IL-4,[176] IL-5, and IL-6,[177] IL-1, IL-2, IFN-γ, and four members of the chemokine family. It is also known that human mast cells release TNF-α when activated.[178] This molecule is believed to play an important part in the recruitment of inflammatory cells from the peripheral circulation, and the proportion of mast cells expressing this cytokine has been found to be increased in asthmatics.[179] Human mast cells also produce IL-4, and the proportion of mast cells expressing IL-4 has also been found to be increased in asthmatics.[176]

MACROPHAGES

Macrophages can be activated by allergen via a low-affinity IgE receptor (FcGR1).[180] They are derived from blood monocytes and are the cells found in largest numbers in the BAL fluid. Macrophages are found in increased numbers after allergen challenge in asthmatic patients.[180] Macrophages from asthmatic subjects release increased amounts of oxygen-derived free radicals,[181] indicating that they have been activated by some endogenous mechanisms. Macrophages produce a great number of mediators, with more than 100 secretory products identified.[182] One important feature of the macrophage is to help determine the characteristics of the inflammatory response. After allergen exposure, alveolar macrophages release a number of inflammatory mediators (LTB_4, PGF_2, thromboxane B_2, and PAF).[183,184] They are also able to release a great number of cytokines.[185] These cytokines include IL-1, IL-8, IL-10, GM-CSF, histamine-releasing factors, and TNF-α.[186,187]

Macrophages normally have a suppressive role on lymphocyte function, but this function may be impaired in asthma after allergen exposure.[188,189] Dendritic cells, which are specialized macrophages in the airway epithelium, are professional antigen-presenting cells[190] and have a very important role in the initiation of allergen-induced responses (see earlier).

NEUTROPHILS

Neutrophils may have a role in asthma because they contain many destructive proteases, are able to secrete arachidonic acid metabolites and leukotrienes, and can produce active oxygen metabolites and cytokines such as IL-8 and IL-1. Several earlier studies have failed to find any difference in baseline neutrophil numbers between asthmatic and nonasthmatic subjects in BAL fluid.[191,192] However, a distinct subtype of asthma has been identified, characterized by neutrophilic inflammation.[91-93] This type of asthma is characterized by the presence of increased concentrations of IL-8 and free neutrophil elastase activity in induced sputum, rather than the increased levels of the matrix metalloproteinase MMP-9 seen in eosinophilic asthma. In addition, neutrophils appear to be present in the sputum of adults[193,194] and children[195] with severe asthma and steroid-resistant asthma.

EPITHELIAL CELLS

The airway epithelium appears to play an important regulatory role in the inflammatory mechanism of asthma. In addition to its function as a barrier to the outside environment, the epithelial lining of airways has a number of metabolic functions. These include regulation of fluid and ion transport, production, secretion, and movement of mucus, and presentation of antigen and foreign substances to immunologic cells within the airway. It has been recently proposed that the epithelium also regulates airway caliber by secreting substances that alter smooth-muscle reactivity.

Bronchial epithelial cells (BECs) also appear to play a direct role in immune modulation.[196] Increasing evidence shows that the BECs from asthmatics show a different secretion pattern in response to various stimuli. Asthmatic BECs secrete more IL-8, GM-CSF, and sICAM-1 than BECs from nonasthmatics in response to exposure to diesel exhaust particles—a key component of traffic-related pollution.[197] In addition asthmatic BEC also secreted RANTES in response to diesel exhaust particles, a response that was lacking in nonasthmatic BECs.[197] Similarly, BECs from asthmatics

secreted increased amounts of IL-8, GM-CSF, TGF-β, IL-4, and IL-13 than BECs from nonasthmatics when exposed to house dust mite allergen.[198] In addition to cytokine secretion, BECs interact with RTDC and seem capable of influencing the way in which these cells interact with T cells.[199]

Injury caused by environmental insults or other stimuli inhibit the ability of the epithelium to produce mediators that regulate airway responsiveness and caliber. After an acute asthmatic exacerbation, cells and mediators of airway inflammation persist within the airway and submucosa, providing a continued stimulus to the epithelium both to produce factors that may enhance reactivity and to disrupt the production of factors that could normally downregulate reactivity. BECs are also able to produce the cyclooxygenase products PGE_2 and $PGF_{2\alpha}$, influencing bronchial smooth muscle tone in either direction, depending on their relative levels of production, which may, in turn, be influenced by other factors such as bradykinin, histamine, and PAF.[200] Increased epithelial permeability to inhaled irritants appears to be responsible for the increased airway responsiveness seen following viral LRI.[201,202]

Interaction between Airway Inflammation and Neural Responses in Asthma

The fact that neural mechanisms are involved in the regulation of airway tone convinced many researchers in the past that neural abnormalities could be involved in the pathogenesis of asthma. This idea has been all but abandoned, but there is now significant evidence that points to important interactions between neural and immunologic mechanisms of inflammation Specifically, it is now established that neural nonadrenergic, noncholinergic peptide neurotransmitters interact with inflammatory mediators during the airway inflammatory process that is characteristic of asthma.[203] These peptide neurotransmitters are stored and released from nerve endings that have a more classic primary function as cholinergic or adrenergic neurons.

Two main types of NANC neurotransmitters exist: inhibitory and excitatory. NO appears to be the most important inhibitory neurotransmitter in the airways. Several enzymes (NO synthases) contribute to its production, and inhibition of these enzymes blocks the neural bronchodilator response in vitro. However, NO may have the undesired effect of increasing airway inflammation by increasing blood flow to the airway, with consequent plasma leakage. Other neurotransmitters such as vasoactive intestinal polypeptide (VIP) and peptide histidine isoleucine (PHI) are also abundant in the lung but seem not to have a physiologic role in airway bronchodilation.[203,204]

The excitatory NANC neurotransmitters are co-localized at the nerve endings of afferent nerves, or C-fibers, and include tachykinins-substance P (SP), neurokinin A (NKA), and neurokinin B (NKB)—named as such because of their rapid spasmogenic effect on smooth muscle; calcitonin gene-related peptide (CGRP), and gastrin-releasing peptide. An increased population of SP-containing nerves may be identified in the airways of subjects who died with severe asthma, suggesting a neural tropism is concomitant with chronic inflammation. Once released, the effects of these neuropeptides are regulated, in part, by distinct peptidases, such as NEP and angiotensin-converting enzyme.[203] Disruption of the airway epithelium (either mechanically or by viral infection) increases the bronchoconstrictor effect of tachykinins, presumably by limiting its degradation.[205]

Bronchial Hyper-responsiveness

Bronchial hyper-responsiveness—exaggerated responses to a variety of seemly harmless stimuli—is a characteristic feature of asthma. However, the relation between asthma and BHR to chemical stimuli, such as methacholine (MCh), is complex.[206] Although both the prevalence and severity of BHR are increased in children with asthma, BHR also exists in nonasthmatic and non-atopic children. The mechanism(s) underlying BHR in children are not well understood. Airway remodeling is thought to play an important role in adults with chronic asthma[207-209]; however, this may not be the case in children and adolescents, especially because most have lung function within the normal range when asymptomatic.[210] Recent work has suggested that different mechanisms may underlie BHR in atopic and non-atopic teenagers, with BHR to inhaled histamine related to classic Th-2 mechanisms in atopic subjects but more closely related to production of IL-10 and interferon gamma (IFN-γ) by T cells in non-atopic subjects.[82] However, Humbert and coworkers[211] have pointed to more similarities than differences in the airway immunopathology in adults with atopic and non-atopic asthma, with infiltration of eosinophils and Th-2 cells secreting IL-4 and/or IL-5 being observed in both variants.

Although some studies show a relation between eosinophils and BHR, it is not clear whether they directly contribute to BHR. Eosinophil cationic proteins can increase cholinergic discharge at the airway smooth muscle neuromuscular junction by disrupting the normal feedback inhibition mediated by muscarinic (M_2) prejunctional receptors,[212] and the cationic proteins, major basic protein, and poly-L-lysine, increase immunoreactive kinins and kallikrein-like activity in vivo.[202] Both these mechanisms could potentially contribute to BHR. We have recently reported that eosinophils play an important role in driving BHR in adolescents with asthma, independent of atopy. This relation was much stronger in girls, raising the possibility that female sex hormones may be involved.

SUMMARY

There is still a lot that we do not know about the mechanisms underlying the initiation and persistence of asthma in children. A genetic predisposition(s), which results in both a delayed postnatal maturation of the immune system and an increased risk of lower respiratory viral infections in early life, appears to markedly increase the risk of developing asthma. The onset of allergic sensitization by 2 years of age and the development of more severe atopy appear to be important risk factors. We still lack data to determine whether the inflammatory mechanisms demonstrated in the airways of adult asthmatics, together with the structural remodeling that occurs, are present in young children with asthma and when this begins. More research is required to understand these mechanisms so that more effective treatments and preventive strategies can be developed.

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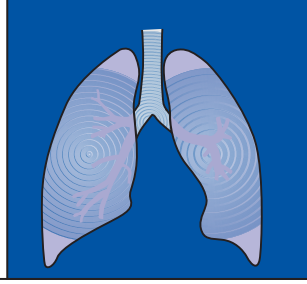

CHAPTER 58 Clinical Features, Outcomes, and Prognosis

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TEACHING POINTS

- There are three common clinical scenarios for asthma in children:
  1. Recurrent coughing and/or wheezing in preschool children
  2. School-age children with asthma
  3. Difficult-to-control asthma
- A diagnostic test for asthma is lacking. Diagnosis depends on clinical patterns of recurrent cough and/or wheeze with confirmatory physical exam findings and diagnostic tests.
- Recurrent cough and/or wheeze in early childhood is common; this is the age when most asthma begins. Prognosis for persistence into later life varies, and is predictable.
- Allergy in early childhood, especially the combination of indoor allergen sensitization and exposure, predicts the persistence and severity of asthma.
- A good assessment of asthma impairment and risk is essential to determine if good control is being achieved and maintained, and will simultaneously educate children and their families on the expectations of good control.
- When assessing asthma control in school-age children, question the child as well as the parent/caregiver.
- Spirometry is an important clinical tool for assessing lung function and asthma control in children. Experience is required to obtain accurate information from spirometry and to interpret the findings in children of different ages.
- Identify children at increased risk of severs attacks, morbidity, and death due to asthma for heightened management.
- Exhaled nitric oxide is a new clinical marker of airway inflammation in asthma that may help practitioners asses control and confirm the diagnosis.

OVERVIEW

Although there are hallmark pathologic features of asthma (e.g., airways inflammation, narrowing, and obstruction), many clinical aspects are quite variable from individual to individual (e.g., disease severity, hyperresponsiveness, natural history, type of inflammation, allergic sensitizations). One approach to this clinical variability is to build on a common foundation of understanding with tailored considerations for the three most common manifestations of childhood asthma: (1) preschooler with recurrent cough/wheeze; (2) school-aged child with asthma; and (3) difficult-to-control or severe asthma in childhood.

There are distinct considerations in clinical features, outcomes, and prognosis that are specific for each of these scenarios. The following introduction briefly overviews some of these key considerations.

Recurrent coughing and/or wheezing in preschool children is common and accounts for much of the morbidity and hospitalizations for asthma. Preschool children have frequent exacerbations and severe events, incurring the highest hospital admission rate of all other age groups for asthma. From a retrospective analysis of children with asthma admitted to a community-based pediatric intensive care unit over a 10-year period, 75% were 6 years and younger.[1] The diagnosis of asthma in young children is challenging in that they are too young to report more subtle symptoms of asthma or the frequency of symptoms, and to perform currently available confirmatory tests (e.g., spirometry). The clinical course in young children is often more episodic: periods of mild symptoms or wellness punctuated by exacerbations. Importantly, the prognosis for younger children with recurrent wheezing to have persistent asthma into later childhood and adulthood varies, such that most young children with recurrent wheezing will grow out of their symptoms by the end of their lower school years; others will persist and ultimately compose most of the children and adults with persistent asthma. Clinical management of these two divergent groups is aided by predictive risk factors that distinguish young children with recurrent wheezing who are likely to persist versus those who will gradually improve on their own.

The *school-age child with asthma* is perhaps the common "bread-and-butter" presentation of asthma in children. Most have mild to moderate disease severity, have associated atopy with inhalant allergen sensitization and allergic rhinitis, and can achieve good control and outcomes with adherence to the national and international guidelines for asthma management. It is generally believed that the large majority of children with asthma can normalize their lives to the extent that the goals of the U.S. National Asthma Education and Prevention Program should be achievable (Box 58-1).

Children may have *difficult-to-control asthma* for a variety of reasons that affect response to therapy, ranging from inadequately addressed comorbid conditions, occult masquerad-

BOX 58-1 Goals of Asthma Management and Control

Minimal or no chronic symptoms day or night
Minimal or no exacerbations; step-wise early intervention to prevent exacerbations from becoming severe
No limitation of activities; have physically active lives
No missed school and/or work due to asthma
Near normal pulmonary function
Minimal use of inhaled short-acting β_2-agonists
Minimal or no adverse effects from medications

From the National Asthma Education and Prevention Program Expert Panel Report II: Guidelines for the Diagnosis and Management of Asthma. National Institutes of Health/National Heart, Lung, and Blood Institute, NIH Publication No. 97-4051, 1997; and Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention. 2005 Update: Workshop Report (http://www.ginasthma.com).

ers of asthma, persistent environmental exposures that increase asthma severity and reduce the effectiveness of therapy, inherent biological variation in disease processes and their response to existing therapies, and the often-present challenges of adherence to controller therapy and exacerbation management.

DIAGNOSING ASTHMA

Without a diagnostic test for asthma, five criteria are typically used to identify asthma in a child (Box 58-2).

General Clinical Features

MEDICAL HISTORY

The most common asthma symptoms are coughing and/or wheezing that can worsen to chest tightness, shortness of breath, tachypnea and/or retractions (Box 58-3). Asthma symptoms often worsen with sleep, typically manifest as diurnal variation with increased symptoms at night and upon awakening in the morning. Asthma symptoms are also commonly triggered and worsened by common exposures and activities. These exposures include irritants (e.g., tobacco smoke, air pollutants, wood-burning, cleaning agents, perfumes, cold air) and inhaled allergens in those with allergen-specific hypersensitivity. Common respiratory viral infections (e.g., rhinovirus, RSV, metapneumovirus) are frequent causes of exacerbations in children with asthma. Activities that commonly trigger asthma include exercise, laughing, and hyperventilation. Common conditions that can also manifest with recurrent coughing and are often comorbid with asthma include rhinitis, sinusitis, gastroesophageal reflux disease, and prolonged postinfectious laryngotracheobronchitis (e.g., pertussis).

BOX 58-2 Diagnosing Asthma

Five criteria are typically used to identify asthma in a child:
Coughing and/or wheezing are recurrent
Other causes of coughing/wheezing are excluded
Risk factors for asthma are identified
The child improves with asthma therapy
Confirmatory physical examination findings and/or diagnostic tests

BOX 58-3 Asthma History

Symptoms
Recurrent coughing and/or wheezing
Symptoms of increasing severity:
- Chest tightness and/or pain
- Shortness of breath
- Tachypnea
- Retractions

Episodic exacerbations

Diurnal Variation
Worsens with sleep/worse at night and upon awakening

Common Triggers
Exercise, cold air, hyperventilation (laughing, crying)
Tobacco smoke and inhaled irritants
Inhaled allergens
Exacerbations: common respiratory viruses

BOX 58-4 Physical Examination for Suspected Asthma

Coughing and/or wheezing:
- Expiratory, polyphonic, high-pitched wheezing
  - Wheezing often not heard
- Resolution or improvement in cough/wheeze with asthma therapy:
  - Inhaled beta-adrenergic agonist (e.g., albuterol, salbutamol)
  - Corticosteroids: oral/systemic or inhaled (2 to 4 weeks' response)

Signs of increasing severity:
- Tachypnea
- Retractions
- Respiratory distress
- Cyanosis

Comorbid findings:
- Atopic dermatitis rash
- Allergic rhinitis, sinusitis

Rule out asthma masqueraders: examination findings NOT consistent with asthma
- Clubbing
- Fine rales
- Failure to thrive

PHYSICAL EXAMINATION

The findings summarized in Box 58-4 can support and, when present, confirm the diagnosis of asthma. During clinical evaluations in the office setting, one often has to rely on the

BOX 58-5 Confirmatory Tests for Asthma

Spirometry
- Airflow limitation
  - Low FEV_1 (relative to percentage of predicted norms)
  - FEV_1/FVC ratio <0.80
- Bronchodilator response (to inhaled β-agonist):
  - Improvement in/resolution of coughing and/or wheezing
  - Improvement in $FEV_1 \geq 12\%$ (or at least 200 mL)*
- Bronchial hyper-responsiveness to a provocative agent*
- Exercise challenge:
  - Worsening in $FEV_1 \geq 15\%$*

Daily peak flow or FEV_1 monitoring:
- Morning-to-PM variation ≥20%*

Exhaled nitric oxide
- Elevated*

*Main findings consistent with asthma.

medical history and patterns of disease to support a tentative diagnosis of asthma because most children may be relatively asymptomatic and without physical signs of asthma during the visit unless they are poorly controlled and are having an acute exacerbation.

Confirmatory tests (Box 58-5) can strengthen the diagnosis of asthma. Standard diagnostic tests that help to confirm the diagnosis of asthma include: (1) bronchodilator response ≥12% (which is greater than normal); (2) bronchial hyperresponsiveness greater than normal, evident during bronchoprovocation challenges (e.g., with methacholine, histamine, exercise, hyperventilation/cold air, mannitol); and (3) diurnal variation in peak flow (i.e., early morning-to-evening) more than 20% (greater than normal). A new "breath test" that measures nitric oxide in exhaled air, a biomarker of airways inflammation, is a useful and increasingly available confirmatory test for asthma. Several recent studies have demonstrated high statistical accuracy for exhaled nitric oxide as a confirmatory test for distinguishing asthma from other causes of chronic cough in adults and children (see Advances in Clinical Assessment of Asthma in Children, later). Induced sputum to detect an increased percentage of eosinophils could also serve as a confirmatory diagnostic test, although the practicality of its implementation in the clinic setting is limited, and consistent, valid results are not obtainable in younger children.[2]

Preschooler with Recurrent Cough/Wheeze: Diagnosis

Preschoolers present some diagnostic challenges because of their young age. It is obvious that infants and young children are unable to provide a medical history themselves and that clinicians are limited to observations made by parents/caregivers. Preschoolers are usually too young to reliably perform spirometry, peak flows, exhaled nitric oxide, and induced sputum, thereby limiting the use of current asthma confirmatory tests in the clinical setting.

Another challenge is that there are several different clinical patterns of recurrent coughing/wheezing that develop in young children and have different prognoses. These clinical patterns implicate differing disease processes underlying the outcomes of disease persistence versus resolution. Indeed, many infants and young children will experience symptomatic bronchitis/bronchiolitis with respiratory viral infections (i.e., "transient wheezer" or "wheezy bronchitis" patterns), without leading to a chronic recurrent condition. Given this scenario, perhaps it is not surprising that asthma in young children may be both overdiagnosed and underdiagnosed, and often not appropriately managed.

The five criteria for diagnosing asthma can be applied to the preschool child:

1. *Coughing and/or wheezing are recurrent:* a typical pattern begins some months after birth with recurrent symptoms, instigated by common respiratory viral infections, with variable symptoms in between. Some infants and toddlers cough, some wheeze, and some do both. The nature of the cough can vary, often presenting as a dry, persistent cough, but it can also be a wet, gagging cough, sometimes with post-tussive emesis. As asthma exacerbations worsen, young children may manifest tachypnea, retractions, and hypoxemia requiring urgent care. The patterns of recurrence or persistence are essential. For example, a single episode of bronchiolitis in the winter months does not forebode persistent disease unless the episode is severe or accompanied by pneumonia. A pattern of recurrent coughing/wheezing episodes with common respiratory viral infections, extending outside of the winter months,[3] and persistence of coughing/wheezing apart from colds,[4] are presentations of recurrent or persistent disease compatible with asthma. It is not uncommon for young children to present with recurrent pneumonias, atelectasis, or bronchitis before symptoms and patterns of persistent asthma become apparent.
2. *Other causes of coughing/wheezing are excluded:* the differential diagnosis for young children with a clinical picture of asthma is particularly broad and deserves special emphasis, in part because of a number of asthma masqueraders that typically manifest in infancy and early childhood; they are listed in Box 58-6. Neonatal onset of symptoms, associated failure to thrive, diarrhea or vomiting, and even focal lung or cardiovascular findings suggest an alternative diagnosis and require further investigations.
3. *Risk factors for persistent asthma are identified:* a series of risk factors identifies young children who are likely to persist with asthma symptoms: allergic manifestations (clinical and/or biological); parental asthma, and patterns of wheezing apart from common colds. The Asthma Predictive Index (API) is a statistically optimized algorithm that was developed via the Tucson Children's Respiratory Study (CRS) to predict which toddlers with a pattern of recurrent wheezing are most likely to have persistent asthma into the school-age years.[4] A modified version of the API incorporates other risk factors for persistent asthma (Table 58-1).[5] Indeed, toddlers who meet these modified API criteria essentially have the clinical picture

BOX 58-6 Asthma Masqueraders (Differential Diagnosis)

Upper respiratory tract conditions
- Allergic rhinitis*
- Chronic rhinitis*
- Sinusitis*
- Adenoidal or tonsillar hypertrophy
- Nasal foreign body

Middle respiratory tract conditions
- Laryngotracheobronchomalacia*
- Laryngotracheobronchitis (e.g., pertussis)*
- Laryngeal web, cyst, or stenosis
- Vocal cord dysfunction*
- Vocal cord paralysis
- Tracheoesophageal fistula
- Vascular ring, sling, or external mass compressing the airway (e.g., tumor)
- Foreign body aspiration*
- Chronic bronchitis from environmental tobacco smoke exposure*
- Toxic inhalations

Lower respiratory tract conditions
- Bronchopulmonary dysplasia or chronic lung disease of preterm infants
- Viral bronchiolitis*

Causes of bronchiectasis
- Cystic fibrosis
- Immune deficiency
- Allergic bronchopulmonary mycoses (e.g., aspergillosis)
- Chronic aspiration
- Immotile cilia syndrome, primary ciliary dyskinesia

Medications associated with chronic cough
- Acetylcholinesterase inhibitors
- β-adrenergic antagonists

Other
- Gastroesophageal reflux*
- Bronchiolitis obliterans
- Interstitial lung diseases
- Hypersensitivity pneumonitis
- Pulmonary eosinophilia, Churg-Strauss vasculitis
- Pulmonary hemosiderosis
- Tuberculosis
- Pneumonia
- Pulmonary edema (e.g., congestive heart failure)

*More common asthma masquerading conditions.

of school-age children with asthma and might be considered to have early-onset asthma (see Outcomes, Prognoses, and Predictors, later). In comparison, there are other additional risk factors for chronic or persistent wheezing in preschoolers, distinct from common persistent asthma: these include small for gestational age; male gender; environmental and in utero tobacco smoke exposure; and pneumonia with bronchiolitis in infancy.

Table 58-1
Modified Asthma Predictive Index

Toddler-aged children (2-3 years old) with a history of recurrent cough/wheeze in the past year and either one major *or* two minor criteria have an increased risk for asthma in later life (school-aged years).

Major Criteria	Minor Criteria
Parent with asthma	Allergic rhinitis
Atopic dermatitis	Wheezing apart from colds
Inhalant allergen sensitization	Eosinophils >4% (blood)
	Food allergen sensitization

Data from Castro-Rodriguez JA, Holberg CJ, Wright AL, Martinez FD: A clinical index to define risk of asthma in young children with recurrent wheezing. Am J Respir Crit Care Med 162:1403-1406, 2000; and Guilbert TW, Morgan WJ, Zeiger RS, et al: Atopic characteristics of children with recurrent wheezing at high risk for the development of childhood asthma. J Allergy Clin Immunol 114:1282-1287, 2004.

4. *The child improves with asthma therapy:* without confirmatory diagnostic tests for asthma in preschoolers, reliance on response to conventional asthma therapy and management is often used to support a tentative diagnosis of asthma. An appropriate response to therapy might include overt clinical improvement in the clinic to an inhaled beta-agonist (e.g., albuterol, salbutamol), or clinical improvement following a course of daily controller pharmacotherapy and/or oral corticosteroids.
5. *Confirmatory physical examination findings and diagnostic tests:* confirmatory physical examination findings in young children can be helpful, especially if they improve with asthma therapy (e.g., bronchodilator in the clinic). Key parameters of the physical assessment of the young child include: (1) general respiratory status and grading of respiratory distress if any observed; (2) respiratory rate, air exchange, presence and character of coughing and wheezing if detected, and other pulmonary findings by auscultation (e.g., rhonchi, rales); and (3) surveying other body systems for evidence suggestive of other disease processes besides or comorbid with asthma: failure to thrive, clubbing, eczematous rash, nasal patency versus congestion or obstruction, oropharyngeal abnormalities (e.g., palatal defects, lack of tonsillar tissue), cardiac findings suggesting anomalies, or lymphadenopathy/hepatosplenomegaly. Children with asthma rarely, if ever, develop clubbing.

School-Aged Child with Asthma: Diagnosis

The five diagnostic criteria for asthma in children, as described in Box 58-2, also apply to the school-aged child:

1. *Coughing and/or wheezing are recurrent:* In school-aged children, in addition to wheezing and cough, other symptoms emerge as the ability of the children to perceive and verbalize symptoms improves (e.g., chest tightness/pain, shortness of breath, exercise intolerance). Other asthma symptoms in children can be subtle and nonspecific, including self-imposed limitation of physical activities, general fatigue, and difficulty keeping up with peers in physical activities.

BOX 58-7 Asthma Triggers

Common viral infections of the respiratory tract:
rhinovirus, respiratory syncytial virus, parainfluenza and influenza viruses, metapneumovirus
Aeroallergens in sensitized asthmatics:
Animal dander: cats, dogs, rodents, horses
Indoor allergens: dust mites, cockroaches, molds
Seasonal aeroallergens: pollens (trees, grasses, weeds), seasonal molds (*Alternaria, Cladosporium*)
Environmental tobacco smoke
Air pollutants: ozone, sulfur dioxide, particulate matter, wood- or coal-burning smoke, endotoxin, mycotoxins
Strong or noxious odors or fumes: perfumes, hair sprays, cleaning agents
Occupational exposures: farm and barn exposures, formaldehydes, cedar, paint fumes
Cold air, dry air
Exercise
Hyperventilation: crying, laughter
Comorbid conditions: rhinitis, sinusitis, gastroesophageal reflux

BOX 58-8 Common Comorbid Conditions

Upper airway disease
Allergic rhinitis
Chronic rhinitis
Recurrent/chronic sinusitis
Atopic disorders of the "atopic march" of childhood
Allergic rhinoconjunctivitis
Atopic dermatitis
Food allergy
Gastroesophageal reflux disease
Vocal cord dysfunction

Most school-aged children with asthma manifest typical patterns and triggers. Symptoms apart from colds are reported more often. Nocturnal awakenings and early morning worsening of symptoms are not uncommon in poorly controlled patients or during prolonged exacerbations triggered by respiratory infections or inhalant allergens. The typical child has asthma symptoms triggered by viral infections, physical exertion, and hyperventilation (e.g., laughing), cold or dry air, and airways irritants (e.g., smoke) (Box 58-7). Most children with asthma are likely to be allergic and, therefore, a variety of inhalant allergens are additional triggers (see Identifying Asthma Triggers, later).

2. *Other causes of coughing/wheezing are excluded:* several medical conditions are comorbid with asthma, can make asthma worse, and can be difficult to distinguish from asthma (Box 58-8):
   - *Allergic rhinitis* is reported in 85% to 90% of children with asthma.[6] Recurrent or chronic sinusitis is often coincident with asthma. Several mechanisms may explain how uncontrolled allergic rhinitis can provoke or worsen asthma: the release of mediators via nasal allergen exposure can cause bronchoconstriction and eosinophil influx into the lungs by neural and immune mechanisms; postnasal drip may cause coughing, bronchial smooth muscle contraction, and lower airway inflammation; and mouth breathing (i.e., lack of nasal breathing) leads to poor air preparation for the lungs, by bypassing the air warming, humidification, and filtration processes that breathing through the nasopharynx provides.
   - *Food allergy and atopic dermatitis*. These conditions, with allergic rhinoconjunctivitis and asthma, comprise a subset of atopic conditions that compose the "atopic march" of childhood. These conditions tend to cluster in families and individuals, beginning with atopic dermatitis and food allergy in infancy, followed by airways allergic disease and asthma in later childhood. Both food allergen sensitization and atopic dermatitis in infants with recurrent wheezing are recognized risk factors for the subsequent diagnosis of asthma.
   - *Gastroesophageal reflux disease (GERD)* can cause episodic coughing and sometimes wheezing that mimics asthma. GERD is believed to worsen asthma through inflammatory and reflex neural mechanisms related to distal esophagitis, as well as microaspiration. Additionally, GERD may be provoked or caused by asthma, especially when asthma is poorly controlled, during asthma exacerbations, or by the medications used to treat asthma.
   - *Vocal cord dysfunction (VCD)* in adolescents can manifest as intermittent, sudden-onset daytime wheezing. In this condition, the vocal cords close inappropriately during inspiration and, sometimes, exhalation, producing shortness of breath, coughing, throat tightness. The wheezing of VCD is often audible laryngeal wheezing and/or stridor. The monophonic wheeze of VCD generally differs from the polyphonic wheeze of asthma, although asthma can also manifest a monophonic wheeze. In most VCD cases, spirometric lung function testing will reveal "truncated" and inconsistent inspiratory and expiratory flow-volume loops, a pattern that differs from the reproducible pattern of airflow limitation in asthma that improves with bronchodilators. Asthma, allergic rhinitis, sinusitis, and GERD, can be underlying causes of VCD.

   Special procedures are sometimes necessary to evaluate for these conditions because symptoms can be subtle or unreliable. For example, GERD can be without any gastrointestinal manifestations, hence, clinically silent in children. Children with chronic sinusitis often do not report sinusitis-specific symptoms such as localized sinus pressure or tenderness, and may have only a lingering cough.
3. *Risk factors for asthma are identified:* Numerous studies have consistently identified atopy to be a risk factor for asthma; therefore, a history of other allergic conditions (allergic rhinitis, allergic conjunctivitis, atopic dermatitis, and food allergies) or parental asthma and atopy is supportive of the diagnosis of asthma.
4. *The child improves with asthma therapy:* It is believed that the majority of children with asthma should obtain good control of their condition with a conventional approach to

asthma management, as described in different national/international guidelines (see Chapter 59, Asthma Treatment). Prior experience with asthma medications (i.e., bronchodilators) may provide a history of symptomatic improvement that supports the diagnosis of asthma. A lack of response to bronchodilator treatments and corticosteroid therapy is inconsistent with underlying asthma and an investigation for other disorders should be initiated. For children presenting with acute symptoms, treatment with a bronchodilator and, if needed, a short course of an oral corticosteroid might bring quick relief and support the diagnosis of asthma. For children presenting without acute symptoms, but with a historical pattern suggestive of asthma, good improvement in symptoms with a conventional course of daily controller pharmacotherapy of adequate duration (e.g., inhaled corticosteroids for 1 to 2 months) along with other measures to reduce airways inflammation, would support the diagnosis of asthma.

5. *Confirmatory physical examination findings and diagnostic tests:* On physical examination, the general approach applies (see Box 58-4), with special emphasis on the common comorbid conditions (e.g., rhinitis, sinusitis, GERD) that can mimic and/or worsen asthma (see Box 58-8). It is common for asthma in children to manifest in the regular clinical setting without diagnostic physical signs of asthma (e.g., expiratory wheezing). The chest examination is often normal but, sometimes, forced expiratory breaths can elicit otherwise undetectable wheezing. Chest radiographs, typically viewed as normal or with minimal bronchial wall thickening in children with asthma, are often obtained at initial evaluation to screen for causes of persistent coughing and wheezing that are not asthma (e.g., tuberculosis, pneumonia, bronchiectasis).

MEASURES OF LUNG FUNCTION

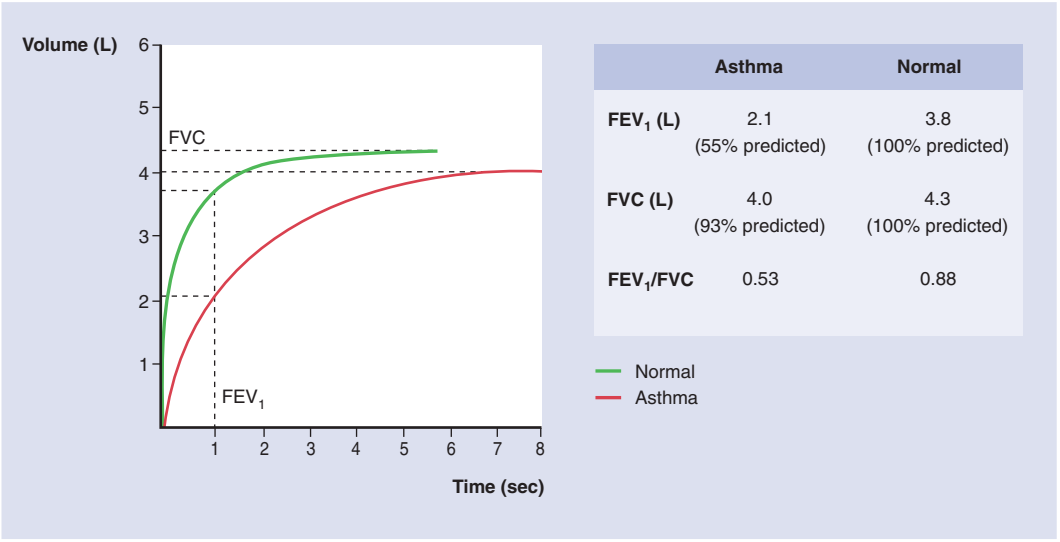
Beginning in school-age years, children develop the ability to perform the confirmatory tests for asthma that are based on measurements of forced expiratory airflow (see Box 58-5). The conventional measure of airflow for diagnosing and assessing asthma is spirometry. For asthma assessments, spirometry measures maximal forced expiratory airflows and lung volumes to determine if either are limited or smaller than adjusted norms, based on height, gender, and ethnicity. In asthma, airway obstruction results in reduced airflow with forced exhalation and smaller partial expiratory lung volumes, such as FEV_1 (Fig. 58-1). Because children with asthma are often hyperinflated and can have larger than normal lung volumes, FEV_1 is adjusted for full expiratory lung volume—the forced vital capacity (FVC)—with an FEV_1/FVC ratio. An FEV_1/FVC ratio less than 0.80 indicates significant airflow obstruction (see Box 58-5).

Airflow limitation in itself is not a hallmark of asthma in children; however, bronchodilator-induced improvement in airflow, or bronchodilator reversibility (traditionally calculated as a percent of change: [{postbronchodilator FEV_1 – prebronchodilator FEV_1}/prebronchodilator FEV_1] × 100) of ≥12% is greater than normal and considered to be confirmatory evidence of asthma (see Box 58-5). Bronchodilator reversibility correlates with and can be viewed as a surrogate marker of airway inflammation and bronchial hyperresponsiveness, and may even be a predictor of irreversible airflow limitation.[7,8] Because airways obstruction can be caused by inflammation and edema that will not improve rapidly with bronchodilator, anti-inflammatory therapy (e.g., an oral and/or inhaled corticosteroid therapeutic trial) may be needed to improve airflow significantly.

Children with asthma often have normal lung function in the resting state, yet are characteristically hypersensitive to a number of provocative stimuli. This lability in lung function is likely a reflection of underlying bronchial hyper-responsiveness (BHR)—another characteristic feature of asthma. Broncho-provocation challenges (using exercise or inhaled methacholine, histamine, adenosine, hypertonic saline, or cold or dry air) can be helpful not only in diagnosing asthma but also in assessing asthma severity and optimizing asthma management.[9] The degree of airway hyper-responsiveness to these exposures correlates to some extent with asthma severity and airways inflammation.[10,11] Broncho-provocation challenges using inhaled broncho-provocative agents are carefully dosed and monitored. For example, using gradually increasing inhaled doses of methacholine, BHR can be demonstrated when an abnormally low dose induces a decline in FEV_1 of ≥20% from baseline. As such, their use in a general practice setting is limited. Exercise challenges (i.e., aerobic exertion or "running" for 6 to 8 minutes) can help to identify children with exercise-induced bronchospasm (EIB). Although the airflow response of non-asthmatics to exercise is to increase functional lung volumes and improve FEV_1 slightly (5% to 10%), exercise can elicit airflow obstruction in children with uncontrolled asthma corresponding to at least a 15% reduction in FEV_1 during or after exercise (see Box 58-5). The onset of EIB is usually within 15 minutes after a vigorous exercise challenge and can spontaneously resolve within 30 to 60 minutes. Exercise challenges can provoke severe asthma exacerbations in at-risk patients; therefore, careful patient selection for exercise challenges and readiness for severe asthma exacerbations are necessary when performing this test.

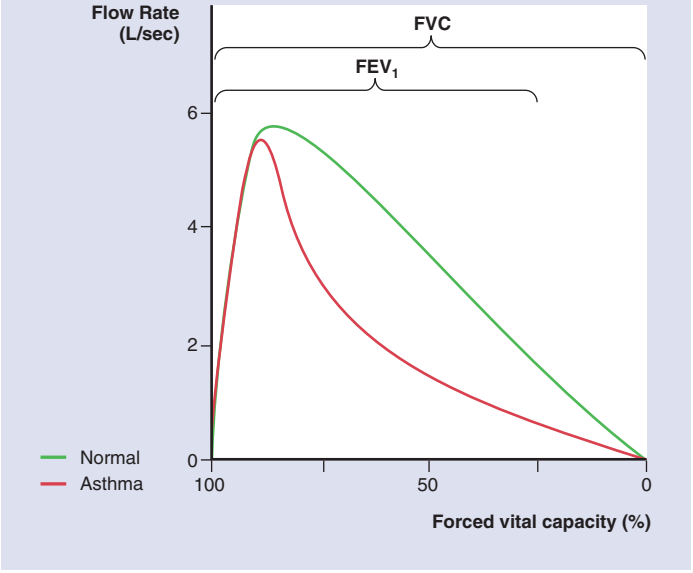
Also typical of asthma is exaggerated variation in airflow, demonstrable by differences in peak flows of greater than 20%, both diurnally (i.e., AM on awakening compared with PM) and day-to-day (see Box 58-5). Non-asthmatics do not have variability in airflow to this degree. Such variability in airflow or peak flows is indicative of more severe and inadequately controlled asthma.

Last, it is necessary to recognize that peak flows, as well as spirometric measures, are completely effort and technique-dependent; the validity and reliability of these measures requires trained and proficient personnel as well as the reproducibility of repeated measures. At least three FEV_1 values or peak flows within 5% is ideal, and the best of three acceptable efforts is used as the final result (*NOT* the average of three acceptable results). Importantly, when asthma is unstable, poorly controlled, or exacerbating, forced expiratory maneuvers such as those generated by spirometry or peak flows can induce bronchospasm and worsen asthma; therefore, one must be wary of performing spirometry or peak flows in a patient with poorly controlled or exacerbating asthma; wary of a patient whose spirometry or peak flows are declining with each effort; and prepared to administer bronchodilator therapy in case of bronchospasm.



	Asthma	Normal
FEV_1 (L)	2.1 (55% predicted)	3.8 (100% predicted)
FVC (L)	4.0 (93% predicted)	4.3 (100% predicted)
FEV_1/FVC	0.53	0.88

A



B

Figure 58-1 Spirometry. A, Volume-time curves. Note how the FEV_1 and FVC lung volumes are obtained. FEV_1 is the volume of air exhaled in the 1st second of a forced expiratory effort. FVC is the total volume of air exhaled during a forced expiratory effort. Both FEV_1 and FVC can be compared with predicted norms (% predicted). The FEV_1 and FEV_1/FVC ratios of the child with asthma are smaller than those of the non-asthmatic child, indicating airflow limitation. The asthmatic child's FVC is close to what is expected. **B,** Expiratory flow-volume loops. Note how peak expiratory flow rates are obtained. Also note the concave or "scooped" appearance of the asthmatic expiratory flow-volume loop when compared with normal; with increasing obstruction, there is greater "scooping." L, liters; L/sec, liters/sec.

Difficult-to-Control Asthma in Childhood: Diagnosis

The child with difficult-to-control asthma can be viewed as a failure of conventional asthma management. Such cases often benefit from a careful review and reassessment of the child, a return to the dogged diagnostician.

If coughing and/or wheezing are recurrent: more rigorous efforts to better understand the coughing or wheezing patterns may help, such as challenges to provoke and observe reported symptoms (e.g., exercise challenges) or overnight observation if the symptoms typically recur at night.

If other causes of coughing/wheezing are excluded: failure to respond to conventional asthma management may be the result of unaddressed comorbid conditions or an occult asthma masquerader. A systematic reconsideration of the differential diagnosis may help to identify such asthma confounders or masqueraders (see Box 58-6):

1. Common comorbid conditions that can worsen or mimic asthma—rhinitis, sinusitis, GERD, VCD—are described earlier.
2. In particular locales, children may be susceptible to develop hypersensitivity pneumonitis (e.g., farming communities, homes of bird owners), pulmonary parasitic infestations (e.g., rural areas of developing countries), or tuberculosis.
3. Uncommon conditions that can mimic childhood asthma include cystic fibrosis, bronchiolitis obliterans, interstitial lung diseases, primary ciliary dyskinesias, humoral immune deficiencies, allergic bronchopulmonary mycoses, atypical mycobacterial disease, congestive heart failure, mass lesions in or compressing the larynx, trachea, or bronchi (e.g. lymphadenopathy), and medication-induced coughing and/or wheezing.

Testing to diagnose or rule out such masquerading diagnoses should be considered: high-resolution CT scans of the chest

or sinuses, pH probe studies for GERD, rhino-laryngoscopy, and/or bronchoscopy.

Risk factors are identified: Ultimately, if potential masqueraders and comorbid conditions have been ruled out, and adherence with therapy has been assured, then children may have severe asthma due to a number of underlying causes, discussed in more detail in the following section on different phenotypes of severe asthma. Briefly, these risk factors include:

1. Pulmonary: fixed airflow obstruction, severe lability in airflow, neutrophilic inflammation
2. Environment: allergen sensitization with high levels of exposure; occupational-like exposures (e.g., ambient endotoxin); aspirin/NSAID hypersensitivity
3. Poor pharmacotherapeutic responders: corticosteroid insensitivity; poor responders to long-acting bronchodilators

The child improves with asthma therapy: Ascertaining adherence with conventional asthma medications can be quite challenging but essential when contending with children with asthma who appear to be treatment failures. A study using digital metered-dose inhaler chronologs to ascertain adherence to conventional inhaled corticosteroid (ICS) controller therapy in children with asthma revealed that, of those who demonstrated treatment failure with an asthma exacerbation, adherence to ICS controller was only 17%, which was far lower than the 55% adherence observed among controlled asthmatics, and even further from the 95% self-reported adherence levels.[12] Extra measures may be needed to enhance compliance and to determine if adequate, prescribed trials of pharmacotherapy have occurred, such as: calendars for tracking all dates and times when medication is taken; enlisting the support of a parent, caregiver, teacher or friend as an asthma "coach" to help support daily adherence and monitoring; and even daily clinic visits or hospitalization to assure daily administration of therapy to determine if the patient is indeed a treatment failure.

Confirmatory physical examination findings and diagnostic tests: The physical examination is used to determine if the physical signs of asthma are consistent with its reported severity, if findings are consistent with a diagnosis of asthma or if asthma masqueraders should be considered. More involved diagnostic tests that support or refute asthma may be necessary (see Box 58-5). Broncho-provocation testing may not only help to confirm the diagnosis of asthma, but can also provide insight into symptom progression and unusual manifestations. For example, an asthmatic who develops upper airway tightness and audible wheezing might, during methacholine challenge, show onset of these symptoms concurrent with truncation of inspiratory flow-volume loops; flexible laryngoscopy might reveal inappropriate vocal cord closure and dysfunction. If severe nocturnal asthma is described, then careful observation overnight might confirm this pattern and, in so doing, confirm the diagnosis of asthma.

ASSESSING ASTHMA SEVERITY AND CONTROL

National guidelines for asthma management recommend the assessment of severity as the basis for patient management. In these guidelines (i.e., National Asthma Education and Prevention Program, National Institutes of Health), asthma severity is categorized into four groups (mild intermittent, mild persistent, moderate persistent, and severe persistent) by ascertaining the frequency of day and nighttime symptoms, spirometric assessment of airflow limitation (i.e., FEV_1 % predicted), and peak flow variability assessed day-to-day (Table 58-2). While these severity criteria have a role in the initial assessment of asthma, there are limitations of this approach as the basis for managing children in clinical practice. These limitations include:

1. Variability of asthma: Determination of asthma severity can fluctuate using these measures.[13]
2. Day and night symptoms: whom do you ask for accurate information, the child and/or parent/caregiver?[14,15]
3. Spirometry and peak flows: challenging to obtain valid measurements in children younger than 6 to 8 years of age. As well, lung function abnormalities change with age in children with asthma such that FEV_1 % predicted is not abnormally low for a large majority of children with asthma.[16]
4. Accounting for controller therapy: for example, how does one designate a severe asthmatic who becomes well controlled on controller therapy?
5. Accounting for exacerbation frequency and severity: a key element of disease severity in children is the frequency and severity of their exacerbations. But how does one classify, for example, a preschooler with a history of

Table 58-2
Classifying Asthma Severity*

	Days with Symptoms	Nights with Symptoms	FEV_1 or Peak Flow	Peak Flow Variability
Severe persistent	Continual	Frequent	≤60% predicted	>30% (day-to-day)
Moderate persistent	Daily	>1 night/week	<80 to >60% predicted	>30%
Mild persistent	>2 days/week but <once daily	>2 nights/month	≥80% predicted	20 to 30%
Mild intermittent	≤2 days/week	≤2 nights/month	≥80% predicted	<20%

*Classification based on clinical features before treatment. The patient's severity classification is determined by the most severe feature.
From National Asthma Education and Prevention Program Expert Panel Report II: Guidelines for the Diagnosis and Management of Asthma. National Institutes of Health/National Heart, Lung, and Blood Institute, NIH Publication No. 97-4051, 1997; National Asthma Education and Prevention Program Expert Panel Report: Guidelines for the Diagnosis and Management of Asthma—Update on Selected Topics 2002; National Institutes of Health/National Heart, Lung, and Blood Institute, NIH Publication No. 02-5075, 2003; Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention. NIH Publication No 02-3659 (original 1995, updated 2002); and 2005 Update: Workshop Report (http://www.ginasthma.com).

several severe exacerbations requiring hospitalization, but infrequent day or night symptoms or rescue medication usage in the two months following hospitalization? A history of severe exacerbations such as life-threatening episodes or requirement for hospitalization, and prior frequent or prolonged use of systemic corticosteroids, should elicit a higher level of concern.

6. Activity limitation and quality of life outcomes: if a child with asthma refrains from participating in physical activities so as not to trigger asthma symptoms, their asthma would be inadequately controlled but not detected by the standard questions.

More recently, asthma control has been introduced as an approach to assess the adequacy of current treatment, and to improve care and outcomes for children with asthma. The U.S. National Asthma Education and Prevention Program (NAEPP)[17] and the Global Initiative for Asthma (GINA)[18] define the goals of asthma control as summarized in Box 58-1. These well-accepted goals imply that the assessment of asthma control is, at best, multidimensional and should include evaluation of these different domains of asthma outcomes: frequency of daytime symptoms, nighttime awakenings, and usage of quick reliever and exacerbation reliever medications; functional status (e.g., exercise tolerance); health care utilization (e.g., urgent visits, emergency department [ED] visits, hospitalizations); missed school or work; quality of life aspects; lung function; and assessment of airways inflammation. Additionally, an understanding of potential exposures that can worsen asthma, current controller medication usage, adherence and the technique used with inhaled controller medications completes a working understanding of an individual's asthma from which a tailored and effective management plan can be derived. Inadequate control of asthma indicates to the clinician the necessity of refining assessments of exposures, triggers, comorbid conditions, and adherence—as well as the possibility of the need to step up the level of therapy to gain control.

Preschool-Aged Children: Assessment

For preschool children up to approximately 7 years of age, the assessment of asthma severity and control is based primarily on symptoms, medication usage, and exacerbations because young children cannot perform the maneuvers required for conventional lung function measurements. The history of asthma is acquired almost completely from the parent(s) or caregivers as preschool-aged children are generally limited in describing their symptoms, their accuracy of symptom frequency and their placement in the context of time. A "3 strikes" rule is a practical concept for determining if a child with asthma is inadequately controlled (Box 58-9). Although this and other simplified algorithms have not been validated as a measure of asthma control in children, they incorporate many of the dimensions of asthma control that are identified in national and international guidelines.

School-Aged Children: Assessment

The general approaches and challenges to assessing asthma severity and control, described earlier, are applicable to the school-aged child with asthma.

BOX 58-9 Indicators of Inadequate Asthma Control

The presence of *any* of the following indicates inadequate asthma control:

Three or more times/week
- Asthma symptoms
- Rescue reliever medication use (e.g., albuterol to treat symptoms)

Three or more times/month
- Night awakenings due to asthma

Three or more times/year
- Quick-relief inhaler fill/refills
- Asthma exacerbations requiring urgent medical visits, prednisone courses, emergency department visits, hospitalizations

ASKING QUESTIONS ABOUT ASTHMA CONTROL

It is believed that optimal history-taking from lower school-aged children (e.g., 5 to 12 years of age) should include input from both the parent and child. Children can accurately recognize asthma symptoms, their common triggers, and their impact on daily activities; although younger children may be unable to accurately quantify the frequency of their symptoms or place them in the context of time. In a study by Lara and colleagues assessing the validity of exercise-related symptom reporting by children with asthma compared with their parents, child-reported coughing and wheezing correlated with lung function changes and observed symptoms due to exercise; in contrast, parent-reported symptoms did not correlate.[14] Guyatt and coworkers observed in children younger than 11 years of age that their symptom reports correlated strongly with changes in quality of life measures, whereas parents' ratings of asthma symptoms showed moderate correlations with FEV_1 and asthma control, but not quality of life measures.[15] Thus, clinicians are likely to obtain important and complementary information from children and their parents.

For children with asthma, there are several guidelines,[18,19] as well as health-related quality of life instruments, clinical diaries, and questionnaires for assessing asthma severity and control: About My Asthma[20] Childhood Asthma Questionnaire,[21] "How Are You?" questionnaire,[22] Pediatric Asthma Quality of Life Questionnaire (PAQLQ),[23] Pediatric/Adolescent Asthma Therapy Assessment Questionnaire (ATAQ),[24] Children's Health Survey for Asthma,[25] Asthma Assessment Questionnaire for Your Child,[26] Rules of Two,[27] and Asthma Control Test (ACT).[28]

Within the numerous questionnaires noted above for assessing asthma control, there are key questions that capture most of the relevant information. The Asthma Control Test (ACT) for children 12 years of age and older, and the Childhood ACT for children 4 to 11 years of age, are two examples of self-administered questionnaires that have been developed and validated with the objective of identifying the most relevant questions (Table 58-3). In the development of both questionnaires, questions about all of the domains of asthma

Table 58-3
Key Questions When Assessing Asthma Control in Children

Questionnaire Examples	Childhood Asthma Control Test*	Asthma Control Test†
For ages	4 to 11 years	12 years and older
Who replies	Child and parent/caregiver	Teenager
Recall period	Past 4 weeks (parent/caregiver only)	Past 4 weeks
Response format	Child: 4-point scale Parent/caregiver: 6-point scale	5-point scale
Questions	**For child:** How is your asthma today? How much of a problem is your asthma when you run, exercise, or play sports? Do you cough because of your asthma? Do you wake up during the night because of your asthma? **For parent/caregiver:** How many days did your child have any daytime asthma symptoms? How many days did your child wheeze during the day because of asthma? How many days did your child wake up during the night because of asthma?	How would you rate your asthma control? How much of the time did your asthma keep you from getting as much done at work, school, or at home? How often have you had shortness of breath? How often did your asthma symptoms (wheezing, coughing, shortness of breath, chest tightness or pain) wake you up at night, or earlier than usual in the morning? How often have you used your rescue inhaler or nebulizer medication (such as albuterol)?

Questionnaire examples from http://www.asthmacontroltest.com.
*Liu AH, Zeiger R, Sorkness C, et al: Development and cross-sectional validation of the Childhood Asthma Control Test. J Allergy Clin Immunol 119:817-825, 2007.
†Nathan RA, Sorkness CA, Kosinski M, et al: Development of the asthma control test: A survey for assessing asthma control. J Allergy Clin Immunol 113:59-65, 2004.

control were included, and key questions were selected via logistic regression analyses as predictors of asthma control.[28,29] These two questionnaires are similar in that each question provides a score such that the sum of the scores constitutes the total test score, and lower scores indicate poorer control. Generally, a total score of 19 or less indicates inadequate control. The key questions that compose these questionnaires appeared to differ slightly, but were generally consistent with NAEPP and GINA guidelines. The optimal combination of seven questions for the Childhood ACT includes four questions for the child and three questions for the parent/caregiver, whereas the five questions for the ACT are all directed toward the older child with asthma.

Measures of Airflow Limitation

Pulmonary function testing is particularly helpful in children with asthma whose symptoms are nonspecific, who are poor perceivers of airflow obstruction, or in whom physical signs of asthma do not manifest until airflow limitation is severe. Forced expiratory airflow measures, such as spirometry, are helpful in diagnosing and monitoring asthma and in assessing efficacy of therapy. However, the validity of spirometric measures is dependent on trained personnel to conduct and interpret the tests, and a patient's ability to properly perform a full, forceful, and prolonged expiratory maneuver, usually feasible in children older than 6 years of age (with some younger exceptions).

Normative values for FEV_1 have been determined for children, based on height, sex, and race. FEV_1 as a percentage of predicted is one of four criteria used to define asthma severity in standard clinical asthma guidelines.[19] FEV_1 measurements are conventional means of assessing airflow limitation and airway obstruction; however, they do not discriminate children who display clinical characteristics of mild, moderate, and even severe asthma. The NAEPP guidelines set >80% FEV_1 % predicted for patients with mild persistent asthma, 60% to 80% predicted for moderate asthma, and <60% predicted for severe persistent asthma. In a comparison of asthma severity in children based on symptom frequency or medication use, Bacharier and colleagues found that the mean FEV_1 was 97.5%, 101.1%, 99.9%, and 95.1% predicted values for children with mild intermittent, mild persistent, moderate persistent, and severe persistent asthma, respectively.[16] In this study, only 6.5% of children with moderate persistent asthma had $FEV_1 < 80\%$ predicted, and only 3.5% of those with severe persistent asthma had $FEV_1 < 60\%$ predicted. Although FEV_1 % predicted did not differ by level of asthma severity, FEV_1/FVC ratios decreased as asthma severity worsened (means of 0.88, 0.86, 0.83, and 0.79, respectively; $P < 0.0001$), and was abnormal in 17%, 20%, and 51% of children with mild, moderate, and severe persistent asthma, respectively. This suggests that FEV_1/FVC is a more sensitive and reliable measure of airflow limitation for assessing asthma severity in children, by accounting for the hyperinflation manifest by many of these children.

ASTHMA EXACERBATIONS IN CHILDREN

An important component of the evaluation of asthma severity and control is exacerbations. In the United States, childhood asthma is the most common cause of childhood ED visits and hospitalizations, accounting annually for 867,000 ED visits and 166,000 hospitalizations. Considering this high frequency of ED visits and hospitalizations for asthma, death caused by asthma is relatively uncommon (0.3 deaths per 100,000 population per year). In the United States, in 2000, asthma was responsible for 223 deaths of children.

A disparate increase in the frequency of severe asthma exacerbations in children living in inner city communities, especially of African-American ethnicity, has persisted in the United States over the past 25 years. A scenario of biological, environmental, economic, and psychosocial risk factors underlie severe asthma exacerbations (see Severe Asthma in

BOX 58-10 Severe Asthma Types in Children

Corticosteroid response

Corticosteroid-responsive: marked improvement in lung function with a 1-week course of oral corticosteroids

Corticosteroid-insensitive:

Chaotic lung function: wide variability in lung function, persisting despite oral corticosteroid course

Non-chaotic lung function: fixed airflow obstruction

Character of inflammation: while on oral and high-dose inhaled corticosteroids

Remodeling without inflammation

Neutrophilic inflammation

Persistent eosinophilic inflammation

Life-threatening exacerbations

Sudden asphyxic: abrupt onset, loss of consciousness or respiratory arrest associated with extremely high $PaCO_2$ (e.g., 113 mm Hg); rapid recovery in hours; neutrophilic inflammation

Gradual progressive: gradual worsening, increased work of breathing over days, respiratory failure due to fatigue, associated with near normal $PaCO_2$; mechanical ventilation for days with gradual recovery over weeks; eosinophilic inflammation

Childhood: Prognoses and Predictors, later). Although a previous hospitalization for asthma is a strong predictor of future severe exacerbations, they can occur in children with all levels of asthma severity (mild, moderate, or severe).

The onset of severe asthma exacerbations can be prolonged or rapid (Box 58-10).[30,31] These exacerbation types can be remarkably distinct. Some exacerbations escalate over days into severe airflow obstruction resulting from progressive inflammation, epithelial sloughing, and cast impaction of small airways. When extreme, respiratory failure due to fatigue develops and typically necessitates mechanical ventilation for numerous days. In contrast, some children experience abrupt onset of severe symptoms from extreme airway reactivity and physiologic susceptibility to airways closure. Such sudden, asphyxic exacerbations usually occur outside of medical settings, are initially associated with extreme hypercapnia (i.e., mean $PaCO_2$ 116 mm Hg), and tend to require relatively brief periods of supportive ventilation (i.e., 34 hours).[30] Sudden asphyxic asthma also appears to have distinct histopathologic features, most notably increased neutrophils and reduced eosinophils when compared with fatal episodes of gradual onset.[32,33] Fatal asthma attacks of sudden onset have also been associated with increased CD8+ T lymphocytes[34] and increased airway mucous glands.[33]

With either type of severe exacerbation, controller therapy should be reinforced, but recognition of the specific type of exacerbation helps to optimize early exacerbation management in order to keep it from becoming life threatening. For example, progressive-onset exacerbations can likely be interrupted with oral corticosteroids. Preparedness for managing such exacerbations should include keeping an oral corticosteroid at home to administer early in the course of a developing exacerbation. In comparison, optimal management of abrupt-onset exacerbations includes any measures to reduce bronchial lability, consideration of daily measures of lung function such as peak flows to identify any subclinical lability or reduction in lung function, and, in extreme cases, having supplemental oxygen, Epi-pens, and providing CPR training for parents and caregivers.

Several studies have revealed that a discriminating risk factor in children who experience severe asthma exacerbations is food allergen sensitization.[35] A relevant question that remains unsettled is whether or not this implicates food allergens as a common trigger of severe exacerbations, or if food allergen sensitization is a biological marker that results from immunologic processes that concurrently render the lungs susceptible to severe exacerbations (e.g., early-onset atopy with food allergy).

PHENOTYPES OF SEVERE ASTHMA IN CHILDREN

Various clinical and/or pathophysiologic phenotypes can be identified in patients whose asthma is more difficult to control, also called severe or refractory asthma, after suboptimal adherence and other confounders are ruled out. There is general information on the characteristics of this subgroup of children, but limited information on why and how the evolution to a severe state occurs. Typically, these are the patients whose medication requirement is escalated without achieving optimal control of symptoms or acute exacerbations. Bratton and coworkers reported on the outcome of almost 100 children with severe asthma (mean age 11 years, range 9 months to 18 years) referred for treatment in a multidisciplinary day program based at National Jewish Medical and Research Center.[36] There were features indistinguishable from pediatric epidemiologic asthma studies: 56% male, 17% minority, and 25% of lower socioeconomic status; median age of asthma onset was 2 years; approximately 80% were classified as atopic by skin testing and 65% were living with a cat or dog in the home at the time of admission. However, several measures of severity and poor control were distinct (Box 58-11): median lifetime hospital admissions per patient were 6.5. Features of severe, life-threatening exacerbations were prominent: 64% had experienced cyanotic episodes, 30% had loss of consciousness and 25% had been intubated for respiratory arrest. Sixty percent of patients were taking oral corticosteroids on admission, with a median dose of 10 mg/day for adolescents, 6.3 mg/day for school-age children, and 0.6 mg/day for preschoolers. Corticosteroid adverse effects were reported in 79%. Nearly one half of the children in the cohort were morbidly obese (body mass index [BMI] ≥95th percentile) or at risk of obesity (BMI ≥ 85th percentile). Marked physical deconditioning was notable with a median functional endurance of 8% of predicted for age. BMI was significantly associated with corticosteroid dose at admission ($r = 0.42$; $P < 0.0001$) and inversely correlated with functional endurance ($r = -0.66$; $P < 0.0001$). Median absence from school due to asthma for the previous school year was 26.5 days.

A separate retrospective review of 164 consecutive school-aged children admitted (median age 14.0 years, median dura-

BOX 58-11 High-Risk Factors for Asthma Morbidity and Mortality

Biophysical
- Previous severe asthma exacerbation(s):
  - Hospitalization for asthma
  - Exacerbation(s) with cyanosis, loss of consciousness, seizure, respiratory arrest, intubation, mechanical ventilation
  - Severe airflow obstruction
  - History of rapidly occurring attacks
- Severe bronchial hyper-responsiveness
- Increasing and large diurnal variation in peak flows
- Decreased chemosensitivity and perception of dyspnea
- Poor response to systemic corticosteroid (CS) therapy
- Routine oral corticosteroid requirement
- Food allergy
  - Frequent missed school due to asthma (≥20 days per year)
  - Obesity
  - Male gender
  - Low birth weight
  - Nonwhite (especially black) ethnicity

Environmental
- Allergen exposure in sensitized patients
- Environmental tobacco smoke exposure
- Air pollution exposure
- Urban environment

Economic/psychosocial
- Poverty
- Crowding
- Mother <20 years old
- Mother with less than high school education
- Inadequate medical care:
  - Inaccessible
  - Unaffordable
  - No regular medical care (only emergent)
  - No care sought for chronic asthma symptoms
  - Delay in care of asthma exacerbations
  - Inadequate hospital care for asthma exacerbation
- Psychopathology in the parent or child
- Family problems
- Alcohol or substance abuse

tion of asthma 11.9 years) to National Jewish for refractory asthma revealed interesting and important clinical phenotypes based on response to oral corticosteroid treatment (see Box 58-10).[37] All were on high-dose inhaled corticosteroid (median 1500 μg/day) and more than 50% were receiving chronically administered oral corticosteroid (median dose 15 mg/day) on admission. Fifty-three percent of these patients received a 7-day course of oral corticosteroid therapy secondary to poor asthma control on admission: 24% were deemed corticosteroid-insensitive based on failure to respond to a 7-day course of oral glucocorticoids by ≥15% improvement in AM prebronchodilator FEV_1. In comparison, the 76% who were corticosteroid-sensitive demonstrated a median improvement in FEV_1 of 45%. Two distinct patterns in the daily spirometry of corticosteroid-insensitive patients were noted in light of a poor FEV_1 response after a 1 to 2 week burst: a "chaotic" pattern characterized by marked variability in lung function; and a "nonchaotic" pattern displaying limited diurnal variability that might be due to a fixed airway obstruction. The risk factors associated with corticosteroid-insensitivity included need for oral corticosteroids at an earlier age, need for higher maintenance oral corticosteroid dose, and black ethnicity—the latter possibly related to a genetic or immune predisposition.[38] Last, although speculative, these two patterns of lung dysfunction in children with corticosteroid-insensitive asthma may represent different underlying disease mechanisms that may be better managed with different interventions.

IDENTIFYING ASTHMA TRIGGERS

Asthma symptoms can be triggered by a range of ubiquitous exposures: respiratory viruses, allergens, tobacco smoke, air pollutants, other airway toxicants, and cold or dry air (see Box 58-7). Exposures that induce airways inflammation, such as viral infections and inhaled allergens, can induce prolonged asthma exacerbations and increase airways hyperresponsiveness to irritant exposures for subsequent weeks. Common air pollutants and tobacco smoke can worsen asthma, especially in those who are predisposed by ongoing airways inflammation and/or genetic factors (e.g., glutathione-*S*-methyltransferase [GST]-null genotypes). Numerous exposures known to incite asthma in some adults in occupational settings (e.g., endotoxin) are currently being recognized as similar triggers of asthma in exposed children. Aspirin sensitivity, also recognized in some adults with asthma, has perhaps been under-recognized in children. Accordingly, a good environmental exposure history is essential for optimal asthma assessment and management.

Common Respiratory Viral Infections

Viral infections (e.g., respiratory syncytial virus [RSV], rhinovirus, parainfluenza and influenza viruses, metapneumovirus) are strongly associated with wheezing episodes in young children. It is uncertain if these infections contribute to aberrant lung growth and/or development or chronic asthma in later childhood, independent of atopy.[39,40] Severe RSV bronchiolitis in infancy (i.e., resulting in hospitalization) has long been suspected and is a risk factor for asthma as well as allergy in adolescence (e.g., animal dander sensitivity).[41] An unsettled question is whether or not severe viral bronchiolitis provides an enhanced pro-allergic Th2 response locally by overexpression of IL-4 or IL-13, or if delayed Th1 function underlies the susceptibility to severe bronchiolitis, allergic sensitization, and persistent asthma. In an emergency department study of respiratory viral pathogens in wheezing children, RSV was the predominant pathogen of wheezing infants, detected in 68% of wheezing children younger than 2 years of age versus 6% of older children.[42] In contrast, rhinovirus was detected in 41% of wheezing infants and 71% of older wheezing children; an emergent wheezing episode in children was most likely in those who had rhinovirus and atopy (positive RAST), nasal eosinophilia, or elevated nasal eosinophil cationic protein.

Two longitudinal birth cohort studies further our understanding of the relationship of common respiratory viral infections and subsequent recurrent wheezing and asthma outcomes. In the Childhood Origins of Asthma Study (COAST), although RSV and parainfluenza were associated with respiratory illnesses of increased severity, the most commonly identified respiratory virus with wheezing episodes was rhinovirus.[3] Many species of rhinovirus underlie its perennial presence such that rhinovirus-associated infantile wheezing episodes in March through November were strongly associated with reported wheezing in the third year of life, more so than RSV-associated wheezing. In the Tucson CRS, lower respiratory tract infections (LRTI: manifest as wheezing, deep or wet chest cough, hoarseness, stridor, shortness of breath) were cultured for common pathogens in the first 3 years of life.[43] Ninety-one percent of LRTIs were cultured: 44% were RSV-positive, 14% were parainfluenza-positive, 14% were culture-positive for other respiratory pathogens, and 27% were culture-negative (rhinovirus was not easily detectable in this study). Followed prospectively, infants with RSV LRTI were more likely to have wheezing symptoms at 6 years of age, but not at later ages (i.e., 11 and 13 years old). None of the other LRTI groups was different from non-LRTI children in the prevalence of asthma symptoms at these follow-up time points. There were also no differences in prevalence of allergen sensitization or lung function among the RSV group, other LRTI groups, and the non-LRTI group at later time points. However, young children who had radiographic evidence of pneumonia or croup symptoms accompanying wheezing were more likely to have persistent asthma symptoms and lung function impairment at 6 and 11 years of age.[44,45] This further supports the premise that individuals with lower airways vulnerability to common respiratory viral pathogens are at risk for persistent airways disease.

Risk factors for recurrent wheezing episodes in early childhood include smaller airways at birth (associated with male gender, small size for gestational age, and tobacco smoke exposure beginning in utero) and reduced IFN-γ (T-helper 1 type) responses in early life. The following linkage of reduced IFN-γ responses with recurrent wheezing episodes, lung dysfunction, and asthma has been observed in multiple studies and may indicate susceptibility owing to impaired antiviral immune responses:

1. Reduced PHA-induced IFN-γ production by cord blood samples was associated with more respiratory viral infections in the first year of life.[46]
2. Following RSV bronchiolitis in infants, reduced IL-2-induced IFN-γ production by peripheral blood cells was associated with persistent asthma, reduced airflow, and bronchial hyper-responsiveness.[47]
3. In experimental rhinovirus infection of adults with allergic rhinitis or asthma, increased symptoms and prolonged viral shedding were associated with lower IFN-γ/IL-5 ratios in induced sputum.[48]

Allergen Sensitization and Exposure

Sensitization to inhaled allergens is expected in children with asthma in the United States. In the Childhood Asthma Management Program (CAMP) that included 1041 5- to 12-year-old children with asthma from eight different U.S. and Canadian centers, 88% of the children were already sensitized to at least one common aeroallergen, and 56% were exposed to high levels of at least one allergen to which they were sensitized.[6] Similarly, in a study of inner-city children with asthma (Inner-City Asthma Study), 94% were sensitized to at least one inhaled allergen, with nearly 80% sensitized to at least two allergens.[49]

A cardinal feature of asthma in children is the association of sensitization and exposure to higher levels of perennial allergens, especially in the home, with disease severity and persistence. In the CAMP study, the combination of allergic sensitization to dog, *Alternaria*, or cat was associated with more severe disease as measured by BHR to methacholine.[6] In contrast, in the National Cooperative Inner-City Asthma Study, the combination of cockroach or rat allergen sensitization and high-level exposure was associated with more hospitalizations, unscheduled medical visits, more days of wheezing, more missed school days, and more nocturnal awakenings owing to asthma.[50,51] Interestingly, a similar pattern of asthma severity was not seen with dust mites or cat allergy in this cohort. Mouse allergen sensitization and exposure is also expected to increase asthma severity in some inner-city locales, although studies have not been able to disentangle the effect of mouse allergen from that of cockroach allergen because of their high correlation.[52-54] It has been shown that poor lung function in children with asthma is longitudinally associated with indoor allergen sensitization and exposure (i.e., cat, dog, mites), suggesting that asthma persistence in childhood is allergen-driven in homes.[55] Another longitudinal birth cohort study observed that sensitization and exposure to cat, dog, and/or dust mite allergens in the home were associated with poorer lung function (i.e., increased airways resistance) as early as 3 years of age.[56]

Determining allergen sensitization and exposure in children: Allergen sensitization in children via IgE can be determined in vivo by skin sensitization and in vitro by detection of allergen-specific IgE in serum or plasma. Skin prick allergy testing is relatively inexpensive and provides results quickly.[57] Tests should be carried out using standardized methods and standardized allergen extracts. The panel of allergens tested will depend on the age of the child and individual case history, and should vary depending on local environment-specific allergens. Perennial allergens that may be in high levels in the home should be prioritized.

Optimally, allergy skin testing should be performed by qualified health care professionals with training and demonstrable proficiency. Results from skin prick tests depend on a series of variables, including extract potency, use of drug treatment by the patient, skill of the tester, and the device used to puncture the skin. There is a very low risk of adverse allergic symptoms due to skin prick testing aside from local itching. Nevertheless, skin test personnel and their clinical sites of operation should be prepared to manage the very rare but unpredictable adverse event. Interpretation of the results and assessment of their clinical significance should be performed by an experienced clinician. Skin prick testing can be performed in children of all ages.[58]

In vitro testing for allergen-specific IgE may be useful if skin prick testing cannot be performed because the child has severe atopic dermatitis, urticaria or dermographism, is

Table 58-4
Indicators of Significant Allergen Exposure in Households*

Allergen	Home Environment History	House Dust Analysis for Major Allergen Content
Cat	Cat(s) in home	Fel d 1 > 8 μg/g dust
Dog	Dog(s) in home	Can f 1 > 10 μg/g dust
Dust mite	In dry climates, increased humidity (home dampness, mold, humidifier or evaporative cooler usage)	Der p 1 + Der f 1 > 2 μg/g dust
Cockroach	Sighting in home	Bla g 1 > 2 U/g dust; Bla g 2 > 10 U/g dust
Fungi	Mold, mildew, water damage, or water collection in home	Mold plate from house dust >25,000 colonies
Rat†	Sighting in home of rats or mice	Rat n 1 > 4 ng/g dust
Mouse‡	Sighting in home of mice	Mus m 1 > 1.6 μg/g dust

*From Nelson HS, Szefler SJ, Jacobs J, et al: The relationships among environmental allergen sensitization, allergen exposure, pulmonary function, and bronchial hyperresponsiveness in the Childhood Asthma Management Program. J Allergy Clin Immunol 104:775-785, 1999.
†From Perry T, Matsui E, Merriman B, et al: The prevalence of rat allergen in inner-city homes and its relationship to sensitization and asthma morbidity. J Allergy Clin Immunol 112(2):346-352, 2003.
‡From Phipatanakul W, Eggleston PA, Wright EC, Wood RA: Mouse allergen. II. The relationship of mouse allergen exposure to mouse sensitization and asthma morbidity in inner-city children with asthma. J Allergy Clin Immunol 106:1075-1080, 2000; and Phipatanakul W, Eggleston PA, Wright EC, Wood RA: Mouse allergen. I. The prevalence of mouse allergen in inner-city homes. The National Cooperative Inner-City Asthma Study. J Allergy Clin Immunol 106:1070-1074, 2000.

unable to discontinue antihistamine therapy, or has had a dangerous allergic reaction to a food. In vitro IgE testing can be conducted at any age using a validated method such as the CAP system fluoroenzyme-immunoassay (FEIA).[59]

Elevated indoor allergen levels associated with asthma severity in sensitized individuals can sometimes be determined via environmental history, although this can be inaccurate. Laboratory-based measurement of major allergen content in house dust samples is available commercially on a limited basis (Table 58-4).

Tobacco Smoke and Air Pollutant Exposure

Environmental tobacco smoke (ETS), air pollutants (e.g., ozone, sulfur dioxide), and endotoxin and mycotoxins aggravate airways inflammation and increase asthma severity. ETS is a risk factor for wheezing problems at all ages. Prenatal ETS exposure is associated, in a dose-dependent manner, with wheezing manifestations and decreased lung function in infancy and early childhood.[60-62] Postnatal ETS exposure is associated with a greater likelihood of transient wheezing in infancy[63] and persistent asthma in childhood.[64] Cigarette smoking has also been strongly associated with persistent asthma and asthma relapses in adulthood.[23] ETS exposure is also associated with food allergen sensitization,[65] allergic rhinitis, hospitalization for lower respiratory tract infections, BHR, and elevated serum IgE levels.[66,67] In a 7-year prospective study, ETS exposure was associated with greater inhalant allergen sensitization and reduced lung function.[68]

Other indoor exposures that have been associated with worsening asthma include wood-burning, nitrogen dioxide (e.g., from gas-burning stoves, kerosene space heaters), endotoxin, and mycotoxins. Outdoor air pollutants associated with worsening asthma include particulate matter, ozone, sulfur dioxide, and diesel exhaust. Some children may be particularly susceptible to common air pollutants (e.g., ETS, ozone, diesel exhaust) such that these exposures might not only make existing asthma worse, but they may also have a causal role. For example, polymorphisms in genes that detoxify oxidant stress products may be relevant to asthma manifestations owing to common exposures. Asthmatic children with common loss-of-function mutations in the glutathione-*S*-transferase M1 and P1 enzymes (GSTM1, GSTP1) are susceptible to ubiquitous inhaled exposures that cause oxidant stress, such as environmental tobacco smoke,[69,70] diesel exhaust,[71] and ozone.[72-74]

Aspirin-Sensitive Asthma

Aspirin-sensitive asthma (ASA) in children has not been studied as extensively as in adults and has perhaps been under-recognized in children. Based on an oral provocation challenge, one study found that 5.0% of children with asthma had a positive challenge, and 15.5% of those with a history of aspirin sensitivity reacted.[75] In contrast to adults with ASA, children with ASA were mostly male (2 : 1), more than 80% were atopic, and although nasal polyposis was rare, urticaria was more common than in adults. The primary mechanism of the pharmacologic action of and intolerance to aspirin and other nonsteroidal anti-inflammatory medications is thought to involve inhibition of the cyclo-oxygenase enzyme, subsequent prostaglandin synthesis, and activation of the leukotriene pathways in the respiratory tract; however, the relation between aspirin sensitivity and airway disease is not clear.

Occupational Exposures

Although occupational exposures that cause or worsen asthma are much more recognized in adults, some children might have chronic exposure to environmental endotoxin or similar airway proinflammatory agents in their home environments. Such exposures, often measured by endotoxin levels in house dust, have been associated with increased asthma symptoms and severity[76,77] and increased wheezing in infancy.[78,79] A recent large U.S. survey revealed that house-dust endotoxin levels were associated with increased asthma prevalence in a dose-dependent manner,[80] suggesting that the association of endotoxin with asthma may be common and not limited to rural settings.

AIRWAY INFLAMMATION AND HISTOPATHOLOGY

Preschooler with Recurrent Cough/Wheeze: Inflammation and Histopathology

Airway inflammation is a critical component in asthma, yet, similar to the assessment of airflow limitation, evaluation of airway inflammation in young children remains a challenging field of research. Research bronchoscopy and markers of airway inflammation studies in very young children with recurrent wheeze have revealed generalized inflammation with no predominant cellular pattern, unlike a primary eosinophilic feature apparent in older children or adults (Box 58-12). Bronchoalveolar lavage (BAL) studies from children with asthma (4 to 15 years), infantile wheeze (5 to 46 months), chronic cough (10 months to 13 years), cystic fibrosis (2.5 to 15 years), and controls (1.5 to 15 years) were undertaken by Marguet and colleagues.[81] Infantile wheezers have few eosinophils in BAL fluid compared to asthmatic children. Two thirds of children with asthma had increased BAL eosinophils, whereas less than one third of infantile wheezers did. An interesting finding in this study was the increase in neutrophils (i.e., BAL neutrophils >10%) in one half of the wheezing infants and in one third of the children with asthma. In another bronchoscopy study by Krawiec and coworkers of preschool children (mean age 14.9 months) with at least two episodes of wheezing or prolonged wheezing for at least 2 months, BAL inflammatory cells and mediators were generally increased compared with healthy controls: total BAL cells/mL, lymphocytes, macrophages/monocytes, polymorphonuclear cells, epithelial cells, and eosinophils.[82] BAL fluid levels of 15-HETE, PGE_2, LTE_4, and LTB_4, but not in PGD_2 and tryptase, were also greater in wheezing children compared with controls. In a retrospective study, the BAL cell profile of children younger than 3 years of age with severe recurrent wheezing (at least three moderate to severe episodes) compared with healthy controls revealed a higher percentage of neutrophils (mean 9% versus 2.1%, $P = 0.003$).[83] The larger number of neutrophils was not associated with detectable bacterial or viral infection, age, sex, or atopic status. These three studies show that, unlike prominent eosinophil and mast cell involvement in adults and older children, the airways inflammation in very young children with recurrent wheezing involves generalized immune upregulation, and tends toward neutrophilic inflammation. It is likely that these studies comprise a mixed group of infantile wheezers, from whom a subgroup will evolve into typical atopic asthma with eosinophil and mast cell involvement, whereas others may have different forms of pulmonary disease (i.e., transient wheezers, non-atopic wheezers).

Evaluation of airway remodeling in young children remains a challenging field of research due in part to ethical constraints of biopsy studies in this age group. Children younger than 2 years of age with severe wheeze and/or cough, accompanied by decreased specific airway conductance and/or bronchodilator reversibility, did not have evidence for cellular or immunologic alterations or thicker epithelial reticular basement membranes on endobronchial biopsy suggestive of airway remodeling when compared to healthy controls and established asthma subjects.[84] In this study, the only participant with a thickened reticular basement membrane on biopsy also had airway eosinophilia. These findings have significant implications: (1) in young children who are symptomatic and have airflow limitation, clinical features do not necessarily correlate with structural changes of airway remodeling or eosinophilic inflammation typical of associations seen in older children and adults with asthma; and (2) other studies of airway injury or aberrant repair are needed to provide more insights into the relation between inflammation and remodeling.

School-Aged Child with Asthma: Inflammation and Histopathology

Our knowledge substantiating the role of airway inflammation in asthma comes primarily from studies of adults with mild to moderate asthma in the absence of inhaled corticosteroid therapy who underwent bronchoscopy with bronchoalveolar lavage with or without endobronchial biopsies. These studies in corticosteroid-naïve subjects have demonstrated characteristic findings: airway epithelial desquamation with varying degrees of inflammatory cell infiltration consisting primarily of eosinophils, mast cells, and activated T lymphocytes[85,86] (see Box 58-12 and Fig. 58-2). A few studies have characterized inflammatory and structural changes in the airways of children with mild to moderate atopic asthma, compared with atopic non-asthmatic and non-atopic wheezing children.[87,88] Prominent BAL eosinophils and mast cells and elevated ECP were found in atopic asthmatics, whereas increased histamine levels were found in asthmatics, regardless of atopic status. Biopsy findings show higher alveolar eosinophils in children with allergic asthma compared to non-allergic asthma.[89] This suggests eosinophil recruitment into the airways in atopy-associated asthma. Another study confirmed typical histopathologic features (i.e., airway eosinophilia and reticular basement membrane thickening) in children with mild to moderate asthma, but perhaps surprisingly, these findings were also present in atopic

BOX 58-12 Histopathologic Findings in Children with Recurrent Wheezing/Asthma

Preschooler with Recurrent Cough/Wheeze

Generalized immune response: increase in neutrophils, lymphocytes, macrophages, and epithelial cells; rarely, increase in eosinophils

School-Aged Child with Asthma (mild to moderate severity)

Similar to adults with asthma: increased eosinophils, mast cells, activated T lymphocytes, epithelial desquamation, basement membrane thickening

Difficult-to-Control or Severe Asthma in Children

Remodeling with minimal inflammation: Smooth muscle hypertrophy, basement membrane thickening, goblet cell and submucous gland hyperplasia

Few eosinophils or neutrophils (patients generally on oral and high-dose inhaled corticosteroids at time of biopsy)

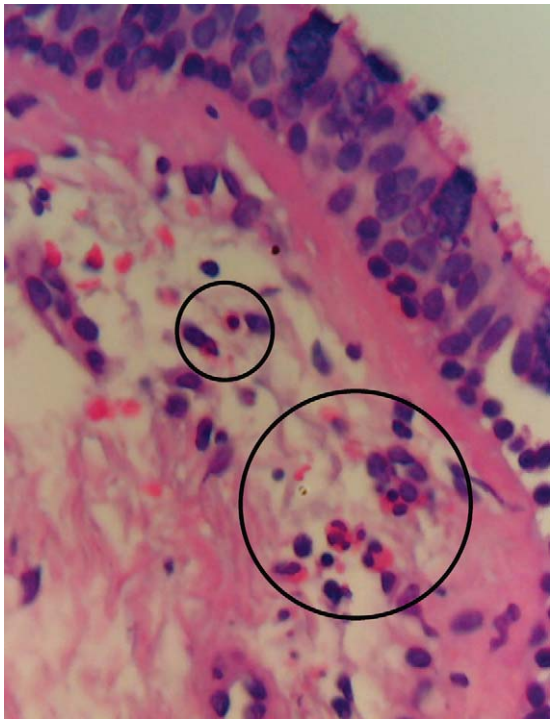


Figure 58-2 Eosinophilic airway inflammation in asthma. Endobronchial biopsy from a child with asthma reveals submucosal eosinophils (*circled*). Hematoxylin-eosin staining. (Courtesy of Dr. Carlyne Cool, National Jewish Medical and Research Center, and University of Colorado Health Sciences Center, Denver, Colo.)

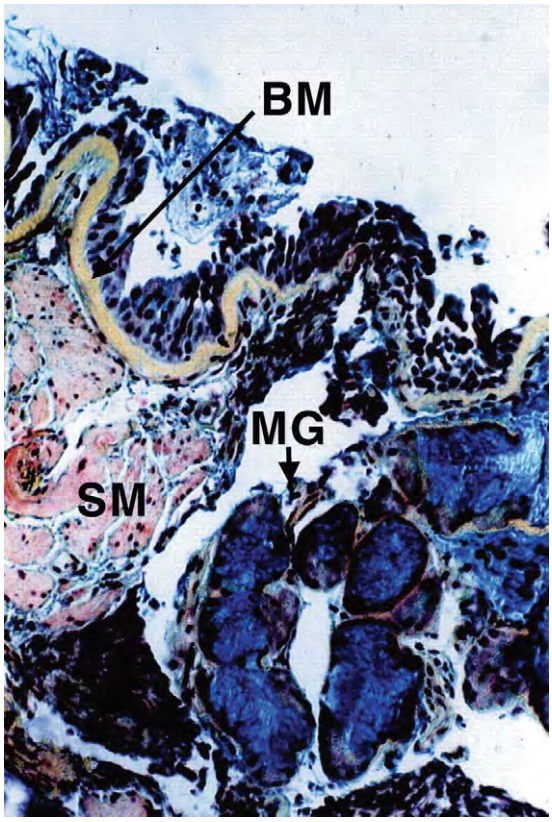


Figure 58-3 Airway remodeling in asthma. Endobronchial biopsy from a 12 year-old male with severe asthma. Pentachrome staining delineates the features of a remodeled airway by staining smooth muscle (*red*), collagen (*yellow*), mucus (*turquoise*), and elastin (*black*). BM, basement membrane thickening; SM, smooth muscle hypertrophy; MG, mucous gland hypertrophy. (Modified from Jenkins HA, Cool C, Szefler SJ, et al: Histopathology of severe childhood asthma: A case series. Chest 124:32-41, 2003.)

non-asthmatic children.[90] However, decreased subepithelial TGFβ-RII expression was found only in asthmatics and not in atopic non-asthmatic children or healthy control subjects. In asthmatic children, the number of eosinophils correlated negatively with TGFβ-RII expression and positively with symptom duration. This study suggests that: (1) downregulation of TGFβ-RII may be a more specific finding than airway eosinophilia and reticular basement membrane thickening in childhood asthma; (2) pathologic changes of airway inflammation in atopic subjects precede the development of persistent asthma symptoms and airway obstruction; and (3) an undetermined threshold has to be reached before clinical features of asthma are manifest. It is also possible that the functional changes occur independent of, or partially related to, histopathologic findings. In moderate asthma in childhood, endobronchial biopsy findings from six children showed typical features of basement membrane thickening and hyalinization, epithelial barrier breakdown, lymphocytic infiltration, and intra-arteriolar platelet aggregation.[91] However, only two subjects had goblet cell hyperplasia and only one subject had eosinophilic infiltration. On electron microscopy, evidence of fibroblast activation, increased submucosal collagen fiber deposition, and mast cell degranulation was found.

Severe Asthma in Childhood: Inflammation and Histopathology

Most of the histopathologic information from BAL and biopsy samples from subjects with severe disease have likely been affected by ongoing treatment. These are patients in whom a clinical or research indication for the procedures would have included evaluation for other conditions because they have been symptomatic despite conventional therapy for severe asthma. In addition, control groups are often composed of children with other clinical indications for bronchoscopic evaluation of the airway or have other medical conditions requiring intubation for surgical procedures; therefore, they cannot be considered healthy controls. To further complicate these comparisons, different histochemical techniques and measurements are employed in different studies.

In recent years, biopsy findings in children with refractory asthma have been reported in several studies. In a case series of six children (6 to 17 years old) with severe refractory asthma, the following histopathologic findings were seen: thickening of the basement membrane, smooth-muscle hypertrophy, and varying degrees of goblet-cell and submucous gland hyperplasia (see Box 58-12 and Fig. 58-3).[92] In five of six subjects, there was minimal to no histologic evidence for airway inflammation, with only mild and patchy submucosal lymphocytic infiltration noted; eosinophils and neutrophils were not present. It is important to note that these subjects were all on high-dose inhaled corticosteroids and routine oral corticosteroids—befitting of their severe asthma status. Payne and colleagues have compared findings in children with difficult-to-control asthma treated with sys-

temic corticosteroids with adults with either mild or severe asthma and adult and pediatric control subjects. Children with severe asthma had reticular basement membrane thickness similar to that seen in the adults with either mild or severe asthma, and significantly greater than both the adult and pediatric control subjects.[93,94] No correlation between reticular basement membrane thickness with age, duration of asthma, FEV_1 (before and after a course of prednisone), exhaled nitric oxide, or mucosal eosinophilic inflammation was found in children with difficult-to-control asthma.[94] Asthmatic subjects with persistent airflow limitation ($FEV_1 < 80\%$ predicted) had higher CD4+ T lymphocyte density than those without, such that CD4+ T cells were inversely correlated with FEV_1. Severe asthmatic children had similar inflammatory cell composition and gene expression for IL-4, IL-5, and RANTES as subjects with other non-asthmatic respiratory symptoms. Furthermore, no tissue differences were found between symptomatic and asymptomatic severe patients after a course of systemic corticosteroids.

Collectively, these studies, albeit limited by small sample size, provide valuable information regarding the pathogenesis of severe asthma. In these studies, findings of airway remodeling are prominent in children, despite treatment with inhaled and systemic corticosteroids, with only minimal evidence for cellular infiltration particularly in the more severe group. It is possible that corticosteroid therapy is sufficient to inhibit eosinophilic inflammation but inadequate to prevent the airway remodeling features seen in these severe cases. Alternatively, airway remodeling proceeds independent of, or only partially attributable to, airway inflammation.

IMMUNOHISTOPATHOLOGIC PHENOTYPES OF SEVERE ASTHMA IN CHILDREN

Two recent studies evaluating the features of airway inflammation in children with refractory asthma following systemic courses of prednisolone suggest different phenotypes of severe asthma based on immunohistopathologic outcomes.[93,95] Payne and colleagues showed minimal active airway inflammation in the majority of children after 2 weeks of prednisolone therapy. There was no difference in the median airway eosinophil scores between the children with severe asthma after prednisone therapy and non-asthmatic children. The investigators found a significant correlation between levels of eNO and tissue eosinophils ($r = 0.54$; $P = 0.03$), with the strongest relation found among the small group of children who remained symptomatic following the prednisolone course.

De Blic and associates investigated two distinct clinical phenotypes—symptomatic and pauci-symptomatic—in 28 children with difficult-to-control asthma (defined as persistent obstructive pattern [i.e., $FEV_1 < 80\%$ predicted] regardless of symptoms) who failed to show an improvement in lung function despite combination treatment with high-dose inhaled corticosteroids (beclomethasone equivalent dose 800 µg/day), inhaled long-acting beta-agonist, and prednisone treatment for 2 weeks.[95] Biopsy and BAL were performed 4 to 6 weeks after the last oral corticosteroid dose. Although both groups had large numbers of eosinophils and neutrophils and Th2-type profiles despite high dose anti-inflammatory therapy, distinctive histologic correlates were found. The symptomatic group had a higher percentage of BAL neutrophils, less percentage of BAL lymphocytes, higher epithelial (but not submucosal) eosinophil and neutrophil counts, higher BAL eosinophil cationic protein, and lower IFN-γ and IFN-γ/IL-4 ratio compared to the pauci-symptomatic group.

In contrast to the phenotypes of severe asthma in the above studies based primarily on persistence of symptoms and/or airflow limitation, Wenzel and colleagues, in her studies of adults with severe asthma, distinguished phenotypes beginning with histologic findings: those with airway eosinophilia (eosinophil [+]) and those without airway eosinophilia (eosinophil [–]).[96] The eosinophil + group were noted to have elevated numbers of T lymphocytes (CD3+, CD4+, and CD8+ cells), mast cells, and macrophages, and thicker sub-basement membranes compared to the eosinophil – group. The eosinophil + refractory asthmatics had more severe disease features with higher prevalence of intubation secondary to respiratory failure. Airway neutrophilia was found to be a remarkable feature in all of the corticosteroid-dependent asthmatics irrespective of their eosinophil status. These studies demonstrate heterogeneity of severe refractory asthma. Although reticular membrane thickness does not distinguish different groups of subjects with asthma, smooth muscle hypertrophy can be a prominent feature.

OUTCOMES, PROGNOSES, AND PREDICTORS

The natural history of childhood asthma reveals that approximately 80% of asthmatics of all ages have disease onset before 6 years of age.[97] However, of all young children who experience recurrent wheezing, only a minority will go on to have persistent asthma in later life. The most common form of recurrent wheezing in preschool children occurs primarily with viral infections. Most are "transient wheezers" or "wheezy bronchitics" who are not at an increased risk of having asthma in later life (Box 58-13 and Fig. 58-4). Transient wheezing is associated with airways viral infections, smaller airways and lung size, male gender, low birth weight, and prenatal ETS exposure.

Persistent asthma commonly begins and coexists with the larger groups of transient and non-atopic wheezers (see Box 58-13 and Fig. 58-4). In early life, the clinical pattern of episodic wheezing, primarily triggered by common respiratory viral infections, generally does not distinguish persistent from transient or non-atopic wheezers. Persistent asthma is strongly associated with allergy, which is evident in the early childhood years as clinical conditions (i.e., atopic dermatitis, allergic rhinitis, food allergies) or by testing for allergen sensitization to inhalant and food allergens (e.g., IgE, allergy skin testing).[4,98] In particular, toddlers with perennial inhalant allergen sensitization and higher levels of exposure in the home are most likely to have persistent asthma in later life.[55] A parental history of asthma is also associated with persistent asthma; with allergy, these risk factors formulate a predictive index for persistent asthma (see Table 58-1).[44] Severity of childhood asthma, determined clinically or by lung function impairment, also predicts asthma persistence into adulthood. These and other "types" of childhood asthma to be discussed in this chapter are not exclusive and may be related in various ways. One pattern of recurrent wheezing in early childhood

BOX 58-13 Recurrent Coughing/Wheezing Patterns in Childhood, Based on Natural History

Transient Early Wheezing
Common in early preschool years
Recurrent cough/wheeze, primarily triggered by common respiratory viral infections
Tends to resolve during the preschool years, without increased risk for asthma in later life
Reduced airflow at birth, suggestive of relatively narrow airways. Improves by school-age

Persistent Atopy-Associated Asthma
Begins in early preschool years
Associated with atopy in early preschool years:
- Clinical (e.g., atopic dermatitis in infancy, allergic rhinitis, food allergy)
- Biological (e.g., early inhalant allergen sensitization, increased serum IgE, increased blood eosinophils)

Highest risk for persistence into later childhood and adulthood
Lung function abnormalities:
- Those with onset before 3 years of age acquire reduced airflow by school age.
- Those with later onset of symptoms, or with later onset of allergen sensitization, are less likely to develop airflow limitation in childhood.

Non-atopic Wheezing
Wheezing/coughing beginning in early life, often with RSV infection; resolves in later childhood without increased risk of persistent asthma
Associated with bronchial hyper-responsiveness near birth

Asthma with Declining Lung Function
Children with asthma with progressive increase in airflow limitation
Associated with hyperinflation in childhood, male gender

Late-Onset Asthma in Females, Associated with Obesity and Early-Onset Puberty
Onset between 8 to 13 years of age
Associated with obesity and early-onset puberty, specific for females

Occupational-Type Asthma in Children
Children with asthma associated with occupational-type exposures known to trigger asthma in adults in occupational settings (e.g., endotoxin exposure in children raised on farms)

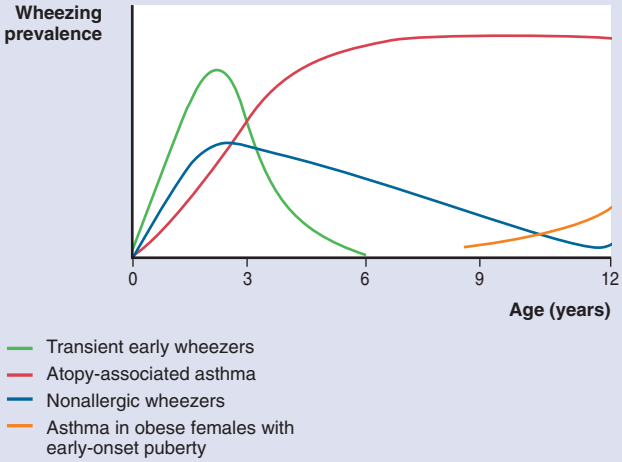


Figure 58-4 Common patterns of recurrent wheezing in childhood. Hypothetical yearly prevalence for four different patterns of recurrent wheezing in childhood (Tucson Children's Respiratory Study, Tucson, Arizona). These patterns differ in their age of onset and prognosis of persistence. This classification does not imply that the groups are exclusive. (Modified from Stein RT, et al: Thorax 52:946-952, 1997; and Castro-Rodriguez JA, et al: Am J Respir Crit Care Med 163:1344-1349, 2001.)

may appear to lead to or be supplanted by another—or different types may seem to occur concurrently in the same individual.

Preschooler with Recurrent Cough/Wheeze: Prognoses and Predictors

The heterogeneity of recurrent wheezing in young children has been well recognized and characterized in longitudinal epidemiologic studies, supportive of the common dictum "Not all that wheezes is asthma."[64,99,100] From the Tucson CRS in which more than 1200 unselected newborns were enrolled, different wheezing phenotypes were identified based on age of onset and persistence. By age 3 years, approximately one third of the cohort had wheezed.[64] Only 40% of these children continued to wheeze by age 6 years (persistent wheezers), representing 14% of the entire cohort having wheezing both before 3 years and at 6 years (see Fig. 58-4). The persistent wheezers were more likely to have a positive maternal history of asthma, elevated IgE levels with normal lung function in infancy, and low lung function with elevated IgE levels at 6 years (see Box 58-13). In contrast, 20% of the total group had at least one episode of wheezing associated with a respiratory tract infection during the first 3 years of life, but had no wheezing at 6 years (transient wheezers). These children were more likely to have diminished airflows in infancy and a history of maternal smoking, and less likely to be atopic. Fifteen percent of the children did not wheeze during the first 3 years of life, but they experienced wheezing by 6 years (late-onset wheezers). These children were likely to be atopic, similar to the persistent wheezers, and were also likely to have mothers with asthma, but did not acquire lung dysfunction by age 6 years as did the persistent wheezers in the cohort.

PREDICTORS FOR PERSISTENT ASTHMA

To distinguish preschool-aged children who are likely to have persistent asthma versus transient wheeze, an *asthma predictive index* was developed based on analyses of the Tucson CRS (see Table 58-1).[4] Two similar versions of the indices were used to classify the children: stringent and loose. The stringent index required *recurrent* wheezing in the first 3 years of life plus one major (parental history of asthma, or

physician-diagnosed eczema) or two of three minor risk factors (eosinophilia, wheezing without colds, allergic rhinitis); the loose index required *any episode* of wheezing in the first 3 years plus the same one major or two of three minor risk factors as the stringent index. Six percent of the preschool children had a positive stringent index and they were predominantly boys, whereas 23.6% had a positive loose index. Preschool children with a positive index were at least 2.6 times more likely to have active asthma in school age than those with a negative index. The positive predictive values for either the positive stringent or loose index for active asthma in school age were 76% and 59%, respectively. In contrast, at least 90% of young children with a negative "loose" or "stringent" index did not develop "active asthma" in school age. Hence, these simple predictive indices are clinical useful means of identifying preschool children at risk for persistent asthma.

ATOPY

Essentially all of the current natural history studies have found that allergic disease or evidence of pro-allergic immune development are significant risk factors for persistent asthma. In the Tucson CRS, early atopic dermatitis, allergic rhinitis, elevated serum IgE levels in the first year of life, and peripheral blood eosinophilia were all significant risk factors for persistent asthma.[4,64] In the Berlin Multicentre Alllergy Study, additional risk factors for asthma and BHR at age 7 years included persistent sensitization to foods (i.e., hen's egg, cow's milk, wheat and/or soy) and perennial inhalant allergy (i.e., dust mite, cat), especially in early life.[55,101,102] In particular, the combination of perennial inhalant allergen sensitization by age 3 years and exposure to high levels of these allergens in the home was a strong predictor of asthma persistence into the teen years.[55] In the Kaiser-San Diego study, milk or peanut allergen sensitization were risk factors for asthma.[103] With these additional considerations, a modified version of the previously described asthma predictive indices adds inhalant allergen sensitization as an additional major risk factor, and food allergen sensitization as an additional minor risk factor (see Table 58-1).[5]

LUNG DYSFUNCTION

The association between early childhood lung function and the different wheeze phenotypes (i.e., transient, persistent, and late onset) has also been explored. In the Tucson CRS, the transient wheezers had lower airflows (using maximal airflow at functional residual capacity [VmaxFRC]) in infancy (2.4 months of age) compared to never wheezers, and remained so at ages 6, 11, and 16 years.[64,104] Persistent wheezers had normal lung function in infancy, but by age 6 years, they had developed lower lung function compared to never wheezers, that persisted as abnormal through age 16 years. The late-onset wheezers did not show significant reductions in airflow measurements when compared with never wheezers.

Other longitudinal studies of smaller cohorts have revealed additional insights to the natural course of asthma. In contrast to the observations reported in the Tucson CRS, Turner and colleagues found reduced lung function in their subgroup of persistent wheezers as early as 1 month of age; their transient wheezers had airflows similar to their never wheezers.[105] In another study from a hospital-based pediatric pulmonary clinic, 129 children with history of wheezing before age 2 years were followed 4 years later and 38% of these children were still wheezing.[99] Persistent wheezers had the lowest lung function (using VmaxFRC) when measured at 17 months of age when compared to intermittent wheezers, coughers, and asymptomatic children. In the National Asthma Campaign Manchester Asthma and Allergy Study, interviewer-administered questionnaire and lung function (specific airway resistance (measured in kPa/second) were obtained at age 3 and 5 years of age. Children in this cohort were classified as never wheezers, transient early wheezers, late-onset wheezers, or persistent wheezers.[100] Similar to the Tucson CRS, transient and persistent wheezers had reduced lung function compared to never wheezers; persistent wheezers had significantly poorer lung function when compared with other groups. In children who had wheezed by age 3 years, using a multivariate analysis, increased airway resistance (OR 5.5, 95% CI 1.2 to 25.9; $P = 0.03$) and especially allergic sensitization (OR 2.8, 95% CI 1.3 to 5.8; $P = 0.008$) were significant predictors of persistent wheezing. There was no association between lung function at age 3 years and late-onset wheeze in children.

Despite strong associations between wheezing patterns and lung function measures in each study, it is unclear if significant discrepancies between lung function and wheezing patterns exist between these studies. Possible explanations include differences in constitutional properties of the airways, timing of injury to the airways, inherent characteristics of the cohorts, and/or group definitions used. Nevertheless, lung function in infancy may not be all that reliable as a predictor of persistent wheeze—particularly with respect to the significant variability of VmaxFRC values between the groups of very young children.

SCHOOL-AGED CHILD WITH ASTHMA: PROGNOSES AND PREDICTORS

School-age children with persistent asthma are at risk for disease persistence into adulthood. This is exemplified in a cohort of asthmatic 7-year-olds living in Melbourne, Australia, who were re-studied for persistence and severity of asthma at 10, 14, 21, 28, 35, and 42 years of age. At age 35 and 42 years, about 70% of the asthmatics and 90% of the severe asthmatics continued to have asthma symptoms.[106,107] In comparison, 38% of "wheezy bronchitics" (i.e., wheezing only with colds) and 15% without asthma in childhood reported asthma symptoms at these ages of adulthood. These observations—that many asthmatic children experience disease remission or improvement in early adulthood, but that severe asthma persists with age—are remarkably similar to those of several other natural history studies of childhood asthma into adulthood (i.e., Aberdeen, Scotland,[108] Tasmania, Australia,[109] and a national British study).[110]

Objective measures of lung function validate and bring further insights to these natural history studies. Longitudinal spirometric measures of lung function in the Melbourne study initially revealed that asthmatic children ages 7 to 10 years old, especially severe asthmatics, had reduced airflow, while wheezy bronchitics (i.e., transient wheezers) had lung function that was not different from non-asthmatics (Fig. 58-5).[111] Over the ensuing years (to age 42 years), these

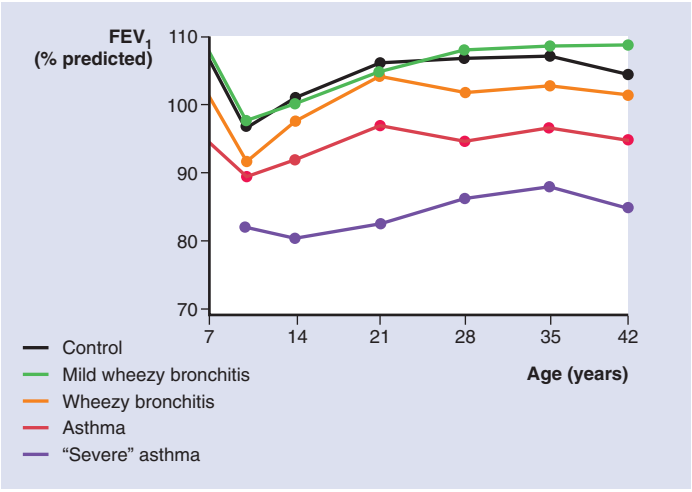


Figure 58-5 Natural history of lung function from childhood to adulthood. Children ages 7 to 10 years were followed to the age of 42 years (Melbourne Longitudinal Study of Asthma, Melbourne, Australia). At age 7, the children were classified into the following groups: Control (never wheezed); Mild wheezy bronchitis (<5 episodes of wheezing, always associated with bronchitis or respiratory infections); Wheezy bronchitis (≥5 episodes of wheezing with bronchitis or respiratory infections); Asthma (wheezing unassociated with respiratory infections); "Severe" asthma (onset of asthma symptoms before 3 years of age, persistent symptoms at 10 years of age, and barrel chest deformity and/or reduction in FEV_1/FVC ratio to ≤0.50). Mean values are shown. (Adapted from Oswald H, et al: Peds Pulmo 23:14-20, 1997; and Horak E, et al: BMJ 326:422-423, 2003.)

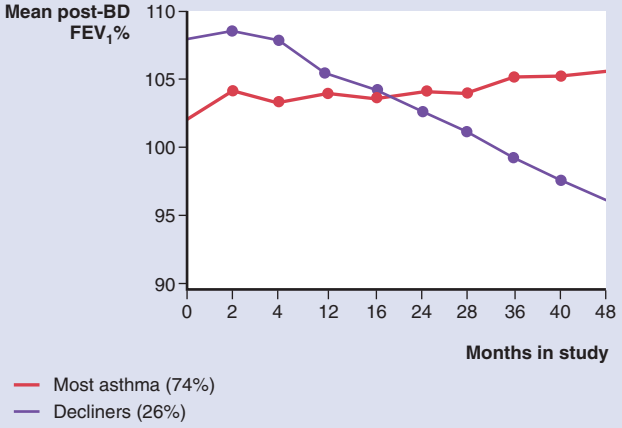


Figure 58-6 Progressive decline in lung function in a sub-group of children with asthma. Repeated measures of lung function (post-bronchodilator FEV_1 % predicted as an indicator of airflow limitation independent of airway smooth muscle tone) were obtained in 990 children, 5 to 12 years of age, with mild to moderate persistent asthma (Childhood Asthma Management Program study, National Institutes of Health/National Heart, Lung and Blood Institute). A sub-group of the asthmatic children (26%) demonstrated a significant and progressive decline in their lung function over this 4-year period (mean reduction of 2.9% per year). In comparison, most asthmatic children (74%) had no significant reduction in lung function over time (mean increase 0.6% per year). Mean values are shown. (Adapted from Covar RA, et al: Am J Respir Crit Care Med 170:234-241, 2004.)

differences in lung function impairment between groups persisted in parallel, without a greater rate of decline in lung function in any group (see Fig. 58-5). In the longitudinal Aberdeen study, greater airflow limitation in asthmatics versus wheezy bronchitics or controls was complemented by a greater proportion of asthmatic subjects with BHR when compared with the wheezy bronchitis or control groups.[108] These findings, consistent in these and other studies, support the importance of the early childhood years in asthma development—the establishment of chronic disease and lung function impairment in lower school-aged children appears to predict persistent asthma in adulthood.

CHILDREN WITH PROGRESSIVE DECLINE IN LUNG FUNCTION

The concept of asthma as a progressive disease has become apparent based on pathologic changes of airway remodeling and from adult longitudinal studies that have shown that adult asthmatics lose lung function at a greater rate than non-asthmatics.[112,113] In children, a somewhat different course has been shown. In community-based studies of school-aged children with asthma, most had mild disease and no further loss in lung function over time when compared with children without asthma.[114,115] This was also reported in the NIH-sponsored Childhood Asthma Management Program (CAMP) in which 1041 children with mild to moderate persistent asthma demonstrated no significant change in post- or pre-bronchodilator FEV_1 % predicted during the 4-year treatment period with controller therapy (budesonide or nedocromil) or placebo, regardless of treatment group.[116] However, 25% of the CAMP participants had progressive reduction in airflow (i.e., postbronchodilator FEV_1 % predicted) throughout the treatment phase (Fig. 58-6 and see Box 58-13).[117] This occurred in a similar proportion of participants in the active treatment and placebo arms. Predictors of progressive decline in lung function included younger age, male gender, and hyperinflation at the start of the study.

Most children with asthma will not have progressive loss of lung function or worsening of disease state, but a minority of children with asthma appear to be susceptible, even those with mild to moderate disease. This underscores the importance of objective monitoring of lung function over time, even in children with mild disease or those who appear well controlled. The etiology of the reduction in lung function in children may be reflective of reduced lung growth, persistent airway inflammation, or airway remodeling.

ADOLESCENT ASTHMA

Apart from those who develop asthma in early childhood that persists into later life, another epidemiologic pattern emerges in later childhood. Males account for most children with asthma in the prepubertal ages, whereas new incident cases of asthma in adolescence are predominantly females. In the Dunedin Multidisciplinary Health and Development study, an association between obesity with asthma and atopy, and an inverse correlation with FEV_1/FVC ratio (but not airway reactivity), was female gender specific.[118] After 9 years of age, 28% of asthma developing in women could be attributed to being overweight. A similar pattern was observed in the

Tucson CRS. Prepubertal females who were overweight were at increased risk for wheezing in adolescence; the strongest association between obesity and asthma risk was among girls with early-onset puberty (i.e., puberty started before 11 years of age; see Box 58-13).[119] In another study by Varrraso and coworkers the combination of early menarche and high body mass index (BMI) was associated with more severe asthma in women.[120] These associations between obesity, early-onset puberty, asthma, and female gender are consistent and provide cursory evidence for a complex interaction between genetic and hormonal influences underlying a subgroup of children with onset of asthma in adolescence.

Severe Asthma in Childhood: Prognoses and Predictors

A disparity in asthma outcomes links high rates of asthma hospitalization and death with poverty, ethnic minorities, and urban living. Over the past two decades, African-American versus white children had three to four times more ED visits, hospitalizations, and deaths due to asthma.[121] This large disparity in poor outcomes for African-American children with asthma has persisted despite broad improvements in asthma therapies and management over the past 25 years.

A combination of biological, environmental, economic, and psychosocial risk factors is believed to increase the likelihood of severe asthma exacerbations (see Box 58-11). Clinical and crucial psychosocial variables have been associated with fatal asthma events, including conflicts between family members and hospital staff regarding medical management of the patient, inappropriate self-care, depressive symptoms and suicidal ideation, and disregard of asthma symptoms.[122] Severe asthma exacerbations, resulting in respiratory distress, hypoxia, hospitalization, intensive care unit management, seizures, and/or respiratory failure, are the best predictors of future life-threatening exacerbations or a fatal asthma episode.[123] Bloomberg and associates observed that prior hospitalization(s) is the strongest predictor of subsequent hospitalization for asthma, with the probability of readmission increasing from 30% after the first admission, 46% after a second, and 59% after a third.[124] Marquette and colleagues observed the asthma mortality rate following mechanical ventilation for an asthma exacerbation was 10.1% after 1 year, 14.4% after 3 years, and 22.6% after 6 years.[125] Severity of previous asthma exacerbations appears to be the best predictor of severe, life-threatening exacerbations.

Some children are at risk for severe exacerbations because their perception of airways obstruction is notably poor. Poor perception of hypoxia, dyspnea, and resistive loads to breathing has also been associated with near-fatal asthma exacerbations (see Box 58-11).[126,127] Reduced lung elastic recoil pressure, usually accompanied by profound hyperinflation, has also been associated with near-fatal asthma attacks, suggesting that properties intrinsic to the lung parenchyma can render the airways susceptible to severe airflow limitation.[128] Whether or not these are intrinsic or acquired states that are reversible is unclear. Severe, life-threatening exacerbations can be characterized as being rapid or gradual in onset and have other distinguishing characteristics that are described earlier (Assessing Severity and Control: Severe Asthma Exacerbations in Children) and in Box 58-10.

ADVANCES IN CLINICAL ASSESSMENT OF ASTHMA IN CHILDREN

Lung-specific measures of dysfunction and inflammation have an essential role in diagnosing and assessing asthma, and following its course over time. Standard measures, generally spirometric, are limited in part by the age and developmental ability of young children to perform valid, reproducible measures. Yet, because the early childhood years appear to be a critical and dynamic period of lung and asthma development, investigators have sought to identify meaningful measures of lung dysfunction and inflammation that can be obtained noninvasively in children at the earliest possible ages.

Lung Physiology in Young Children

Traditional pulmonary function testing is challenging in preschool children. Spirometry and peak flow measurements can be reliable between 5 to 8 years of age. Impulse oscillometry (IOS) is a pulmonary function measure of respiratory system resistance and reactance at different frequencies. Forced oscillation involves the application of sine waves through a loudspeaker to the airway opening via a mouthpiece—through which the subject breathes normally for short periods of time. Measurements are carried out during tidal breathing over a 30-second interval and are easily performed with at least three efforts recorded. Given its relative ease of use (e.g., does not require forced exhalation), it is a reproducible and suitable measure of lung function in younger children.[129] Marotta and coworkers performed pre- and post-bronchodilator spirometry and IOS in 4-year-old children at risk for asthma.[130] Young children with asthma had increased reduction in IOS resistance to bronchodilator; no difference in baseline FEV_1 or IOS resistance was observed. Some investigators believe that reactance at low frequencies is a reflection of peripheral airways function.[131]

Using three different lung function measures, Nielsen and Bisgaard evaluated the bronchodilator response of 92 children 2 to 5 years old, 55 of whom had asthma.[132] Compared to non-asthmatic controls, children with asthma had increased specific airway resistance (sRaw) using whole body plethysmography, increased respiratory resistance using an interrupter technique, and increased respiratory resistance using IOS at 5 Hz. All children, including non-asthmatics, responded to terbutaline, although children with asthma improved to a significantly greater extent. The investigators found sRaw via body plethysmography was the best pulmonary function measure for distinguishing the asthmatic from non-asthmatic children based on bronchodilator response.

As with measurements of airflow limitation, procedures to assess BHR in infants and young children have unique challenges. Measurement of BHR indirectly using cold air (4 minutes of isocapnic hyperventilation) or dry air (6 minutes of eucapnic hyperventilation) challenge with sRaw as an outcome may be useful and practical alternatives to pharmacologic challenges in young children.[133] Using a dry air challenge, magnitude of response was found to be associated with wheeze phenotype. Persistent wheezers had a larger increase in sRaw following eucapnic hyperventilation challenge compared with never wheezers, but no significant differences between never wheezers, late-onset, or transient wheezers were seen.[100]

Exhaled Nitric Oxide (eNO)

Nitric oxide is produced by at least three distinct nitric oxide synthases (NOS): constitutively expressed NOS (cNOS 1 and 3) from the endothelium and inducible NOS (iNOS 2), upregulated by proinflammatory cytokines. Its exact role (i.e., as a mediator, immune modulator, or marker of epithelial damage and/or allergic inflammation) in airway inflammation is not clearly understood. However, hundreds of studies have been published on eNO in humans, including those demonstrating associations between eNO and other measures related to asthma in children, such as bronchodilator response, BHR, atopy indicators (e.g., skin test reactivity and serum IgE), and other biomarkers such as serum eosinophil cationic protein and sputum eosinophilia.[134,135]

Measurement of eNO, in parts per billion (ppb), is a noninvasive procedure that can easily be performed in children. Guidelines for standardized eNO measurement have been developed and published jointly by the American Thoracic Society and the European Respiratory Society.[136] Normal reference values with the recommended technique are available for children 4 to 17 years old.[137] eNO can be obtained in children as young as 2 years of age using online[138] and offline methods.

Noninvasive biomarkers support the presence of inflammatory changes in young children with recurrent wheeze. eNO levels are elevated in patients with asthma,[139] increase during acute exacerbations,[140] decrease after oral or inhaled corticosteroid therapy,[141,142] and correlate with other markers of inflammation, particularly eosinophilic inflammation.[11,135] Infants and young children with recurrent wheezing episodes presenting with acute wheeze had higher mean eNO levels (14.1 ppb) compared to first-time viral wheezers (8.3 ppb, $P < 0.05$) and healthy matched controls (5.6 ppb, $P < 0.001$).[142] In addition, their eNO levels were reduced by ~50% after corticosteroid therapy to a level comparable to the other two groups. This is evidence for airway inflammation during exacerbations in infants with recurrent wheeze, but what specific inflammatory feature(s) elevated eNO is uncertain.

Several studies have shown high diagnostic accuracy of at least 80% of eNO for asthma.[143-145] This relates to the combined consistency of having high eNO for patients with diagnosed asthma and low eNO for patients without asthma. Two studies have demonstrated the diagnostic accuracy of eNO in young children as well.[146,147] One study determined that eNO had better diagnostic accuracy compared to IOS-measured lung function and bronchodilator response: an eNO cut-point of 1.5 standard deviation above predicted distinguished children with probable asthma from healthy controls (sensitivity 86%, specificity 92%).[146]

In addition to studies that have evaluated the diagnostic potential of eNO levels, studies have also included applications for clinical use of eNO to assess asthma control. Assessing asthma control based on beta-agonist use, day- and night-time symptoms, and spirometry, an eNO value >21 ppb was a reliable predictor of poor asthma control, whereas eNO levels of 11 and 15 ppb corresponded with good and acceptable control, respectively.[148] A similar study also demonstrated lower eNO levels in children with good compared with poor asthma control (29 ± 11 and 86 ± 56 ppb, respectively; $r = -0.51$, $P = 0.001$).[149] The eNO levels also tracked well with assessment of asthma severity according to the NHLBI guidelines ($r = 0.44$, $P = 001$) and adherence to controller therapy ($r = -.75$, $P = 001$). Studies in adults[150,151] and children[152] have also supported the use of eNO (and also sputum eosinophilia) to predict loss of asthma control using an inhaled corticosteroid reduction model. In addition, eNO has been shown to be a useful tool to strategize treatment. In an adult study, the strategy using eNO allowed for greater ICS reduction without an increase in asthma exacerbations.[153] In a pediatric study that integrated eNO in the treatment algorithm, incorporating eNO allowed for greater improvement in bronchial responsiveness and reduction of eNO levels, without increasing cumulative ICS usage.[154]

In conclusion, eNO measurement holds promise as a useful clinical tool for diagnosing and assessing asthma in children. eNO measurements are easily performed, completely noninvasive, and reproducible and reliable in children. eNO correlates with several clinical parameters and may be a clinically useful predictor of response to therapy and/or loss of asthma control. It has also been shown to be helpful as a treatment strategy tool. Some limitations of its usage are: correlations with other measures of disease severity are modest; once corticosteroid therapy is instituted, associations with disease severity are weaker; tobacco smoking reduces eNO levels; and it is unclear if certain subgroups of children with asthma are not well characterized by their eNO measures. If used prudently, eNO measurement can probably best serve asthma patients as an additional assessment tool, along with symptom reporting and lung function measurement.

Induced Sputum

Induced sputum analysis has gained favor especially in pediatric asthma research because of its ability to directly measure airway inflammatory cells and mediators with fair association with BAL samples, without the risks of bronchoscopy. Although the relation between induced sputum and BAL can be robust, sputum is relatively rich in neutrophils and with fewer lymphocytes when compared with BAL; sputum fluid is likely reflective of larger airways. Nevertheless, in children with mild to moderate asthma, technical and ethical issues limit the application of bronchoscopy/bronchoalveolar lavage in the assessment of airway inflammation. Hence, sputum induction is an attractive alternative to bronchoscopy.

Children with controlled or uncontrolled asthma have higher sputum eosinophils compared to normal subjects, even in the presence of normal lung function.[155] Sputum eosinophil count correlates with various measures of chronic and current asthma control, such as prednisone use, beta-agonist rescue use, and frequency of nocturnal symptoms. In addition, it also correlates with the degree of atopy, BHR, bronchodilator reversibility, and markers of inflammation including eNO; it inversely correlates with airflow obstruction as measured by the FEV_1/FVC ratio.[11] Both elevated eNO and sputum eosinophil count indicate an increased risk of failed ICS reduction in children.[152] In adults, two studies have shown that the incorporation of sputum eosinophil count as a treatment strategy tool versus clinical guidelines approach led to a significant reduction in severe exacerbations and hospitalizations without a requirement for higher ICS dose.[156,157]

Although sputum induction is a relatively safe, noninvasive procedure that allows for a direct assessment of cellular and molecular mechanisms that may be used as a diagnostic or monitoring tool, the procedure can be time-consuming and demands standardization in collection, processing, and interpretation of samples; hence, its current application in pediatric asthma is confined to research. Sputum induction involves inhalation of hypertonic saline (3% to 5%) for 12 to 30 minutes after pretreatment with albuterol inhalation. It is time-consuming, requiring 20 to 30 minutes to collect the sample and 2 hours to process in the laboratory. Variable success rates ranging from 68% to 100% have been reported,[158] which could be due to differences in sputum induction methods such as induction with or without a bronchodilator pretreatment, or differences in criteria to define a satisfactory sample. Marked bronchospasm can occur in 8% of patients despite pretreatment with a bronchodilator.

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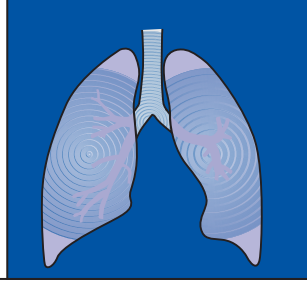

CHAPTER 59 Treatment

Louis I. Landau and Fernando D. Martinez

TEACHING POINTS

- There are age-related patterns of disease, drug treatment, and use of devices.
- Effective patient and family education is critical.
- Make the correct diagnosis, abolish symptoms, and maintain optimal lung function.
- Address environmental measures where appropriate.
- Individualize drug treatment with relievers, preventers, and controllers.
- Ensure correct use of inhaler devices.
- Any attack of asthma is a failure of prophylaxis and treatment should be reviewed.
- Use the minimum drugs necessary to maintain a child free of symptoms during all normal activities.
- Work with the child, the family, and the schools to optimize treatment.
- A cure is not yet available, but research at this time looks promising.

DIAGNOSIS

Appropriate treatment is dependent on the correct diagnosis being made. As described in the previous section, this is primarily determined by evaluation of accurate and appropriate historical information. Physical examination may help support the diagnosis, define severity, and exclude alternative diagnoses. Diagnostic tests are of limited value in most children with asthma. Lung function measurements will be useful in older children, particularly when historical events are not clear. Objective measures of the degree of airway obstruction with response to bronchodilators is then helpful. Most children who are old enough should have spirometry performed. In those with severe disease, spirometry will be repeated at each visit. A small group of those with troublesome asthma may be improved with peak flow monitoring at home,[1] some for a short period until symptoms are controlled, whereas others with persisting unstable asthma may continue regular peak flow monitoring to document early deterioration and the need for increasing medication.

A chest radiograph may be helpful for very young infants in whom alternative diagnoses are more common, for those with severe disease, and for those with localizing signs on physical examination. However, chest radiographs are not necessary, or useful, for all children with mild asthma.

Skin allergy testing, RAST testing, and total IgE measurements may be useful additional tests to document atopy in those with an uncertain diagnosis. Rarely will they provide additional information to identify specific environmental allergens responsible for symptoms. Children with such reactions usually have a clear history. One can predict that most children will show a skin and RAST response to house dust mites in those areas where they are prevalent, grass and tree pollens, molds, and cat fur. Some will respond to various food agents, but without a history of relevant symptoms, this need not necessarily indicate clinically significant allergy to that substance. Production of specific IgE is a normal phase in the development of tolerance to many foods. More than 90% of those with respiratory symptoms caused by food allergens will also have an associated skin disorder. Occasionally, these tests may be quite helpful in convincing the parents that the child is not allergic to a particular substance and does not require elimination of that substance from the diet.

The assessment of asthma is usually based on the pattern of wheeze and breathlessness. Cough is usually associated with these symptoms. Some have argued that asthmatics may present with cough alone and have called this entity *cough variant asthma*. Evidence would suggest that cough without wheeze is reasonably uncommon in childhood asthma.[2] Those children with cough alone are less atopic and less responsive to challenges with cold dry air, exercise, or methacholine and more responsive to capsaicin, suggesting that they have what could be called a *hypersensitive cough receptor syndrome*, which is not particularly responsive to asthma medication.

Some children present with recurrent atelectasis incorrectly diagnosed on chest radiograph as recurrent pneumonia.[3] This appears to be related to increased mucus production leading to plugs of eosinophils and mucus which can form casts of the airways. This pattern is sometimes called *hypersecretory asthma*.

The diagnosis of asthma is particularly difficult during the first year of life. Wheezing associated with lower respiratory illness occurs in more than 30% of infants during this period. Uncommonly, it may be due to conditions such as cystic fibrosis, milk aspiration, or congenital structural abnormalities. In many cases it may relate to smaller airway caliber as a result of a respiratory infection on top of intrinsic factors, which include a familial predisposition, male gender, or maternal smoking during pregnancy. In approximately one third to one half of infants the wheezing will represent the early onset of asthma. These children often have more fre-

quent wheezing and are atopic, but it may be difficult to differentiate those with smaller airways and viral-induced wheeze from those with early-onset asthma.

SEVERITY

The asthma severity of each child should be assessed so that treatment can be individualized. Most of the information can be obtained from an accurate history of symptoms, although some cases will require supporting objective evidence with lung function measurements. Children must be asked specifically if they have a wheeze and/or cough and whether this occurs regularly or intermittently. This can often be determined by asking (1) whether the child wakes at night because of cough or wheeze; (2) whether he or she has cough or wheeze on waking first thing in the morning requiring urgent bronchodilator therapy; (3) whether the child's sport or physical activity is limited by cough, wheeze, or tightness in the chest; (4) how frequently the child requires bronchodilator for symptom relief; (5) whether a metered-dose inhaler lasts for less than 4 to 6 weeks (i.e., used more than twice daily); and (6) whether school attendance has been affected by symptoms. Information regarding the use of medication should be sought because inappropriate medications such as antibiotics, antihistamines, and nonprescription medications may be given for symptoms that are actually caused by asthma.

Poorly controlled asthma will be recognized by the presence of these symptoms, excessive use of reliever medication, inadequate length of response to reliever medication, and supporting evidence of abnormal lung function.

Treatment will be based on the pattern of symptoms, which can be classified as infrequent episodic (50% to 75% of childhood asthmatics), frequent episodic (20% to 30%), and persistent (5% to 20%). The latter can be defined as mild persistent, moderate persistent, or severe persistent. Criteria for this classification are shown in Table 59-1.

Patients at high risk for life-threatening asthma may be recognized by (1) repeated visits to the doctor or emergency department or admissions to a hospital, especially the intensive care unit; (2) previous life-threatening attacks; (3) poor compliance with treatment, especially in teenagers and young adults; (4) poor perception of symptoms; (5) persistently abnormal lung function measurements; (6) denial of asthma; and (7) overt psychosocial problems. However, it must be recognized that, although low, there is a risk of dying from asthma in every child with asthma, and every child should be carefully assessed and appropriately managed to minimize that risk.

PRINCIPLES OF MANAGEMENT

Asthma is a disease associated with airway inflammation and characterized by hyper-responsiveness of the airways with reversible airway obstruction. There are many differences between children and adults with asthma, and management in children cannot be extrapolated from adult care. About 30% of children will have respiratory symptoms consistent with asthma during childhood, and many will cease to wheeze. Because two thirds of children with asthma have mild symptoms that can be easily controlled and are not necessarily associated with increasing morbidity in adult life, aggressive treatment cannot be justified at this time in this group. In those with moderate to severe symptoms, there is certainly sufficient evidence that better control of symptoms, usually with inhaled corticosteroids, can be supported.

Most children who wheeze are young and are not able to coordinate well enough to use metered-dose inhalers (MDIs) or dry powder inhalers (DPIs) effectively. However, spacer devices and other aids ensure that children from the first year of life can still be treated with aerosol medications, provided the method of delivery is suited for the age of the patient.

There appears to be an age-related difference in response to medications, with younger children less responsive to β-agonists and rarely responding well to high-dose steroids. This should be taken into account when planning treatment regimens so that unnecessary excessive doses of medication that would cause side effects without benefit are avoided. The immediate aims of treatment are (1) to make the correct diagnosis; (2) to abolish symptoms; and (3) to maximize lung function.

In the long term, one should aim for the following:

1. Maintain the child symptom free.
2. Maintain best lung function at all times. Those with persistent asthma will have spirometry at each consultation. Those with troublesome symptoms may have a peak flow meter at home. The aim is to ensure lung function remains within normal limits for each individual child and that diurnal variation in peak flow is less than 10%.
3. Avoid need for extra bronchodilators.
4. Prevent the restriction of normal childhood activities.

Table 59-1
Severity of Asthma

Pattern	Infrequent Episodic	Frequent Episodic	Persistent
Wheeze, tightness, cough infection, or exercise	Occasional (e.g., with viral)	Most days	Every day
Nocturnal asthma	Usually absent	<Once per 4-6 wk	>Once per wk
Asthma on waking	Usually absent	<Once per 4-6 wk	>Once per wk
Hospital admission in past year	Absent	Usually not	Usually
Previous life-threatening attack	Absent	Usually not	May have a history
Bronchodilator use	Infrequent	Needed most wk	Needed most days
FEV_1 (% predicted)	Normal	Normal/low	Usually low
Mean peak flow variability* over 2 wk	10-20%	20-30%	>30%

*Mean peak flow variability % = (highest – lowest)/highest × 100

5. Prevent the development of irreversible airway obstruction.
6. Reduce risk of death from acute attacks of asthma.
7. Avoid unnecessary side effects from medications.

GINA and Asthma Foundations in many countries provide guidelines to management.[4]

PATIENT EDUCATION

An extensive education program involving the child, the parents, other health professionals, and the physician in co-management is vital to ensure complete understanding of the natural history of the disease and the roles of particular medications. Without this understanding, adherence will be severely compromised.[5] It is also important that health professionals address real concerns of the parents that may not be related purely to the symptoms presented at consultation. Written material in the form of action plans with detailed personalized information as illustrated in Figure 59-1 may be useful to improve adherence, although Cochrane reviews reported too few results available to confirm their value. Peak flow meters may be of additional value for those with troublesome asthma and poor perception of symptoms. However, peak flow meters are not necessary to improve control of symptoms in the vast majority of children.[6] Support groups can help with information and encouragement.

Recent studies have shown that less than 50% of patients adhere to daily prescribed medication.[7] Physicians cannot predict, better than chance, which of their patients will comply. Good control of *frequent* asthma symptoms requires physicians to assume the role of teachers developing a complete plan with active participation by patients. Clinicians

ASTHMA MANAGEMENT PLAN FOR YOUNG PEOPLE

Name: _____ Date: _____ Best peak flow _____
(6 years and over)

WHEN WELL — **PEAK FLOW**

Take preventer (if prescribed): _____ Above:

Dose: _____ How often: _____

Take reliever: _____ Dose: _____ _____

(Take only when necessary for relief of symptoms)

Before exercise, take: _____

WHEN NOT WELL — **PEAK FLOW**

At the first sign of a cold or if asthma symptoms get worse:

Take reliever: _____ Between:

Dose: _____ How often: _____ _____

Take preventer if prescribed: _____ And

Dose: _____ How often: _____ _____

When your symptoms get better, return to the treatment when well.

IF SYMPTOMS GET WORSE — **PEAK FLOW**

Extra steps to take:

- _____ Less than
- _____
- _____ _____
- Emergency medication: _____ Dose: _____
  Take: _____
  _____
  _____

If you follow this plan but your symptoms get worse, see a doctor immediately or call an ambulance.

AMBULANCE **DOCTOR** **HOSPITAL**

Figure 59-1 Asthma management plan for young people.

must make it possible for patients to tell them what they are and are not willing to do, so that it is more likely that the prescribed drugs are used effectively.[8]

From the very beginning of a patient visit, an equal physician-patient partnership should be promoted. Good or effective communication and health education are critical to the success of the physician-patient interaction and both should begin at the start. The presenting complaint is often not the patient's chief concern. It is important to identify and deal with major concerns. A direct question (which cannot be answered with just a "yes" or "no") like "What really concerns you?" is one way of giving parents or families permission to tell their concerns even though often they are embarrassed to do so.

Patient education should begin with a description of the pathogenesis of asthma in plain language, emphasizing how airway inflammation, mucus production, and bronchoconstriction can each contribute to airway obstruction. Patients are confused by the multiple terms used to describe asthma, including *bronchitis*, *asthmatic bronchitis*, *wheezy bronchitis*, *reactive airways disease*, and *hyper-reactive airways disease*. What patients and families really want to know is, "will this condition impair or interfere with a normal active life," but they rarely ask the question directly. Emphasizing that there is a wide spectrum of severity in children and adults with asthma but that most are able to lead active and productive lives sets the right tone and provides motivation for the patient to play an active role in controlling and managing asthma. It is often worthwhile to point out that there are many Olympic athletes with asthma who manage to win gold medals.

Setting goals for preventive therapy is important. Many families do not like the idea of giving their child medicine over a long period, particularly if the child seems well. It is important to set the goal of gradually reducing inflammation and, once good control is established, to try to reduce the amount of medication needed to maintain the child in that state. Thus parents can be encouraged to take any appropriate practical environmental control measures as a way of reducing the need for medication. It is important to establish criteria, such as experiencing a cold without asthma symptoms, that let parents know how to assess how well controlled are their children's airways.

With respect to drug therapy, it is important to be explicit about how the medicines work; how to take the medicines correctly, including the use of spacers; and the potentially harmful effects of drugs. The latter is essential to identify specific patient or family concerns. Most patients are very concerned about drug toxicity whether or not they articulate this concern. Some confuse muscle-building or anabolic steroids with anti-inflammatory steroids. Others have seen patients with considerable facial swelling following systemic doses of corticosteroids and may be terribly worried about their use. They need to be reassured that in the conventional inhalation doses currently recommended, the risks of serious asthma far outweigh the side effects of the medication, including inhibition of growth, and that the regimen that is being recommended represents the most favorable risk-to-benefit ratio. Following an extensive meta-analysis, Allen and colleagues[9] concluded that children treated with inhaled beclomethasone were more likely to reach predicted or normal heights than children whose asthma was not treated with preventive medication. Since that report, there have been reports in adults indicating risks to be considered including an increased incidence of cataracts in those receiving moderate to high doses of *inhaled* corticosteroids.[10] Because there is still considerable controversy about the possibility that inhaled steroids may inhibit growth, even when used in conventional doses, it is reassuring for patients to know that once the asthma is brought under *good* control, the dosage of inhaled steroids will be reduced. It also helps for patients and families to understand that poorly controlled asthma can lead to impaired growth as well and that risks and benefits have been weighed carefully in developing the treatment plan. The physician's task is to recommend a regimen that maximizes prevention and the use of the least medication over the long haul consistent with good control of asthma.

The physician should provide a plan of action in case of deterioration and especially in an emergency. Before presenting the actual drug regimens being recommended, it is worth stressing that once families understand how the chart is constructed, they can easily follow the clinician's directions for changing dosages or medications in response to a variety of conditions that are likely to occur. Although the actual drug regimen will no doubt change with newer and presumably more effective therapeutic or preventive agents, the *method* of communicating or writing out the recommendations is core. The format can be adapted for use by clinicians who may wish to use different drug regimens as part of a long-term treatment plan.

When indicating the first sign of a cold, it is important to emphasize that this refers to the *earliest* signs, such as a scratchy throat and not waiting until there are full blown signs and symptoms, such as thick nasal mucoid discharge, prominent cough, or wheeze. Once there is cough or wheeze, the treatment is given up to every 4 hours. When there has been no cough or wheeze for 1 week, the revised medication regimen can be discontinued.

The basic strategy for this plan is to eliminate the symptoms of asthma quickly with an intensive regimen and then to decrease the number or dosage of medications. From a psychological point of view, patients are more motivated to adhere to a regimen if they believe they are improving. This is reinforced if they see that some medications are either being reduced or discontinued. Finally, it is easier for patients to follow a set routine. Some compromise in this optimal regimen may be needed if cost of medication or compliance is an important issue.

Developing a long-term plan and teaching a patient or a family to follow it will probably require several visits. These visits will be necessary to get patient feedback, provide the additional health education, adjust the pharmacologic regimen, and also correct any misunderstandings. In applying the regimens as outlined, the aim is to make the patient as symptom free and as physically active as possible. With respect to inhaled corticosteroids, the strategy of aggressively treating asthma early may, in fact, lead to less use of this medication long-term.

Following the recommendations of the Expert Panel Report Guidelines for the Diagnosis and Management of Asthma,[11] an increasing respiratory rate, breathlessness, use of accessory respiratory muscles, alertness, and change in

color (cyanosis) to assess severity of a wheezing episode have been used to recommend a short-acting β_2-agonist by nebulizer or 4 to 8 puffs by metered-dose inhaler in a spacer, up to every 20 minutes, if needed. If there is no response, emergency care must be sought immediately.

Tailoring the therapeutic plan to the family's routine or lifestyle is essential to encourage adherence to the therapeutic programs. For example, for children who have a long school day and find it difficult to take the medication at school, it may occasionally be preferable to introduce a long-acting β-agonist earlier than usual.

The image of a clogged nose has been used as a way of communicating how airway inflammation, swelling, and mucus lead to airway clogging or obstruction. Persuading families to start or increase treatment early is a key to successful management. Many families treat asthma as they would a headache; if it is mild, ignore it and hope it will disappear. It is important to teach them a better metaphor: treat asthma as if it were a fire. If you saw smoke in your kitchen, would you sit down and say, "Let's see what develops"? This question usually elicits a smile, indicating that patients and families get the message.

TRIGGER FACTORS

Continued exposure to allergens and other trigger factors may be associated with worsening of asthma. Avoidance of trigger factors should be considered at all times to maximize potential for improvement of the asthma.

Sensitization in utero does appear to occur, but most studies do not show any benefit from restrictive diets during pregnancy, and severe restriction can be detrimental with impaired nutrition to the mother and the fetus. At present, apart from avoidance of maternal smoking, there are no other proven strategies for prenatal avoidance.

Some avoidance measures may be justified after birth in those at high risk. It is not easy to accurately identify those at risk. Although cord blood IgE levels have been found by some to be elevated, albeit at very low levels, in those with a risk of asthma and atopy, many who become asthmatic do not have high levels, so this is not a clinically useful test for prediction of atopic disease. At present, the family history is the most useful criterion, with increasing probability of atopy when one parent, and especially two parents, or siblings have such a history.[12] The season of birth has been associated with increased airway responsiveness, especially in Finns exposed to birch pollen allergen.[13] Exposure to high levels of house dust mites in the first year of life has been reported to be associated with troublesome asthma symptoms over the next 8 years.[14]

Some foods and additives may trigger attacks of asthma. There are no foods that affect all asthmatics, therefore their role needs to be considered individually in each patient. A common trigger is the preservative sodium metabisulfite, commonly present in dried fruits, sausages, wines, and other drinks, which releases sulfur dioxide, especially in the presence of acid drinks. Cold drinks may lead to increased airway responsiveness, especially in Asian children. There are anecdotal reports of asthma attacks caused by monosodium glutamate and tartrazine, but no consistent findings. Occasionally foods such as nuts, shellfish, strawberries, eggs, and cow's milk will produce an acute response, but this is usually associated with generalized anaphylaxis and is obviously recognized. If uncertain, a double-blind challenge in a recognized clinic may be necessary.

Attempts have been made to influence the induction of asthma in early childhood by dietary modification. Maternal restriction of cow's milk, eggs, and nuts during pregnancy and postnatally with subsequent breastfeeding followed by soy supplements and a restrictive infant diet without cow's milk, eggs, or fish has been reported to be associated with some decrease in eczema and gastrointestinal symptoms[15] but rarely with a decrease in asthma.[16] Wheeze has been noted to be less with breastfeeding in the first few months,[17] but more so in non-atopics,[18] possibly related to reduced respiratory infections in nonasthmatic early wheezers. The effect on asthma is not consistent, and the observations have been associated with multiple changes in the environment, and these need to be sorted out before any restrictive diets can be recommended. There is no evidence that soya replacement is significantly better than cow's milk formula. At present, one could suggest that those infants born to parents with a strong family history of atopy should be breastfed during the first year of life and that in the latter half of the first year of life foods be introduced carefully, one at a time, with a particular preference for less allergenic foods such as rice, vegetables, and noncitrus fruits and avoidance of eggs and nuts.

Aeroallergens are the agents to which most asthmatics develop long-term sensitization, and this sensitization is associated with persistence of symptoms. A direct causal relation is not always clear, and further studies must be done to clarify this association between sensitization and symptoms. It is very likely dose dependent.[19] Exposure to animals such as dogs and cattle during the prenatal period and early postnatal life is associated with reduced asthma and atopy.[20] The German Multicenter Allergy Study did not find any relation between early indoor allergen exposure and the prevalence of asthma, wheeze, and bronchial responsiveness at 7 years.[21] In fact, long-term and early life exposure to stables and farm milk induces a strong protective effect against development of asthma, hay fever, and atopic sensitization.[22] This may be induced by a subject's exposure to endotoxin leading to tolerance to allergens.[23] However, it may be reasonable to exclude furry pets in those who are already sensitized, particularly cats whose fur is often coated with saliva with enzymes that assist passage across the epithelial surfaces. It may take many months for the environment to clear of cat fur allergens.[24] There is no evidence that particular dogs are nonallergenic.

Even though house dust mite sensitization is one of the more common associations with continuing asthma,[25] avoidance measures have rarely proved successful. In a 5-year controlled study from birth, house dust mite avoidance measures resulted in a 61% reduction in mite allergen concentration, but no difference in asthma/atopy prevalence with an increase in prevalence of eczema.[26] Methods for reducing allergen levels in laboratory may not work in the home and may not result in clinical benefit: studies are ongoing.[27] Extreme measures such as admitting subjects to a hospital or living in alpine environments does appear to be associated with a decrease in sensitization to house dust mite and improvement in symptoms and lung function. Less extreme

measures do not often work. Murray and Ferguson[28] have shown benefit with pillows encased or replaced regularly, mattresses encased with thick plastic, bedding warm washed, and humidity kept at less than 50%. Pulling up carpets, high-grade filters, ascaricides, and special vacuum cleaners have not consistently shown significant benefit. In inner-city children with asthma, reductions in the levels of cockroach and dust mite allergens were significantly correlated with reduced complications of asthma.[29] The Cochrane review concludes that chemical and physical methods aimed at reducing exposure to house dust mite allergens cannot be uniformly recommended.[30]

Pollens, particularly in some environments, have been shown to be important allergens, but it is difficult to do much that will influence exposure. Molds, particularly *Alternaria*, are again important inducers of sensitization, but they are outdoor allergens, and little can be done except ensuring that the humidity in the house is decreased. Cockroach allergens may also be important, and cockroach eradication may be helpful in some inner-city environments.

Exposure to environmental tobacco smoke is associated with increased asthma symptoms, and maternal smoking has been documented to be associated with increased wheeze in infancy, decreased lung function, and increased airway responsiveness, and to be responsible for up to 20% of acute attacks of asthma and for an increase in emergency room visits.[31,32] An improvement has been documented with cessation of parental smoking.[33] Active smoking becomes an important trigger for progression of symptoms and should be discussed with all children at around the age of 10 years.

Although external pollution is an important cause of lower respiratory symptoms, particularly bronchitis, and for the triggering of asthma symptoms, it has not been shown to be a major factor associated with an increased prevalence of asthma.[34] Ozone[35] and traffic pollutants[36] have been reported to be associated with increased airway responsiveness and atopy to local allergens and may initiate exacerbations in those with asthma. Public health measures to reduce pollution will be of benefit. Filters and ionizers have not been found to have any clinically significant benefit.

Drugs are not a common cause of asthma attacks in children. Aspirin and other nonsteroidal anti-inflammatory drugs and some complementary medicines very occasionally cause symptoms in younger children. β-Blockers, taken orally or as eye drops, should be avoided or used with caution because these can certainly cause severe asthma in children.[37] Paints and other fumes can usually be avoided. Gastroesophageal reflux has been reported to be associated with exacerbations of asthma, but this has not been found to be common in children. Obstructive sleep apnea and rhinitis have also been associated with increased asthma symptoms, but this does not seem to be a particularly common association in children. It is recommended that children with chronic asthma receive influenza vaccination. The benefits for this in children with asthma have not been documented.

Exercise is an important trigger of asthma but should not be avoided. With appropriate warm-up sprints (so that tachyphylaxis can be induced) and premedication with β_2-agonists or sodium cromoglycate if necessary, a more sustained period of exercise will not cause significant symptoms. Approximately 30-second sprints every 2 minutes for 10 to 20 minutes have been shown to be a useful warm-up.[38] Physical training improves cardiopulmonary fitness, but has little impact on lung function. It is likely that improved fitness will lead to better quality of life.

Physiotherapy is used in asthma for specific purposes. Those with mucous plugging and subsequent atelectasis will benefit with physiotherapy as well as adequate treatment of their asthma. This group often needs steroids to reduce the mucus hypersecretion. Physiotherapists have an important role as part of the health care team in educating the children on useful exercises and the correct techniques in use of their aerosol devices.

The association of asthma with obesity,[39] particularly in adolescent girls, may justify consideration of dietary advice. Adequate trials to document benefit have not been done.

DRUG TREATMENT

It is being increasingly demonstrated that many different genetic polymorphisms can contribute to asthma susceptibility and asthma severity (see Chapter 56). These polymorphisms also influence the variability in the patient's response to drugs, both therapeutic and adverse (pharmacogenetics). Polymorphisms can impact on drug metabolism, target receptors, or unintended targets. Polymorphisms in the β_2 adrenergic receptor, particularly the 16th and 27th amino acid positions, may affect the response to β-agonists so that good responders or those who may have adverse effects with regular β-agonist use can be identified. Differences in interaction with the Arg 16 allele have been reported in different ethnic groups (Puerto Rican versus Mexican).[40] The mechanism is unknown. Polymorphisms on leukotriene C4 synthase or 5-lipoxygenase enzyme sites may identify variation in response to leukotriene modifiers. There is genetic variation in response to steroids, their metabolism, and the susceptibility to adverse events—such as a decrease in bone density.[41]

Current concepts on the use of drugs in asthma are based on the treatment of the underlying inflammatory disease as well as prevention and treatment of acute attacks of asthma associated with environmental triggers.[42] These attacks of asthma may be treated with reliever medications such as β_2-agonists, ipratropium bromide, and theophylline. The underlying disease process is generally controlled with inhaled corticosteroids, sodium cromoglycate, nedocromil sodium, leukotriene modifiers, and rarely theophylline. Maximum efficacy/safety is usually achieved by use of inhaled medications.

Inhaler Devices

Inhaler devices for children include MDIs with or without spacer, DPIs, or nebulizers (Table 59-2) (see Chapter 17). Clear instructions are essential. Children must be observed repeatedly using these devices to ensure their technique is satisfactory because they will often revert to bad habits despite careful instructions. Most children older than the age of 7 years can use an MDI, a DPI, or the breath-activated autohaler. Some may be helped with a large volume (750 mL) spacer, which will improve deposition and may, in some cases, allow larger doses to be given to have an effect similar to a nebulizer during an acute attack. Some children will need

Table 59-2
Medication Delivery for Young Children

Route of Administration	Less Than 4 Yr	4-6 Yr	7 Yr and Older
Nebulizer	Yes	Yes	Yes
MDI/small volume spacer/mask	Yes		
MDI/large volume spacer		Yes	Yes
DPI		Sometimes	Yes
MDI			Yes

Always assess compliance and delivery technique when symptom control or response to medication is poor.
DPI, dry powder inhaler; MDI, metered dose inhaler.

a nebulizer if they have severe acute attacks of asthma or troublesome chronic asthma.

Children from 4 to 7 years can use an MDI with the large volume spacer. The aerosol can be inhaled through the mouth as a single breath or with panting tidal maneuvers—both being equally effective. Only 1 to 2 actuations at a time should be used because any larger number significantly allows deposition and reduces the available respirable particles.[43] Spacers should be washed with detergent and left to dry, not wiped, to minimize electrostatic forces that cause increased aerosol fallout. Some can use the DPI, but deposition is unreliable in those younger than 5 years old,[44] especially during symptomatic periods when inspiratory flow rates are low. For many DPI devices, a rate of at least 30 L/minute is required for optimal de-aggregation and appropriate deposition of particles. It is not clear whether the breath-actuated autohaler is of significant benefit in this age group.

In children younger than age 4, MDIs with a small volume spacer and face mask can provide adequate deposition and similar therapeutic response to that seen with nebulizers.[45,46] In some societies, access to and cost of these devices are a particular problem, and a large plastic coffee cup or half of a 1-liter plastic soft drink bottle may be modified to produce a reasonable spacer device.

Nebulizers are effective because large doses can be administered and breathing pattern does not have as significant an effect on deposition. They can be used with oxygen if needed, but they are bulky and expensive and not necessary for most asthmatics. An MDI and spacer with up to 10 puffs of β_2-agonist will produce the same or better result than a nebulizer.[47] Nebulizers with a venturi design to drive air or oxygen through the fluid and with a separate expiratory valve provide a better dose of drug. Use of novel incentive spacer devices such as the Funhaler (Visiomed, Nedlands, Western Australia, Australia) appear to be associated with improved adherence and likely efficacy.[48]

RELIEVER MEDICATIONS

β_2-Agonists

The initial treatment for children with a mild episode, which if it recurs, does so less than every 2 months and there are no symptoms between attacks, is with intermittent short-acting aerosol β_2-agonists such as salbutamol/albuterol or terbutaline. β_2-Agonists act through the β_2-receptor, which is a G protein–linked receptor in the cell membrane. Stimulation causes activation of adenyl cyclase, which opens K^+ channels and catalyzes the production of cyclic adenosine monophosphate (cAMP). β_2-Agonists relax smooth muscle, decrease vascular permeability, increase mucociliary clearance, and decrease mucus secretion. They may modulate mediator release from mast cells. There appears to be an age effect, with these agents having little effect in normal infants under the age of 12 months and increasing effect from 1 to 5 years.[49] They have a greater effect in infants born preterm than others in the first year of life, and this may be related to the greater amount of smooth muscle seen more peripherally in the airways of these infants. Receptors are certainly present, and β_2-agonists in the early months of life can block the response to mediator challenge.[50] The drugs are safe and effective. They produce acute bronchodilation and prevent exercise-induced bronchoconstriction. They should almost always be used by aerosol. Once again, there may well be significant differences in deposition with age, although these have not been well defined. Inhalation of agents through the nose and breathing patterns of infants lead to reduced deposition in younger infants. However, a lack of response rarely justifies increasing the dosage in infants because it is unlikely that they will respond to the higher dosages. It is important to use the minimum dosage needed to produce the beneficial effect without side effects.

Salbutamol/albuterol and terbutaline have similar β_2 selectivity, although fenoterol may be somewhat less selective. Duration of action is normally up to 4 to 6 hours, with maximum effect for 1 to 2 hours, and an onset of action between 3 and 10 minutes.

MDIs are available as salbutamol 100 μg and terbutaline 250 μg. Usually 1 to 2 puffs are used in normal symptomatic periods, but up to 10 puffs in a spacer may be used during a severe acute attack. DPIs usually contain the equivalent of two puffs. Nebulizing solutions contain the equivalent of 2.5 mg or 5 mg of salbutamol, or 10 mg of terbutaline per mL and approximately 0.02 to 0.03 mL/kg of these solutions is usually used.

Common side effects of the β_2-agonists include tremor, tachycardia, headache, and hyperactivity.[51] Large doses may be associated with hypokalemia and alteration of the ST segment on electrocardiograms. In vitro tolerance or tachyphylaxis to β_2-agonists is seen with long-term use. Tolerance to both side effects such as tremor and to protection against inhalational challenge is also shown with regular use. The clinical significance is not clear, especially because the bronchodilator response does not appear to be significantly affected. Some epidemiologic studies have documented an association between long-term use (more than four times daily) and increased morbidity and mortality,[52,53] but this relationship is not consistent and has not been proved to be causal, clinically significant, or a particular problem in children. However, increased airway responsiveness has been shown with withdrawal of β_2-agonist after long-term use,[54] and this observation in association with the metabolic and cardiac effects that can be seen with these agents provide biological plausibility for a potential risk. Thus, it appears reasonable to attempt to ensure minimal use of β_2-agonists to the level that will control symptoms. It must be remem-

bered that some children will still require β_2-agonists long-term and that, in these situations, the benefit outweighs the potential risks.

Long-Acting β_2-Agonists

Long-acting β_2-agonists such as salmeterol, eformoterol, and bambuterol have lipophilic side chains, which ensure tighter binding to receptor sites and action up to 12 hours. They generally have a slightly slower onset of action than short-acting β_2-agonists, hence short-acting agents are usually necessary for bronchodilation during acute episodes and for protection against challenges,[55] although formoterol onset of action is not much longer than short-acting agonists and is being suggested for rescue as well as maintenance therapy.[56] Some anti-inflammatory activity is argued, although this has not been confirmed, and long-acting β_2-agonists must be used with inhaled corticosteroids and not alone. They are available as MDIs; salmeterol has 25 μg/puff and eformoterol has 6 μg/puff and are usually administered as two puffs twice daily. Side effects are the same as for short-acting β_2-agonists.[57] There have been concerns regarding the risk of long-acting β_2-agonists in view of the studies regarding regular short-acting β_2-agonist use and occasional reports of increased exacerbations and deaths with their use, but the studies are confounded by severity of asthma and access to health care services. No clinically significant tachyphylaxis has been observed and it is recommended that they should be used only in association with inhaled corticosteroids. Reports suggest that the combination of the long-acting β_2-agonist and regular-dose inhaled corticosteroids may be more effective than higher-dose inhaled corticosteroids, and they are currently used for long-term management in that situation. In adults with inadequately controlled asthma on lower-dose inhaled corticosteroids, added long acting β-agonist is superior to added leukotriene receptor antagonist.[58]

PREVENTIVE AGENTS

Preventive agents are used to prevent exacerbations and are thought to do this by control of the inflammatory process. Inhaled corticosteroids are used in those with continuing asthma, whereas sodium cromoglycate, nedocromil sodium, or a leukotriene modifier may be used in those with mild to moderate asthma, even though a long-term effect on the inflammatory process is not well documented. Indications for the introduction of preventive agents are not clear-cut, but most would agree that any of the following: continuing symptoms; the need for β-agonists more than twice weekly; attacks of asthma more than every 2 months; any life-threatening attack of asthma; abnormal lung function in the interval phase; and interference of normal lifestyle because of symptoms would justify the introduction of preventive agents. There is argument whether to use a low dosage of inhaled corticosteroids and increase if necessary or to start with a high dosage to gain maximum control and to define an effective baseline and then reduce the dosage while maintaining the effect. Both are probably appropriate—those with mild to moderate symptoms could start at a low dosage inhaled corticosteroid because it is unlikely that any increase will be required; those with moderate to severe disease should be brought under best control with a high dosage or oral corticosteroid then weaned to the minimum required to maintain that state.

Inhaled Corticosteroids

Inhaled corticosteroids are anti-inflammatory agents that exert their effect after binding to a glucocorticoid receptor in the cytoplasm, which then moves into the nuclear compartment where it regulates the transcription of target genes, leading to a number of actions including the modification of arachidonic acid metabolism, synthesis of prostaglandins and leukotrienes, as well as restoring disrupted epithelium, decreasing vascular leakage, inhibiting cytokines, preventing activation and migration of inflammatory cells, and augmenting β_2-receptor responsiveness. Inhaled corticosteroids lead to a reduction in the eosinophil numbers and eosinophilic cationic protein concentration and in numbers of activated CD4+ T cells. The anti-inflammatory effect is accompanied by a reduction in exhaled nitric oxide (eNO).[59] Inhaled corticosteroids are associated with decreased airway responsiveness to histamine and the late reaction to allergens, but they do not alter the early allergen response; do not modify the disease process; and do not induce permanent cure because these responses may return after cessation of treatment—even when used for many years.[60-63] Inhaled corticosteroids are available or are being developed as beclomethasone dipropionate, budesonide, fluticasone propionate, flunisolide, mometasone furoate, ciclesonide, and triamcinolone acetonide in doses of 50, 100, 250, 400, and 500 μg per puff. Rapid topical biotransformation reduces the amount of active metabolite absorbed. Budesonide and fluticasone are more potent and lipophilic than beclomethasone, triamcinolone, or flunisolide—and this is associated with increased activity, decreased absorption, and first-pass hepatic cytochrome P-450 metabolism. This tends to allow improved effect with smaller doses and decreased side effects.[64] Mometasone and ciclesonide are very potent with predicted fewer adverse effects.[65,66] In childhood, most physicians aim to obtain a response on less than 400 μg/day beclomethasone equivalent because the maximum improvement is seen between 100 and 400 μg and this dosage limits potential for side effects. When taking more than 800 μg/day, the dose-response curve flattens with less significant improvement for the same increase in dosage and greater risk of side effects. The agents are administered via MDIs, PDIs, and nebulizers. A large-volume spacer with an MDI will decrease side effects as a result of raining out of larger particles, which are then swallowed or deposited in the mouth.[67] A mouth rinse following PDIs will decrease absorption and side effects. Some have documented increased deposition with PDIs and recommend a reduction in dosage when changing to this form of administration.[68] Budesonide is available as a nebulizer solution. This is rarely needed, although it may be helpful in some infants with troublesome symptoms. In this case, goggles and face cream should be used and/or the face washed after administration to decrease topical side effects. If possible, attempts are made to administer these drugs in young infants through MDI, small volume spacer, and face mask.

Some studies have suggested that a greater improvement in lung function is achieved if steroids are introduced sooner

after a diagnosis of asthma is made, suggesting prevention of irreversible changes.[69] Selection bias cannot be ruled out in these studies, and the CAMP and PEAK studies suggest that presymptomatic introduction of steroids in young children is not justified.[63,70] Biopsy studies in infants have not confirmed consistently present asthma inflammation in this age group.[71]

Side effects have been reported with all dosages, although they appear to be clinically insignificant below 400 μg/day. Suppression of the hypothalamic-pituitary-adrenal (HPA) axis with reduced cortisol levels[72] has been reported, but few studies show a clinically significant effect below 800 μg. Cushingoid appearance can be seen in some children following the use of inhaled corticosteroids, but there appears to be significant individual variation. The effects on bone turnover and growth are inconsistent but a potential concern. The problem is confounded by the fact that asthma itself will have an effect on growth and pubertal development and it becomes difficult to separate the two. Some investigators have not documented any effect on growth, serum calcium and phosphorus, bone density, or osteocalcin levels,[73] but others have shown delayed puberty with subsequent catch-up[74]; some have found reduced osteocalcin levels,[75] and some documented decreased growth, measured by knemometry,[76] at dosages above 400 μg/day.[77] At present, there are no indications that long-term use of modest dose inhaled corticosteroids is associated with clinically significant reduced bone density. A significant effect on growth has been demonstrated in mild asthmatics given 400 μg/day. This evidence of a systemic effect on growth appears to be temporary with no effect on adult height reached.[78,79] Linear growth was not affected in young children at 200 μg/day, but was reduced temporarily at 400 μg/day and especially 800 μg/day. Hoarseness, oral thrush, and cough are relatively common and can usually be minimized by using spacers. Purpura, bruising, psychological disturbances, and posterior subcapsular cataracts have been reported occasionally.

Corticosteroids are usually given twice daily, although some clinicians have documented benefit when used once daily[80]; others would suggest that they should be given around 3 PM because this has been documented to produce maximum effect with oral corticosteroid medications.[81] One should aim to reduce the dosage to the minimum needed with occasional increases for intercurrent exacerbations. Consideration of reduction in dosage should be given every 6 months if the patient is symptom free. It has been suggested in adults that satisfactory control can be achieved with episodic *as needed* administration in mild asthma but further studies are required in children.[82]

If there is no response to a regular dosage of inhaled corticosteroids, a variety of options are available, none of which has been consistently proved to be superior.[83] Most would add long-acting β_2-agonists. Combination products are now available. Others would consider leukotriene-receptor antagonists or theophylline as appropriate. Some increase the dosage of inhaled corticosteroid, but further benefit with dosages above 800 to 1000 μg/day is difficult to demonstrate. It may be preferable to use a more powerful locally acting corticosteroid. Troleandomycin (TAO) has been suggested to be steroid sparing. It does increase the half-life,[84] but it also increases the side effects.[85] Some children appear to be steroid resistant. The mechanism is uncertain, although changes in receptor binding have been suggested. It is important to recognize this phenomenon to avoid unnecessary side effects with overuse when the drug is not likely to be effective.

Sodium Cromoglycate

Sodium cromoglycate has been shown to be an effective preventive agent in some children and is good particularly for preventing the bronchoconstriction associated with exercise. It also decreases both the immediate and late response following an allergen challenge. It is a mast cell stabilizer but stronger mast cell stabilizers such as β-agonists do not block the late allergen response. It may influence cytokine production and release, and it appears to have some effect on nonadrenergic, noncholinergic nerve endings and neuropeptides. Long-term treatment may lead to reduced airway responsiveness, but this is not consistently found. It must be used by aerosol and is usually given as two puffs of 5 mg per puff MDI two or three times daily or in a nebulizer solution with 20 mg of sodium cromoglycate for wheezy infants.[86] In some countries, only a 1 mg per puff MDI is available. It is generally free of side effects, although some complain of the taste and develop cough following inhalation. It is no longer widely used.

Nedocromil Sodium

Nedocromil sodium is similar to sodium cromoglycate. No significant differences between sodium cromoglycate and nedocromil sodium have been reported[87-89] and neither is as effective as modest-dose inhaled corticosteroids.[78] It is now rarely used.

Leukotriene Modifiers

Viruses may lead to increased airway responsiveness associated with mucosal damage and the presence of cysteinyl leukotrienes in airway secretions.[90] Leukotriene modifiers have been found to produce some symptomatic relief in infants and toddlers with viral-induced wheeze.[91] The availability of leukotriene-receptor antagonists (Zafirlukast, Montelukast) and leukotriene-synthesis inhibitors (Zileuton) provides new mediator-specific therapy for asthma. Their specific role is not yet clear. They have been shown to block airway response to challenge and, in chronic asthma, to lead to improved lung function, reduced symptoms, and some steroid sparing. They appear less effective than steroids,[92-94] with 17% of an asthmatic cohort showing increased FEV_1 with use of both steroids and leukotriene modifiers; 23% to inhaled corticosteroids only; and 5% to leukotriene receptor antagonist only.[95] They are well tolerated, although hypereosinophilia as a part of Churg-Strauss syndrome has been reported, but rarely in children. It is not certain whether this is or is not due to the antileukotrienes or is a consequence of steroid withdrawal. Specific recommendations are not yet clearly defined, but inhaled corticosteroids remain first-line therapy for most children with moderate persistent asthma, whereas leukotriene modifiers may prove useful in mild asthma especially if an oral preparation is required. They may be useful for viral-induced wheeze in young children.[96] They

appear to increase the number of symptom-free days, ED visits, and parental time at work in the months following a diagnosis of viral-induced wheeze. In occasional patients, leukotriene modifiers may be tried with inhaled corticosteroids as an alternative to the combination of inhaled corticosteroids and long-acting β-agonists and possibly in those in whom steroid reduction is sought.

Oral Steroids

Oral prednisolone or methylprednisolone may be used in a very small group of children as a trial to diagnose asthma, for acute management of a severe attack, and in some with troublesome chronic asthma for long-term treatment. High dosages of 1 to 2 mg/kg may be used to achieve control, but it should then be reduced to the lowest possible dosage, and this may be as low as 1 to 2 mg/day. In those with severe disease, most will use oral prednisolone intermittently for episodes of acute deterioration. Long-term treatment can be associated with reduced growth, HPA axis suppression, hypertension, posterior subcapsular cataracts, and psychological changes.

Nonsteroidal Anti-inflammatory Agents

Many other anti-inflammatory agents have been tried in those not responding to moderate dosages of steroids. Methotrexate appears to help some but it is not uniformly effective.[97] Changes seen with cyclosporine are small and of doubtful clinical significance. Gamma globulins have been used, but consistent benefit has not been confirmed.[98] It has been noted that gold may have a steroid-sparing effect.[99] Nifedipine has been associated with a reduction in circadian peak flow variation.[100] PAF antagonists[101] and inhaled diuretics are being tried experimentally, but as yet have no clinical application.

Omalizumab is a recombinant humanized monoclonal antibody directed against IgE to inhibit the immune response to allergen exposure. Omalizumab is directed against the binding site of IgE for its high affinity Fc receptor. It prevents free serum IgE from attaching to mast cells and other effector cells and prevents IgE-mediated inflammatory changes. A Cochrane review[102] reports that omalizumab is significantly more effective than placebo in enabling more patients to reduce or withdraw inhaled corticosteroids, but the level of clinical value is debatable. It is approved in some countries for use in children 12 years and older with evidence of asthma and atopy not controlled by inhaled corticosteroids. It is administered by regular subcutaneous injection, is well tolerated, and reduces asthma exacerbations. It is expensive. Further assessment is necessary.

Theophylline

Theophyllines have been widely used in the past. They are inexpensive but have a low therapeutic benefit to potential toxicity ratio. They are bronchodilators with considerable extrapulmonary effects. Some have argued that they have an effect on the late response to allergen challenge and that they have anti-inflammatory activity as a result of more selective phosphodiesterase inhibition in small doses.[103] They produce some muscle relaxation, increase mucociliary clearance, inhibit mediator release, suppress edema, stimulate ventilation, and reduce diaphragmatic fatigue. With long-term use they do not lead to a reduction in the inflammatory infiltrate or nonspecific airway hyper-responsiveness. They are used in some intensive care units in severe acute attacks to reduce diaphragm fatigue and to produce central nervous system stimulation. They are usually given at dosages of approximately 5 mg/kg of regular theophylline up to six doses hourly, or 7 to 8 mg/kg of the slow-release preparation every 12 hours, but are rarely used today. Side effects are seen even at therapeutic doses. Some are due to direct irritation of the gastrointestinal tract, such as nausea and vomiting, whereas others are associated with increased serum levels and include vomiting, hematemesis, tachycardia, and dysrhythmia. With long-term use, headache, learning difficulties, sleep disturbance, and behavioral problems[104] have been reported, but theophyllines are more likely to exacerbate these symptoms in those predisposed. Uncommonly, convulsions and death may occur.

Anticholinergic Agents

Anticholinergic agents such as ipratropium bromide and tiotropium bromide block the postganglionic efferent vagal pathways leading to bronchodilation associated with decreased vagal tone.[105] They block reflex bronchoconstriction to irritants but have no effect on the early or late response to antigen challenge or on the inflammatory response. Some would suggest that these agents have an additive effect to β_2-agonists with acute attacks of asthma and should be used for anyone with moderately severe symptoms, and some would consider that they be used occasionally for long-term management. They may be useful for those who have significant side effects such as tremor with high-dose β_2-agonists. They are administered as an MDI using two to four puffs of 20 μg/puff, or as a nebulizer with 250 μg/dose. They have a slow onset of action, with maximum effect at 30 to 60 minutes. They have few systemic side effects, although paradoxical bronchoconstriction has been reported possibly owing to the effect on M1 and M2 receptors, which may cause increased acetylcholine release as well as the block of M1 receptors at the neuromuscular junction and of M3 receptors on smooth muscle and mucous glands. High dosages given frequently to young infants cause significant skin vascular dilation. Currently, they are used in some centers in association with β_2-agonists for the acute management of asthma.[106] A Cochrane systematic review suggests that ipratropium bromide was of no additional benefit in children with mild to moderate acute asthma and should be considered only in school-aged children with severe acute asthma.[107] They may very occasionally be used long-term in those requiring high-dose corticosteroids or those who experience significant side effects with β_2-agonists. Some reported better response in infants under 18 months of age,[108] although this has not been confirmed. Some investigators consider that they may have a role in infants with chronic lung disease of prematurity.

Other Agents

Ketotifen is a potent oral H_1-antagonist that was shown to increase β_2 receptor density on lymphocytes with reduced

levels, and it has been suggested that this agent was a useful preventive agent in asthma.[109,110] Benefit has been reported but not consistently with oral antihistamines[111]—there being a small effect compared with placebo and potential side effects such as drowsiness and dry mouth.

Antihistamines may be used for many of the associated symptoms that occur in asthmatics such as rhinitis, eczema, and conjunctivitis but currently have no role in the management of the asthma. Cough suppressants and demulcents should not be used in the treatment of asthma. Antibiotics are rarely needed because bacterial infections, except for *Mycoplasma*, *Chlamydia*, and pertussis, do not cause asthmatic wheezing and secondary infections are uncommon in children in developed countries.

DIET

There are reports of reduction in both asthma symptoms and improved lung function with exposure to pollutants in asthmatics taking antioxidants in the diet[112] as well as a potential for reduced development of asthma in those who are atopic with the use of lactobacillus[113] or omega-3 fatty acid supplements. Further studies are needed to confirm the role of these dietary interventions.

ALTERNATIVE THERAPIES

Many asthmatics resort to alternative health therapies.[114] Most have not been found to be effective when appropriately controlled trials have been undertaken. Ionizers[115] and acupuncture[116,117] were shown to be ineffective in controlled trials. Most studies of chiropractic, herbal medicines, homeopathy, yoga, specific breathing exercises, and hypnosis have also been disappointing, although suggesting some individuals may gain nonspecific benefit. The Cochrane reviews concluded that recommendations on their use cannot be made because of the limited evidence available.

IMMUNOTHERAPY

The role of immunotherapy in asthma continues to be debated. At present, avoidance of known triggers and pharmacotherapy are more appropriate initial approaches to management because they give good control without significant side effects. This makes immunotherapy with its moderate benefit and significant side effects less justified as an early intervention. Efficacy has been documented,[118] but the effect is mild and less than that obtained with anti-inflammatory agents and associated with more side effects, including death. It will be considered occasionally in highly selected children who are sensitive to a single allergen such as grass pollen, mites, or *Alternaria* and when it can be done under specialist supervision and safe conditions. Usually it must be given for at least 3 years. Some argue that it reduces the number of children that progress from rhinoconjunctivitis to asthma.

ONGOING TREATMENT

Specialist and multidisciplinary clinic referral should be considered in anyone who has a life-threatening attack of asthma, frequent hospital admission, poor parental management, uncertainty of diagnosis, and poor response to regular treatment and regular doses. The natural history of childhood asthma is usually for improvement, and the possibility of a decrease in drug treatment or cessation of therapy should be considered every 6 months.

MANAGEMENT OF ACUTE ATTACKS

In spite of the availability of good preventive treatment, acute attacks still occur and are responsible for considerable hospital admissions and missed school days.

Assessment of Severity

Good management will be based on accurate assessment of each attack. Historical information is vital with clear documentation of the duration of symptoms, cause of the exacerbation, severity of symptoms, current medication, prior hospitalization, and past history of events such as syncopal episodes. Physical examination for tachycardia, tachypnea, cyanosis, changes in demeanor, silent chest, use of accessory muscles, subcutaneous emphysema, and pulsus paradoxus of greater than 20 mm Hg should be undertaken to categorize severity as mild, moderate, or severe (Table 59-3). Attempts to develop reliable and predictive asthma scores have not been successful. Few extra investigations are needed. A chest radiograph is not routinely done but should be considered with differential chest signs that may indicate a complication such as lung collapse or pneumothorax. It may also be justi-

Table 59-3
Initial Assessment of Severity of Acute Asthma in Children

Symptoms	Mild—Probably Manage at Home	Moderate—May Need Hospital Admission	Severe—Admission Required
Altered consciousness	No	No	Yes
Physical exhaustion	No	No	Yes
Speaks in:	Sentences	Phrases	Words
Pulsus paradoxus	Not palpable	May be palpable	Present
Central cyanosis	Absent	Absent	Present
Wheeze on auscultation	Present	Present	Present
Use of accessory muscles	Absent	Moderate	Marked
Sternal retraction (in young children)	Absent	Moderate	Marked
Initial PF or FEV_1 (% predicted or % child's best)	>60%	40-60%	<40%
Oximetry on presentation before treatment (SaO_2)	>95%	92-94%	<91%

fied with unexplained deterioration or failure to respond to treatment. Peak flow or spirometric measurements can be made in older children without severe distress and should be performed when possible. Oximetry has proved to be a good predictor of subsequent progress.[119] Those with oxygen saturation of greater than 95% are likely to respond rapidly and be discharged. Those at 91% or less are very likely to require admission to a hospital and this should be considered in the context of other clinical indicators. Those between 92% and 94% should be given aggressive therapy to achieve the most satisfactory response. These measures should be used with other indicators to determine the need for hospitalization. Each acute attack of asthma is a failure of prophylaxis and preventive treatment should be reviewed at follow-up.

Treatment

Treatment will usually be initiated at home with regular β-agonist treatment. Repeated β_2-agonists should be given for an acute attack of asthma not responding to standard treatment in the community while seeking medical attention. Failure to respond should make one consider an alternative diagnosis such as inhaled foreign body but, if thought to be due to asthma, lead to a visit to the emergency room or doctor's office where a β_2-agonist would be given through a nebulizer with oxygen if necessary (Table 59-4). Mild to moderate episodes can be treated with an MDI and spacer using 6 to 10 puffs, which can be given with 30 seconds between each actuation or 2 puffs every 5 minutes. Some centers use additional ipratropium bromide, suggesting that this results in a 10% increase in response and a greater duration of response.[120] If the child responds to this treatment, he or she should be observed for 1 to 4 hours and then sent home with continuing treatment. If the child does not respond optimally, steroids should be added.[121] Oral prednisolone may be used, or when severe, intravenous hydrocortisone in a dose of 4 mg/kg or either prednisolone or methylprednisolone in doses of 1 to 2 mg/kg will generally be used. There is some evidence that high-dose inhaled corticosteroids may be equally effective for mild asthma in the emergency department, but a combination of inhaled and oral corticosteroids does not provide additional benefit.[122] Although there has been controversy regarding the effects of steroids, their benefit in moderately ill patients has been documented.[123] The optimal dose is not known. An effect can usually be documented between 4 and 12 hours. Some clinicians have recommended a single dose of corticosteroids in the emergency department,[124] whereas others have not shown that this significantly alters the natural history.[125] It does appear that if the child needs oral or intravenous corticosteroids for an acute attack of asthma, then a short course should be given. Very large doses may be associated with side effects such as peptic ulceration, hypertension, behavioral disorder, and myopathy.

Those not responding to treatment over 1 to 4 hours will require admission to a hospital. Admission criteria are based on duration and severity of clinical signs, peak flow, SaO_2, and lack of response to bronchodilator, but admission is often influenced by health service access, social circumstances, past history, and comorbidities. The mainstay of treatment is repeated β_2-agonist (Table 59-5) in various dosing regimens, depending on response. Addition of ipratropium bromide will be considered in those with more severe attacks either initially or only in those who do not show a good response to β_2-agonist and steroids.

Careful clinical monitoring is essential with peak flow measurements in those able to perform the maneuver and SaO_2 in those with moderate to severe disease. If there is a continued deterioration or failure to respond, blood gases may be justified to document the level of $PaCO_2$. Supplemental oxygen should be given to maintain SaO_2 above 93%.

Inadequate response to these regimens will warrant admission to the intensive care unit and may justify the addition of intravenous aminophylline. This is usually given as a single dose of 6 mg/kg over 30 minutes followed by 1 mg/kg/hour to maintain serum levels in the therapeutic range. The loading dose may be reduced or omitted if the child is on theophylline. The effects of aminophylline are not clear. An effect can be detected on lung function within 6 hours. Apart from bronchodilation, it may help by stimulating ventilation and decreasing diaphragmatic fatigue. Aminophylline has been required less frequently because regular or even constant β_2-agonist inhalation has been used. In fact, some argue that it increases the toxicity without significant benefit.[126,127] Some

Table 59-4
Initial Management of Acute Asthma in Children

Treatment	Mild—Probably Manage at Home	Moderate—May Need Hospital Admission	Severe—Admission Required
MDI and spacer or nebulized short-acting β-agonist	Single dose	3 doses at 20-min intervals if required, and 1 to 4 hourly thereafter	Continuous initially then hourly; when stable, decrease to second hourly
Oxygen	No	Up to 8 L/min by face mask to achieve $SaO_2 > 93\%$	Up to 8 L/min by face mask to achieve $SaO_2 > 93\%$
Nebulized ipratropium with β-agonist	No	Optional	250 μg/4 hr may be used (1 mL of 0.025%)
Corticosteroid	No	Consider	Yes; oral or IV
Aminophylline	No	No	Possible
Observation	For 1 hr, if improvement maintained—discharge home	1 Hr after last dose, if improvement maintained—discharge home; if not, admit	Continuous and admit

Table 59-5
Recommended Dosages for Bronchodilators for Acute Exacerbations

Treatment	Formulation	Dosage	Comment
Albuterol/ salbutamol	Metered-dose inhaler (MDI) (90 μg/actuation or 100 μg/actuation)	2 actuations inhaled, may be repeated every 1 to 5 min for a total of 6 to 10 actuations if necessary. Then repeat between 20 min and 4 hr as required.	Monitor response via peak flows or spirometry, if possible. If improved, decrease frequency of administration, if not improved, switch to nebulizer.
	Nebulizer solution 0.5% (5 mg/mL) or more dilute preparations.	0.05-0.15 mg/kg/dose up to 5 mg inhaled via nebulizer every 20 min for 1-2 hr if required. 0.5 mg/kg/hr by continuous nebulization	If improved, decrease to 1 treatment every 1-6 hr, if not improved, use continuous inhalation.
Terbutaline	MDI (200 μg/actuation or 250 μg/ actuation)	2 actuations inhaled, may be repeated every 5 min for total of 12 actuations if necessary. Then repeat 20 min and 4 hr as required.	Maximum 15 mg/hr
	Nebulizer solution (5 mg/2 mL)	0.2 mg/kg/dose to a maximum of 2 mL/4 hr as required.	
	Injectable solution 0.1 mg/mL in 0.9% sodium chloride or 0.5 mg/mL	0.01 mg/kg up to 0.3 mg injected subcutaneously every 2-6 hr as needed. 10 μg IV over 10 min as loading dose, then 0.4 μg/kg/min increased as needed by 0.2 μg/kg/min.	Inhaled bronchodilator preferred. Should expect to use 3-6 μg/kg/min for final maintenance dose.
Epinephrine/ adrenalin	Injectable solution: 1 : 1000 (1 mg/mL)	0.01 mL/kg up to 0.3 mL injected subcutaneously every 20 min for a total of 3 doses.	Inhaled bronchodilator preferred.
Ipratropium bromide	MDI (18 μg per puff or 21 μg per puff)	2 Puffs up to 4 times daily.	
	Nebulizing solution (250 μg/mL)	0.5 to 1.0 mL diluted to 2-3 mL up to 4 times daily.	

report benefit of intravenous magnesium sulfate for severe acute asthma[128]—but there are inadequate data to justify routine use.

Continuous nebulized β_2-agonists[129] or intravenous β_2-agonists will generally be used in those with continuing severe airway obstruction.[130] Experience with continuous nebulized β_2-agonists has been encouraging with reduced need for other interventions. Sedation or antibiotics is rarely required. Repeated assessment is important, and occasionally the child may require intubation and ventilation[131] if the $PaCO_2$ continues to rise and the child tires. Intubation and ventilation should be performed by experienced pediatric practitioners because children with severe acute asthma can be very difficult to manage during induction and maintenance. Air leaks and hypoxic ischemic encephalopathy may occur. Administration of β-agonists into the ventilator circuit can be difficult.

LONG-TERM MANAGEMENT

Successful long-term management is achieved by adherence to a treatment strategy by the family, health care providers, and temporary caregivers such as teachers. Recently published guidelines provide algorithms that recommend currently agreed-upon good clinical practice (Tables 59-6 through 59-8). However, treatment must be individualized, and the ideal for each child will differ; choice provides an opportunity to find the most suitable regimen based on initial assessment and to then move up or down the protocol depending on the response. The proportion of children in each classification of severity will vary with age.

INFREQUENT EPISODIC ASTHMA

Children with infrequent episodic asthma (50% to 75%) will usually require only intermittent inhaled short-acting β_2-

Table 59-6
Maintenance Medication for Children

Classification of Severity	Common Features	Maintenance Therapy
Infrequent episodes	Episodes more than 6-8 wk apart. Attacks generally not severe and short. Physical examination and spirometry between attacks normal.	Nil preventive treatment; prn use of short-acting β-agonist.
Frequent episodes	Attacks <6-8 wk apart. Attacks more troublesome. Increasing symptoms between attacks. Abnormal spirometry when symptomatic.	Consider sodium cromoglycate/nedocromil sodium/leukotriene modifier. Use inhaled corticosteroids in minimum effective dose plus prn use of short-acting β-agonists.
Persistent	Symptoms most days. Nocturnal asthma >3/wk. Attacks <6-8 wk apart. Daily use of short-acting β-agonist. Abnormal lung function. History of A&E visits or hospital admissions.	Inhaled corticosteroid using minimum effective dose. If high dosages of inhaled steroids are required long-term, consider specialist referral. In this situation, consider other drugs to minimize corticosteroid dosage (e.g., long-acting β-agonists, leukotriene modifiers, or omalizumab.)

A&E, admissions and emergency (department).

Table 59-7
Recommended Dosages for Bronchodilators for Long-Term Care

Drug	Formulation	Dosage
Albuterol/salbutamol	Metered-dose inhaler (MDI) (90 μg/actuation) (100 μg/actuation)	2 Actuations inhaled up to every 4-6 hr
	Dry powder inhaler (DPI) (200 μg/capsule)	Contents of 1 capsule inhaled every 4-6 hr
	Nebulizer solution 0.5% (5 mg/mL)	0.10-0.15 mg/kg up to 5 mg in 2 mL sodium chloride inhaled via nebulizer every 4-6 hr
Terbutaline	MDI (200 μg or 250 μg per actuation)	2 Actuations up to every 4 to 6 hours
	DPI (500 μg per actuation)	1 Actuation up to every 4 to 6 hours
Formoterol	MDI (21 μg per actuation)	1 Actuation 12 hourly
	DPI (12 μg per capsule)	1-2 Capsules 12 hourly
	DPI (50 μg per blister)	1 Blister 12 hourly
Ipratropium bromide	MDI (18 μg/actuation or 20 μg/actuation)	2 Actuations inhaled up to 4 times daily (maximum 12 actuations/day)
	Nebulizer solution (250 μg/mL)	1 mL up to 4 times/day in older children
Salmeterol xinafoate	MDI (25 μg/actuation)	0.5 mL up to 4 times/day in younger children
	DPI (50 μg/actuation)	2 Actuations twice daily
		1 Actuation twice daily

Table 59-8
Recommended Dosages for Inhaled Glucocorticoids and Other Preventers

Drug	Formulation	Dosage
Beclomethasone dipropionate	Metered-dose inhaler (MDI) (42, 50, 100, 250 μg/actuation)	1-2 Actuations inhaled twice daily
	Dry powder inhaler (DPI) (100 μg/actuation)	Dose dependent on severity of asthma and previous response
Flunisolide	MDI (250 μg/actuation)	2 Actuations inhaled every 12 hr up to 15 yr
		4 Actuations inhaled every 12 hr if required over 15 years
Triamcinolone acetonide	MDI (100 μg/actuation with spacer included)	1-2 Actuations inhaled twice daily and increased if needed
Fluticasone	MDI (50, 250 μg/actuation)	1-2 Actuations twice daily
	DPI (100, 500 μg/actuation)	
Budesonide	MDI (50, 100, 200 μg/actuation)	1-2 Actuations twice daily; dose dependent on severity of asthma and previous response
	DPI (100, 200 μg/actuation)	1 Actuation twice daily
	Nebulizer suspension (250 μg/mL, 500 μg/mL)	250 or 500 μg twice daily for severe chronic asthma where an MDI with spacer or PDI not effective
Fluticasone/salmeterol	MDI with salmeterol (25 or 50 μg) and fluticasone (100 μg, 125 μg, 250 μg or 500 μg)	1 Twice daily
Budesonide/eformoterol	DPI with budesonide (100 μg, 200 μg or 400 μg) and eformoterol (6 or 12 μg).	1 Twice daily
Sodium cromoglycate	MDI (1 mg or 5 mg per actuation)	2 Twice daily or before exercise
	Nebulizing solution (20 mg in 2 mL)	1 Ampule 2 to 4 times daily
Nedocromil sodium	MDI (2 mg per actuation)	2 Twice daily or before exercise
Montelukast	4 or 5 mg chewable tablets	Once or twice daily
	4 mg granules	
	10 mg tablets	
Zafirlukast	10 mg and 20 mg tablets	Twice daily

agonists. The parents should be aware of signs such as runny nose, itchy throat, or cough for early recognition of an attack so that treatment can be instituted early. Treatment is usually continued until free of symptoms for at least 48 hours.

FREQUENT EPISODIC ASTHMA

Children with symptoms at least every month but with clear periods in between (10% to 20%) should be given a regular preventive agent. This will usually be low-dose inhaled corticosteroids, but may be sodium cromoglycate or a leukotriene modifier. Choice will depend on the pattern of asthma and patient preferences.

PERSISTENT ASTHMA

Children with troublesome symptoms on most days (5% to 20%) will require inhaled corticosteroids once or twice daily with added bronchodilator as required. The starting dosage of inhaled steroids will depend on asthma severity. If symptoms are not well controlled, then regular peak flow measurements may be needed to monitor response to additional treatments that could be higher-dose inhaled corticosteroids, added long-acting β_2-agonist, theophylline, ipratropium bromide, oral steroids, leukotriene-receptor antagonists, or other preventive agents. With inhaled corticosteroid used by an MDI, a spacer device should be used, and mouth rinsing and spitting out when dry powder devices are used. There is some evidence that eNO monitoring may assist in optimizing inhaled corticosteroid treatment in children with persistent symptoms,[132,133] but its clinical usefulness has not been confirmed.

The family must be aware of action to take if the child does not respond to the regular bronchodilator or if the

response does not last 3 to 4 hours. This may be related to the normal circadian rhythm—the family must be comfortable that they can cope at that time. The reason for decreased peak flow and increased symptoms at night is not certain, but factors that may contribute include reduced catecholamines, reduced cortisol levels, increased vagal tone, cold dry air, allergens such as house dust mites, gastroesophageal reflux, and sleep state. Asthma has a tendency to interfere with activities at school, and efforts should be made to minimize any disruption. Teachers must be informed about asthma symptoms and how to respond. Schools should have an asthma-friendly policy regarding administration of drugs. The family should provide the teacher with details of treatment that may be required at school.

In the past, long-stay special schools and residential units were required for troublesome asthmatics. This is rarely necessary today because children can be managed in a mainstream school program and can achieve excellence in study and sport and not be held back by their asthma.

SPECIFIC PROBLEMS

Infants

The wheezing infant is more difficult to manage because the diagnosis is often uncertain and response to therapy is decreased. Many have a transient wheezy illness associated with viral infections, which settles over the first 1 to 3 years and is not associated with risk factors considered to be important for the development of asthma. Some will have other diagnoses such as viral bronchiolitis, cystic fibrosis, milk inhalation, and congenital abnormalities. Others will have chronic lung disease of prematurity or bronchopulmonary dysplasia. Some of these may be associated with asthma, and some may require the same treatment, although each must be considered individually as they may respond differently to various therapeutic interventions. Referral to a specialist may be justified.

The pathophysiology of wheezing in this age group is associated with smaller absolute size of the airways, decreased collateral channels, more peripheral airway smooth muscle, decreased static elastic recoil, and a mechanically disadvantaged chest wall so that wheezing is noted with milder degrees of airway obstruction. Due to less developed collateral ventilation and other developmental factors, hyperinflation occurs more readily, and carbon dioxide level rises earlier in the course of the disease, so artificial ventilation will not be required at levels that may justify assisted ventilation in older children. Lung function measurements are not easy in this age group. Arterial oxygen saturation may help, but decisions regarding the progress of the disease are generally dependent on clinical observation of alertness, feeding, cry, chest movement, and signs of hypoxia.

β_2-Agonists will generally be used, although response will be decreased. In the first year of life there is a negligible response in most infants, although some may respond, and a therapeutic trial may be justified, especially in the second 6 months. Some will show a significant decrease in Sa_{O_2} that may be related to shunting by vascular dilation in unventilated zones or bronchoconstriction to the tonicity or acidity of the aerosol. Anticholinergic agents are favored by some, although significant benefit has not been documented. For the spectrum of wheezy infants younger than 2 years of age, inhaled corticosteroids have been reported to produce a transient improvement in Vmax but no benefit sustained at 3 months.[134] Inhaled corticosteroids and sodium cromoglycate can be effective, although not consistently, in those with early onset asthma and are tried in those with persistent disease. There is early evidence that leukotriene modifiers may be effective, but more long-term studies in young infants are needed.[135] The metabolism of theophylline is decreased in this age group and dosage adjustments need to be made.

Adolescents

Adherence with treatment during adolescence as a result of perceptions related to drug taking, body image, and being seen to be different is a problem, and this is associated with a significantly higher death rate from asthma in this age group. Smoking is common in those with asthma, and unfortunately the number is no less than in the general community in spite of the potential for significant deleterious effects on subsequent lung health. It appears to be part of the risk-taking behavior that is normal in this age group. It is an important time for establishing rapport, improving educational techniques, and providing guidelines for better care. Denial is associated with a significant increase in the risk of death.

Severe Persistent Asthma

Rarely in children, asthma may appear resistant to standard therapies. Alternative diagnoses such as inhaled foreign body and structural abnormalities need to be excluded. Compliance/adherence as well as the appropriateness and correct technique of aerosol devices must be evaluated and addressed. Genetic and acquired steroid-resistant patterns of asthma have been described and may be related to abnormal steroid receptor activity, continued environmental exposure to irritants or allergens, and/or the presence of a neutrophilic rather than eosinophilic inflammation. Treatments to consider for these possibilities include environmental adjustment, leukotriene modifiers, other anti-inflammatory agents, and, very rarely, long-term subcutaneous β-agonist infusions.[136]

CESSATION OF TREATMENT

Because asthma symptoms subside in 60% of childhood asthmatics, cessation of treatment should be regularly considered. Every 6 months, weaning could be considered if the child has remained asymptomatic. This should be gradual and with the assistance of lung function measurements.

FUTURE MANAGEMENT

The future for the management of asthma will be prevention of the disease. Asthma prevalence has increased in the last 25 years, so it should certainly be possible to reduce the prevalence by at least one half. Environmental manipulation may help; however, it is likely that it will be more important to identify those at risk and consider early intervention with environmental modification, anti-inflammatory agents, or vaccination to modulate immunologic maturation during the

critical period in early infancy when the predisposition to asthma appears to be set. Although asthma cannot be cured at present, the increasing understanding of the development of asthma symptoms in early childhood may mean that early intervention in the future will lead to a cure.

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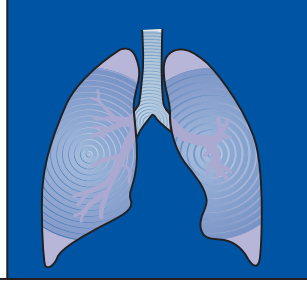

CHAPTER 60 Overview

Mark A. Anselmo and Larry C. Lands

TEACHING POINTS

- Cystic fibrosis is the most common autosomal recessive life-limiting illness in North American whites.
- The estimated incidence of cystic fibrosis in the United States is 1 in 2906 white and 1 in 10,338 nonwhite live births.
- Affected humans demonstrate dysfunction of a multifunctional cyclic-AMP regulated ion-channel protein, the cystic fibrosis transmembrane conductance regulator (CFTR).
- There has been a consistent and significant improvement in birth-year cohort patient survival.
- Although respiratory difficulties remain the most common suggestive complaint, failure to thrive and gastrointestinal complaints also frequently lead to diagnosis.
- The diagnosis is based on typical phenotypic findings and/or history accompanied by laboratory confirmation of CFTR dysfunction or identification of two CFTR mutations.
- Quantitative pilocarpine iontophoresis test (QPIT) remains the most discriminatory initial test.
- Mutation analysis has supplanted nasal potential difference as the next step for confirmation in a symptomatic but sweat-test–negative child.
- Access to carrier screening is now available to couples of all racial and ethnic groups, recognizing that the sensitivity of screening is reduced in these groups.
- Enhanced nutritional status is the principal benefit in patients diagnosed via newborn screening.
- With improved median survival, diabetes, bone disease, multiresistant pathogens, hormone dysregulation, and cancer are significant problems for the adult cystic fibrosis population.

Pediatric pulmonology training centers differ in many aspects; however, all trainees, past and present, are linked by a common fiber: the care of the patient with cystic fibrosis (CF). Cystic fibrosis is a chronic multisystem disease and the most common autosomal recessive life-limiting illness in North America. Although the primary cause of morbidity and mortality in CF is related to the respiratory system, disease can manifest itself in the digestive, reproductive, and integumental systems. There are approximately 60,000 persons with CF worldwide, with an estimated incidence of 1 in 2906 white and 1 in 10,338 nonwhite live births in the United States.[1-3] Specifically, the incidence of CF in Hispanic and African-American births is 1 in 9200 and 1 in 15,000, respectively.[4]

Affected humans demonstrate dysfunction of a multifunctional cyclic-AMP regulated ion-channel protein, the CFTR. The gene encoding the 1480 amino-acid polypeptide spans 230 kilobase pairs on the long arm of chromosome 7.[5] Although primarily a chloride channel, CFTR has been implicated in the regulation of other membrane channels, such as the epithelial sodium channel (ENaC)—as well as calcium-activated chloride and potassium channels.[6-8]

Inherited in an autosomal recessive manner, affected individuals require deleterious mutations in both alleles of CFTR, whereas carriers are asymptomatic. There are more than 1400 mutations presently known and this number is continually growing as the disease is being investigated in previously under-represented ethnic groups and mildly affected individuals.[9] The most common mutant allele results from a deletion of a nucleotide triplet encoding for phenylalanine at amino-acid position 508 in the normal protein. This ΔF508 mutation accounts for approximately 66% of mutations worldwide.[10] The frequency of ΔF508 in CF disease varies with ethnicity: in Hispanics (46%), Jews (30%), African Americans (48%), and native Americans (less than 5%). After the ΔF508 mutation, substitution mutations such as G542X (2.4%) and G551D (1.8%) are the next most common mutations in the United States (Table 60-1).

CFTR dysfunction can be grouped into one of six general classes (Fig. 60-1). In class I defects, such as G542X, the transcription of the mRNA is either prematurely stopped or out-of-frame and no protein is synthesized. In class II mutations, such as ΔF508, N1303k, G85E, and G91R, premature degradation of CFTR occurs secondary to defective protein processing. Class I and II patients are typically severely affected and experience pancreatic insufficiency. Class III and IV abnormalities demonstrate altered CFTR regulation and conductance, respectively. Mutations such as G551D (III) and R117H (IV) have residual activity and patients tend to be pancreatic sufficient, although pulmonary disease is variable. Class V mutations lead to abnormal splicing of the CFTR mRNA without alteration of the nucleotide sequences. These mutations can vary widely in severity, depending on the efficiency of translation from mRNA to protein. A severe splicing error mutation, 621 + 1G > T, produces no functional mRNA, whereas intervening sequence 8 (IVS-8) mutations, which affect exon 9 splicing, demonstrate variable severity. Class VI mutations promote early degradation of membrane-associated CFTR.[8]

Defective CFTR alters transepithelial movement of ions and water in the respiratory, gastrointestinal, hepatobiliary,

Table 60-1
CFTR Mutation Frequency, United States

Gene Frequency (Total)			
Delta F508	68.6%	W1282X	1.4%
G542X	2.4%	N1303K	1.4%
G551D	2.1%	R553X	0.9%
African American			
Delta F508	48.0%	A559T	2.0%
3120 > 1G → A	12.2%	R553X	2.0%
2307 insA	2.0%	Delta F311	2.0%
Hispanic (Sw)			
Delta F508	46.0%	R1162X	1.6%
G542X	5.4%	R334W	1.6%
3849 + 10 kb C → T	2.3%	W1282X	0.8%

CFTR, cystic fibrosis transmembrane conductance regulator
Adapted from Bobadilla JL, Macek M Jr, Fire JP, Farrell PM: Cystic fibrosis: A worldwide analysis of CFTR mutations—correlation with incidence data and application to screening. Hum Mutat 19:575-606, 2002.

Table 60-2
CFTR Function and Phenotype

Percent Normal CFTR Function	Expected Clinical Manifestations (Must Consider Wide Variation in Phenotype)
50-100	Carriers and persons with normal genotype—no symptoms
10-49	No known abnormality
<10	Congenital absence of vas deferens
<5	Positive sweat test
<4.5	All of the above plus progressive pulmonary infection
<1	All of the above plus pancreatic exocrine insufficiency

CFTR, cystic fibrosis transmembrane conductance regulator.
Adapted from Davis PB, Drumm M, Konstan MW: Cystic fibrosis. Am J Respir Crit Care Med 154(5):1229-1256, 1996.

epidermal, and reproductive systems. One widely supported hypothesis contends that CFTR function below a certain threshold releases ENaC from regulation. Unfettered ENaC actively absorbs sodium; chloride and fluid follow, altering the airway surface liquid layer (ASL), thereby dehydrating the airway. Accumulation of thick viscous secretions further impairs mucociliary clearance leading to chronic pulmonary infection and airways obstruction. This volume hypothesis has been strengthened by a mouse model in which increased sodium absorption by the airways epithelium produces a phenotype similar to CF.[11] The airway epithelium is also the site of intense inflammation and neutrophil recruitment. Inflammatory molecules including interleukins-6 and 8, tumor necrosis factor alpha, and leukotriene B_4 are found in elevated levels in CF airways and/or in vitro studies of CF epithelial cells. Therefore, it is surmised that CF airway pathology results from a combination of ASL alteration, chronic infection, chronic inflammation, and diminished innate immunity. In other organ systems, level of CFTR activity generally correlates with disease manifestations (Table 60-2).

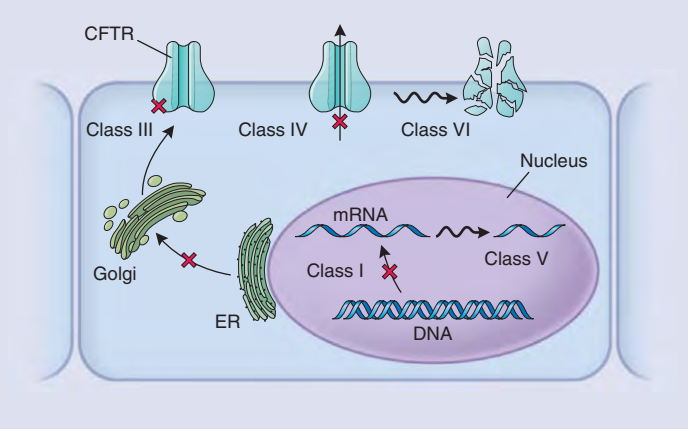

Figure 60-1 Classes of cystic fibrosis transmembrane conductance regulator (CFTR) dysfunction.

SURVIVAL IN CYSTIC FIBROSIS

There has been an astonishing improvement in CF patient life expectancy since the mid-20th century. Between 1940 and 1964, U.S. patient survival was 20% by age 5 years, 10% by 10 years, and there were no adults. By 2001, the average life span was estimated at 33.4 years and by 2004, the predicted median survival was 35.1 years.[1,12] Canadian survival curves, as grouped by birth-year cohort, demonstrate the consistent and significant improvement in patient survival, culminating in 100% survival for patients born recently (Fig. 60-2). The birth-year cohort improvement in survival has been mirrored by an equally impressive improvement in average cohort weight, with children born after year 2000 demonstrating an average weight percentile of more than 40% predicted (Fig. 60-3). Although nutritional status is an independent prognostic factor, an improved body mass index (BMI) correlates with an improved FEV_1 (Fig. 60-4). Not surprisingly, percent predicted FEV_1 per age has improved since 1990 (Fig. 60-5). These impressive statistics imply that children diagnosed today will continue to benefit from innovative treatments and therapies and survival will continue to improve. In 2004, the percentage of registered patients 18 years or over increased to 41.8% in the United States.

CYSTIC FIBROSIS CARE CENTERS AND FOUNDATIONS

The care for the CF patient has evolved from a few specialty centers caring independently for this orphan disease to highly integrated and complex networks active in the United States, Canada, the United Kingdom, Europe, and Australia. Through these national programs, we meet on an international level to efficiently exchange knowledge and strategy on how to improve care and control of CF while improving patient quality of life. CF foundations provide research grants, training in quality improvement, and updated care guidelines and have become instrumental in therapeutic development. This international level of coordination has been paramount in the constantly improving survival curves as demonstrated by our patients.

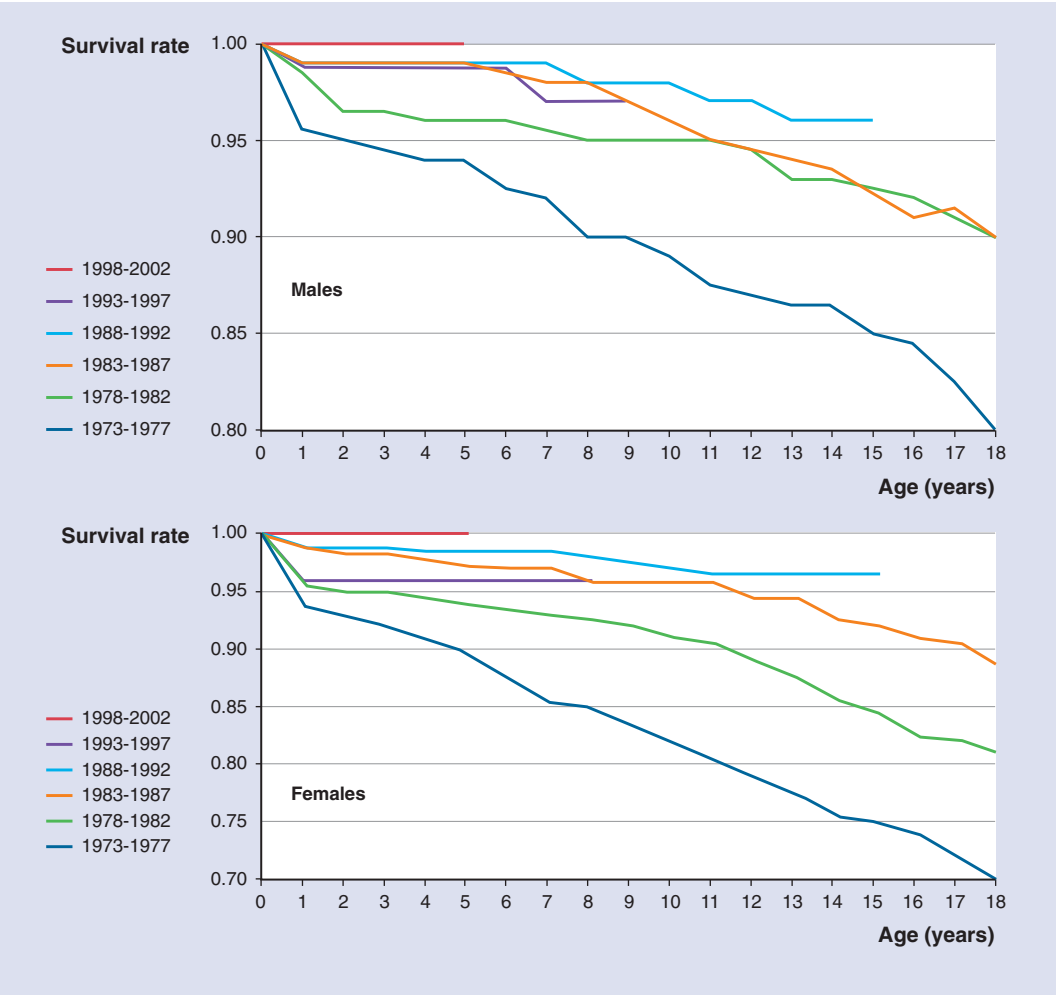

Figure 60-2 Canadian survival rate 1973 to 2002 as grouped by sex and birth cohort. (Redrawn from Canadian Cystic Fibrosis Foundation, Report of the Canadian Patient Data Registry, 2002.)

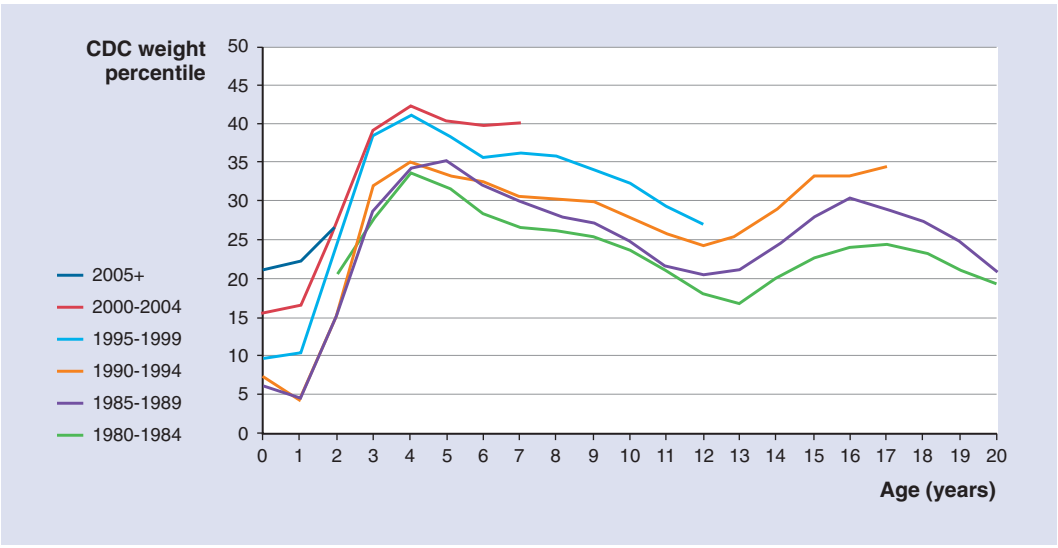

Figure 60-3 Mean weight percentile versus age by year of birth. The weight profile of cystic fibrosis patients has steadily improved in each successive birth cohort. CDC, Centers for Disease Control and Prevention. (Redrawn from Cystic Fibrosis Foundation, 2006 Patient Registry, Bethesda, MD.)

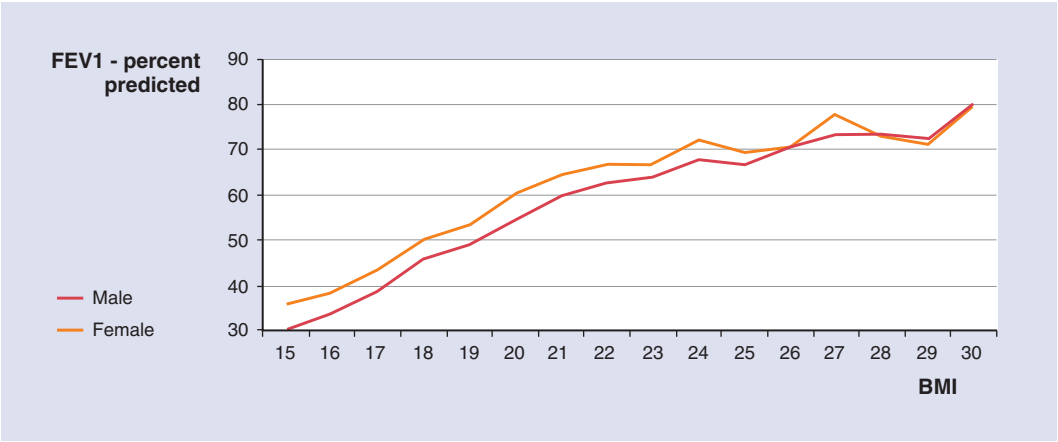

Figure 60-4 FEV_1 percent predicted versus body mass index (adults). FEV_1 is positively correlated with BMI. (Redrawn from Cystic Fibrosis Foundation, 2006 Patient Registry, Bethesda, MD.)

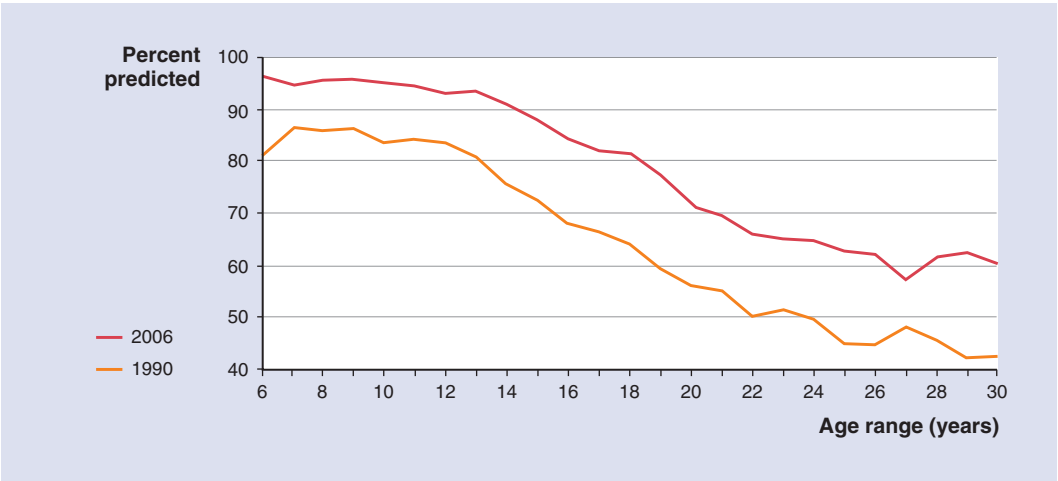

Figure 60-5 Median percent predicted FEV_1 versus age. Median FEV_1 has improved 10 percentage points at all ages from 6 to 30 since 1990. (Redrawn from Cystic Fibrosis Foundation, 2006 Patient Registry, Bethesda, MD.)

HISTORICAL ACCOUNTS OF CYSTIC FIBROSIS

Although first regarded as a unique disease by American pediatric pathologist Dorothy Andersen in 1938, we can surmise that CF has a long human history. Using coalescence theory, Wiuf and colleagues have determined that the age of the ΔF508 mutation is 11,000 to 34,000 years.[13] Using standard population genetics modeled on the overall frequency of CF alleles, Reich and Lander have also estimated that the ΔF508 mutation may predate the expansion of anatomically modern humans.[14] Historical references from medieval times describe the salty-when-kissed infant who was hexed and therefore, soon to die.[15] In 1595, Peter Pauw described an autopsy of a bewitched 11-year-old girl with a swollen, hardened, and gleaming white pancreas.[15] In 1606, Alonso y de los Ruyzes de Fonteca, professor of medicine at Henares in Spain, wrote that it was known that the fingers tasted salty after rubbing the forehead of the bewitched child.[16] Emilia Chopin, a young sister of the great French-Polish composer, suffered chronic cough, hemoptysis, and weight loss. She succumbed to a massive gastrointestinal hemorrhage at 14 years of age. Frederic Chopin (1810-1849) himself was described as sickly and delicate after birth.[17] He suffered from respiratory complaints, recurrent diarrhea, and fatty food intolerance. Despite an intense 11-year relationship, Chopin fathered no children.[18] Chopin's death was attributed to laryngeal and pulmonary tuberculosis. However, Cruveilhier, an authority on tuberculosis, reportedly said to Chopin's sister Ludovika, "The autopsy did not elucidate the cause of death—enlarged heart—no pulmonary tuberculosis—pulmonary alterations—a disease which has never been seen before."[19] Although unconfirmed, it is possible that Chopin had CF.

The modern history of CF has involved scores of talented investigators, too many to provide due credit in this modest review, who have pursued this disease from pathologic description to physiologic studies, on to molecular genetics and culminating in proteomic investigations. An abridged timeline of discovery follows:

1905, Landsteiner publishes case of pancreatic abnormalities with delayed passage of meconium.[20]

1933, Blackfan and Wolbach present pancreatic pathology and suppurative lung disease in 13 infants who were suspected of having vitamin A deficiency.[21,21]

1936, Renowned Swiss pediatrician Guido Fanconi describes familial fibrotic pancreatic lesions and bronchiectasis.[22]
1938, Dorothy Andersen describes neonatal intestinal obstruction, intestinal and respiratory complications of 49 patients, and coins the term *cystic fibrosis* of the pancreas.[23]
1945, Farber coins and prefers the term *mucoviscidosis* as he hypothesizes that the disease is caused entirely from thickened mucus.[13,24]
1946, Andersen and Hodges present the first hard evidence that CF is inherited in an autosomal recessive manner.[25]
1948, Paul di Sant'Agnese, a pediatrician, notices that a high number of CF patients presented in heat prostration.
1953, Di Sant'Agnese presents to the American Pediatrics Society data demonstrating a great difference in the sodium concentration between the sweat of children who suffered from CF and healthy controls, leading to the sweat test.[26]

Of equal significance, CF was now more than simply a state of thickened mucus, but an error in the transport of electrolytes across epithelial surfaces. This was of paramount importance because there was a paradigm shift to investigate CF as a disease with dysfunctional electrolyte transport at its very core. This single observation of an astute clinician researcher changed the very way CF was viewed!

1959, Gibson and Cooke publish the method of iontoelectrophoresis, to be the basis for the modern quantitative pilocarpine iontoelectrophoresis test (QPIT), the standard diagnostic test for CF.[27]
1981, Knowles demonstrates that the CF airway epithelium was ineffective in secreting chloride ions.[28]
1983, Quinton reports that the general defect of the CF sweat gland was impermeability to the return of chloride anions.[29,30]
1985, Evidence accumulates in favor of aggressive intravenous antibiotic treatment.[31]
1985, Organ transplantation becomes possible for patients in terminal stages.[32]
1985, Genetic linkage between the putative CF gene and serum paraoxonase, as well as two random fragments of complementary DNA, is discovered.[33]
1985, Knowlton and colleagues assign the gene to chromosome 7.[34] In Toronto, Canada, Tsui localizes the CF gene to an area of 1% of the human genome.[35] Wainwright further localizes the gene to a specific band of chromosome 7.[36]
1989, Tsui, with Collins and Riordan, report the location and genetic analysis of the CF gene in a triumphant triplicate publication.[5,37,38]

Advances in understanding the molecular biology and function of CFTR have occurred since 1989. Although there is a relation between pancreatic function and genotype, linking mutation to severity of lung disease is not evident.[39] Because genotypically similar patients follow disparate courses, the presence of other genes that modify disease severity has recently drawn attention. Rate of *Pseudomonas aeruginosa* infection varies with polymorphisms in mannose-binding lectin.[40-42] Two polymorphisms of the transforming growth factor beta-1 gene are associated with more severe lung disease in patients homozygous for ΔF508 and more putative modifying genes are presently being investigated.[43] Additionally, environmental influences, including treatment regimens, interact significantly with genetic predisposition. Although genetic mutations in CF are still being discovered, attention has turned to protein function and action. Presently, many trials looking at improving nascent CFTR function are underway, as are studies improving action of other chloride channels.

CLINICAL AND LABORATORY DIAGNOSIS

Presenting Signs and Symptoms

CF is most commonly diagnosed after clinical suspicion is confirmed by a diagnostic test. There were 909 newly diagnosed CF patients in the United States in 2004, and the median age of diagnosis was 6 months.[1] Chronic respiratory difficulties remain the most common suggestive complaint leading to diagnosis (Table 60-3). A history of chronic cough, chronic production of sputum, recurrent pneumonia, asthma not responsive to care, and the presence of typical CF organisms such as *Staphylococcus aureus* and *P. aeruginosa* require further investigation. The sinuses are affected in children with CF; therefore, documented recurrent sinusitis in children requires investigation for underlying disease. The respiratory examination can be entirely normal or demonstrate one of many nonspecific abnormalities. Nasal polyps are rare in healthy children and indicate a need for testing. Schamroth sign, colloquially known as *digital clubbing*, never occurs in asthma and signifies the need for further investigation.

Alongside pulmonary complaints, patients usually present with signs and symptoms of gastrointestinal disease. In the neonatal period, meconium ileus and cholestatic jaundice can lead to an early diagnosis. Outside of the neonatal period, infants and children often demonstrate a lower BMI and failure to thrive, despite a voracious appetite. Pancreatic

Table 60-3
Reason for Diagnostic Testing

Diagnosis Suggested by:	Number in U.S. Registry	Percent of Total
Acute or chronic respiratory symptoms	11,015	48.49
Failure to thrive/malnutrition	9026	39.74
Steatorrhea/abnormal stools/ malabsorption	7174	31.58
Meconium ileus/other intestinal obstruction	4663	20.53
Family history	3082	16.74
Neonatal screening	1159	5.10
Electrolyte imbalance	1070	4.71
Genotype	858	3.78
Rectal prolapse	786	3.46
Nasal polyps/sinus disease	742	3.27
Prenatal screening	507	2.23
Liver problems	269	1.18
Edema	156	0.69
Unknown	272	1.20
Other	665	2.93

*Patient may have more than one symptom at diagnosis.

insufficient patients present especially foul smelling, bulky, and greasy stools. Pancreatic function, although not entirely normal, is sufficient in 15% of CF patients—thereby complicating the clinical diagnosis. Such patients may present with recurrent pancreatitis. A high index of suspicion in cases of rectal prolapse, allergic formula intolerance, or severe gastroesophageal reflux is required if patients are to be diagnosed in a timely fashion. Hepatosplenomegaly can be documented in patients with CF-related liver dysfunction, which presents mainly in the first decade of life.[44]

Patients can rarely present with sequelae of fat-soluble vitamin deficiency. Hypovitaminosis A can lead to xerophthalmia or pseudotumor cerebri.[45,46] Unexplained hemolytic anemia or hemorrhagic disorders owing to vitamin E or K deficiencies, respectively, can be the manifesting signs of cystic fibrosis.[47] Because CF patients lose relatively large amounts of salt in their sweat, they are susceptible in hot temperatures to hyponatremic hypochloremic metabolic alkalosis. Even in the 21st century (although rare), children are diagnosed after the parent tasted salt when kissing the child on the forehead.

A negative family history does not rule out CF because only 17% of CF patients have a family member diagnosed before them.[12] *S. aureus* sepsis has occurred in patients who were diagnosed with CF after the event. Men can present with azoospermia; however, debate exists as to whether bilateral congenital absence of the vas deferens without other organ involvement should be considered as CF. In any event, a patient demonstrating signs and symptoms of CF, or siblings of newly diagnosed patients, should undergo diagnostic sweat testing.

Persistent abnormalities on chest radiographs and/or the presence of bronchiectasis are indications for further testing. Pulmonary function testing can be nonspecific, although obstruction on spirometry that may or may not be reversible with bronchodilator can be documented before diagnosis. Older children and adults may present with a history of recurrent bronchitis, asthma, pancreatitis, infertility or nonspecific gastrointestinal complaints.

Laboratory Evaluation of CFTR Function

Diagnosis of CF requires clinical evidence in addition to laboratory confirmation (Table 60-4). Typical phenotypic findings or siblings of confirmed patients must be accompanied by laboratory confirmation of CFTR dysfunction or identification of two CFTR mutations. Prenatal and newborn screening present special situations where a diagnosis of CF is provided with laboratory evidence alone.

THE SWEAT TEST

Before 1959, the laboratory diagnosis of CF was exceedingly difficult. Suspected children would first provide two stool specimens to confirm the absence of proteolytic enzymes followed by duodenal intubation for the presence of trypsin. After di Sant'Agnese's discovery in 1948, noninvasive diagnosis became possible, but was limited by difficulties and inconsistencies in sweat collection.[26] In 1959, Gibson and Cooke used the electrical properties of iontophoresced pilocarpine to stimulate sweating, using gauze or filter paper to collect the sweat and send for chemical examination.[27] The test has been modified from the initial description and one variation, the QPIT remains the most discriminatory diagnostic sweat test today as 98% of known CF patients have had a positive sweat test.[48] The QPIT is a diagnostic test and should be performed on all patients suspected of having CF.

A sweat chloride ($SwCl^-$) result greater than 60 mmol/L is consistent with CF.[49] A result between 40 and 60 mmol/L is borderline and indicates a need for further investigation—initially genetic testing. A $SwCl^-$ result less than 20 mmol/L is accepted as negative. Levels between 20 and 40 mmol/L are normal with a high degree of certainty, however, $SwCl^-$ values increase with age; therefore, some clinicians have suggested that the cutoff for a positive result in infants should be 30 mmol/L, as opposed to 40 mmol/L, to decrease the chance of a false-negative result.[49-51] There are causes of false-positive and false-negative sweat testing (Table 60-5). If present in a homozygous or heterozygous fashion, there are a number of mutations that can manifest with symptoms yet provide a truly normal sweat test (Table 60-6). There are other sweat-testing devices and protocols including conductivity and osmolarity; however, they have not been accepted

Table 60-4
Diagnostic Criteria for Cystic Fibrosis

Clinical Features (Phenotype)
Chronic cough and sputum production
Persistent infection with characteristic pathogens (*Staphylococcus aureus, Pseudomonas aeruginosa*)
Airflow obstruction on spirometry, with or without response to inhaled bronchodilator
Chronic chest radiographic abnormalities, including bronchiectasis
Sinus disease; nasal polyps
Gastrointestinal and Nutritional Abnormalities
Pancreatic exocrine insufficiency; recurrent pancreatitis
Meconium ileus; distal intestinal obstruction syndrome
Obstructive Azopermia in Males
One or More of Above Clinical Features Plus
Laboratory Evidence of CFTR Dysfunction
Elevated sweat Cl^-
Deleterious mutation in both CFTR alleles
Characteristic bioelectric abnormalities in nasal epithelium in vivo

CFTR, cystic fibrosis transmembrane conductance regulator. Adapted from Rosenstein BJ, Cutting GR: The diagnosis of cystic fibrosis: A consensus statement: Cystic Fibrosis Foundation Consensus Panel. J Pediatr 132:589-595, 1998.

Table 60-5
Selected Causes of False-Positive and False-Negative Sweat Test Results

Causes of False-Negative Sweat Test Results	
Technical Problem with test	Skin edema
Malnutrition	Mineralocorticoids
Causes of False-Positive Sweat Test Results	
Malnutrition	Fucosidosis
Atopic dermatitis	Mucopolysaccharidosis
Hypothyroidism, hypoparathyroidism	Glycogen storage disease type I
Adrenal insufficiency	Glucose-6-phosphate dehydrogenase deficiency
Munchausen-by-proxy	Hypogammaglobulinemia
Klinefelter syndrome	Familial hypoparathyroidism
Technical issues	Autonomic dysfunction
Anorexia nervosa	Familial cholestasis syndrome

Table 60-6
Examples of CFTR Mutations Associated with Normal or Borderline Sweat Test Results

3849 + 10 kb C → T	D1152H
R117H	IVS8 (5T)
G551S	L206W
A455E	2789 + 5 G > A
H199Y	ΔF508-R553Q

as diagnostic tests, leaving confirmation via QPIT. Any positive test should be repeated and further confirmation is sought by genetic mutation analysis.

GENETIC MUTATION ANALYSIS

The single gene abnormality in CF is theoretically ideal for genetic testing; however, with more than 1400 known deleterious mutations of CFTR, testing can be inconclusive, especially in ethnic groups with less disease prevalence and mildly affected patients. There are four major roles for genetic testing: (1) it should be performed after the diagnosis is made because the information adds to epidemiologic studies of CF and can provide information regarding pancreatic function; (2) identification of mutations allows for prenatal and family-specific carrier screening; (3) molecular genetics can move into first line testing in the case of a patient with convincing symptoms and a borderline or normal QPIT result; and (4) mutation analysis improves sensitivity when coupled with immunoreactive trypsinogen testing (IRT) as part of a newborn screening (NBS) program.[52] In many countries and continents, there are regional differences with respect to common mutations and most screening programs require a tailored local screening genetic analysis that covers a large percentage of mutations in the indigent population. If the initial screen is noncontributory, extended analysis, by either a research laboratory or by a private for-profit laboratory, is often required. Quality control is always a significant factor and diligence is required with results. Genetic testing may not always confirm the diagnosis and care must be taken with interpretation of results, such as in the case of the R117H mutation where phenotype depends on the length of the polythymidine (poly T) tract of intervening sequence 8 (IVS8). Individuals with a 5T polymorphism produce less CFTR than those with 7T and 9T alleles. If paired with a second CFTR mutation, the R117H/5T allelic combination will usually cause classic CF, whereas R117H/9T will not cause any disease. There are reported patients homozygous for the 5T allele who demonstrated nonclassic CF.[53]

NASAL POTENTIAL DIFFERENCE

Patients with clinical features of CF and a borderline or normal SwCl result can present as a significant diagnostic dilemma because even genetic testing may not uncover both mutations. An examination for characteristic bioelectric abnormalities of the nasal epithelium can be performed at certain specialized centers. The test is performed in vivo. After the basal potential is read, sodium conductance is blocked with amiloride and the site is irrigated with a chloride-free solution containing isoproterenol, which will stimulate CFTR. Unlike normal airway epithelium, CF epithelium will not respond with chloride ion secretion to isoproterenol challenge. The test requires a high level of technical expertise and is simply not an effective diagnostic test at centers that do not perform it regularly. Large gene screen analysis has supplanted nasal potential difference as the next step for confirmation in a symptomatic but sweat test–negative child.

Preconceptual Screening

Despite incredible advances in CF care and improved median survival, many couples who already have a child with CF often decide to avoid having another child with CF.[54,55] Traditionally, couples with an immediate family history of CF are offered preconceptual screening for mutations. In 1999, the National Institutes of Health advocated that CF carrier screening be offered to all couples either pregnant or planning to become pregnant, but not to the general population.[56] The American College of Obstetricians and American College of Medical Genetics published cooperative guidelines supporting this policy and introduced a 25-mutation screening panel.[57] The ACOG guidelines recommend offering CF screening to individuals with a personal or family history of CF, and also to any couple in whom one or both partners are white and are planning a pregnancy or seeking prenatal care. Access to screening is now available to all North American couples, recognizing that the sensitivity of screening is reduced in low carrier frequency groups. The panel includes disease causing mutant alleles with a frequency in CF patients of >0.1%.[58]

General Carrier Screening

With an estimated white CF carrier frequency of 1 in 26, no currently available cure and accessible genetic testing, some have championed general population carrier screening.[3,59,60] Massie and colleagues estimate that a 12-mutation screen in Australia would identify 85% of carriers.[61] If instituted, a general population screen theoretically would decrease the incidence of CF. In Canada, the CF birth rate in 1988 was 1 in 2714 but declined by 25% to 1 in 3608 in the ensuing 12 years. The decline coincides with the discovery of the CF gene and the authors contended that increased use of carrier screening and prenatal diagnostic services is responsible for the CF birth rate decline.[62] In Brittany, France, a 15.7% reduction in CF prevalence at birth was attributed to the introduction of a newborn screening program (NBS) for CF and prenatal diagnosis leading to termination of subsequent pregnancies.[63] Opponents to general carrier screening argue that such a program would offset the economic benefit of an NBS program because the incidence of CF would decline.[64] Concurrent general population screening and newborn screening programs do not make economic sense. More importantly, general population screening brings a deeper ethical question for jurisdictions: Is CF a disease that should be treated and eventually cured, or should CF be eradicated by genetic selection? There is no easy answer.

Prenatal Diagnosis

The ability to sample genetic material from the developing placenta and amniotic fluid has enabled the early diagnosis of

certain genetic conditions before 20 weeks of gestation, thereby providing the ability to make informed reproductive choices. With respect to CF, if both parents are carriers of identifiable CFTR mutations, they can be provided the genotype of the developing fetus. This group includes couples with a child with CF, family history of CF, or those identified through preconceptual or general carrier screening. There are two methods presently available: chorionic villous sampling (CVS) and amniocentesis. CVS can be done transcervically and safely between 10 and 13 weeks of gestation and, in very experienced hands, it carries a miscarriage procedure risk of 1 in 200. The procedure-induced chance of miscarriage in experienced hands following mid-trimester (16 to 20 weeks) amniocentesis appears to be 1 in 300. Early amniocentesis (≤13 weeks) has been found to carry a risk of loss rate near 1 in 50 and carries further risk of talipes equinovarus of 1% to 2%, therefore CVS is preferred for pregnancies 13 weeks or less. There is no evidence to support CVS over amniocentesis between 14 and 16 weeks.[65] CVS and amniocentesis for CF are not suggested for parents of unknown genetic potential because the risk for CF is much less than the miscarriage risk (1 in 3000 versus 1 in 300). As of 2004, 507 CF patients in the U.S. registry had been diagnosed prenatally, indicative that parents do not always consider abortion. Advance knowledge facilitates the acceptance of the new baby and allows for preparation in perinatal and neonatal management. The involvement of a genetic counseling team is indispensable during such periods for CF parents planning a subsequent pregnancy.

Newborn Screening Programs

In most countries, the diagnosis of CF depends on the presence of symptoms in the patient and recognition by the clinician before diagnostic testing is performed. According to the Canadian CF Foundation Patient Data Registry in 2000, 40% of patients were diagnosed after 1 year, 9.6% after 10 years, and 2% after 30 years of age.[66] Unfortunately, these children were often markedly symptomatic at the time of diagnosis, many with growth delay and evidence of pulmonary disease. Accordingly, a strong effort to determine the effect of early diagnosis on outcomes has been undertaken. Newborn screening (NBS) for CF involves the quantification of serum trypsinogen from the regularly obtained dried blood spot; no separate specimen collection is required. An elevated serum trypsinogen level is an indirect indication of pancreatic injury, which is present in most newborns affected with CF. In most programs, newborns demonstrating an abnormally high level of immunoreactive trypsinogen (IRT) are flagged for complementary genetic mutation analysis using a tailored local screen. Infants with a positive IRT and who are subsequently found to carry at least one CFTR mutation are referred for confirmatory QPIT. Some jurisdictions employ a "failsafe" protocol where an elevated IRT alone will lead to an investigational QPIT, presumably in patients who carry rare mutations not on the local screen. In 2003, the Centers for Disease Control (CDC) and the U.S. CF Foundation (CFF) co-supported the clinical utility of newborn screening in cystic fibrosis. Newborn screening in the United States is associated with diagnosis at a median age of 0.5 months, whereas the median age for diagnosis in non-meconium ileus patients is 14.5 months.[67] Certainly growth and cognitive development (in those patients who demonstrated low plasma vitamin E levels) were improved in patients diagnosed by newborn screening.[68,69] The evidence for pulmonary outcomes has been mixed and survival benefit evidence depends on retrospective analyses.[70] Lai and colleagues retrospectively segregated CF patients in the registry from 1986 to 2000 as to whether they were diagnosed by meconium ileus, newborn screen, family history alone, or by symptoms. They contend that the children diagnosed by symptoms had a statistically significant shortened survival versus those who were diagnosed by screening. The cost-benefit analysis of neonatal screening using an immunoreactive trypsin/DNA two-stage screening protocol supports the use of screening if patients were to be diagnosed 6 months before becoming symptomatic. The cost-effectiveness data assumed patients would be less ill if diagnosed with newborn screening. The decision by the CF foundation and the CDC to endorse screening is not simple, as there are negative aspects to NBS. First, as with any screening program, there will be false negatives. Combining overlapping data from Wisconsin, Colorado, and Massachusetts, there was a total of 20 babies missed by newborn screening out of 553 known CF children born between 1994 and 2003. Therefore, care providers must maintain a high index of suspicion, even in the era of newborn screening.[52,71,72] Second, depending on their perceptions about the likelihood of CF, depressive symptoms in parents can occur during the waiting period between a positive NBS result and a diagnostic sweat test.[73] Third, the possibility of exposing asymptomatic babies to pathogens in the clinic setting is concerning. As a result of these negatives, the CDC recommends the involvement of a CF specialty center, available genetic counseling, and strict infection control measures be an integral part of a CF NBS program. Present evidence indicates moderate benefits versus a low risk in the case of NBS for CF.[74]

Fecal Elastase Testing

In 2004, 89.9% of patients in the U.S. CF Registry were prescribed enzyme supplements, though most patients do not have a recorded test of pancreatic function.[75] Historically, the percentage of absorbed fat after 3 days of stool collection was used to determine pancreatic sufficiency. Recently, a single random stool sample test that determines the amount of stool elastase has been introduced, simplifying collection and analysis. Elastase is one of more than 20 enzymes produced by the pancreas and it is secreted in response to cholecystokinin.[76] Elastase is stable in the intestinal tract and the concentration increases in the colon owing to water adsorption allowing quantification in egested stool. In patients with CF, 87% had a fecal elastase level less than 100 μ/g stool with the mean value of 1.6 μ/g.[77] An additional 1.5% of patients studied had a level between 100 and 200 μ/g. Therefore, the positive predictive value for pancreatic insufficiency using a cut-off value less than 100 μ/g stool is excellent in patients with CF. Levels of > 100 μ/g stool are indicative of pancreatic sufficiency. Performing fecal elastase testing on 1074 patients, Borowtiz found 24 patients with pancreatic insufficiency not on pancreatic enzyme supplement. Additionally, of 141 patients with normal elastase levels, 81 were on enzyme

supplements.[77] Determination of fecal elastase in CF is quick, has demonstrated good sensitivity and specificity for identifying CF patients with pancreatic insufficiency, and functional pancreatic status should be determined in all patients. Centers in the United Kingdom recommend twice yearly assessment of pancreatic function in children found to be pancreatic sufficient until 2 years of age, and yearly thereafter to ensure continuity of pancreatic function.[78]

EMERGING TRENDS

Improvement in patient survival has permitted the emergence of health issues unique to an aging CF population. Diabetes, bone disease, multiresistant pathogens, hormone dysregulation, and cancer have affected the adult CF population and programs have established routine protocols for some of these emerging problems.[79] Many of these problems have their origin or can manifest in the pediatric population, thereby requiring awareness and treatment before transition to adult centers.

CYSTIC FIBROSIS–RELATED DIABETES

The 2004 CF patient registry stated 16.1% of U.S. CF patients had either glucose intolerance or CF-related diabetes (CFRD) (Fig. 60-6).[1] As expected, the prevalence of CFRD increases with age; consequently, there will be a parallel increase in the total number of patients with CFRD as the average age of the patient population increases.[80] Despite differences in etiology from non-CF diabetes, microvascular complications such as diabetic retinopathy and nephropathy are evident in CFRD and will likely increase in prevalence as CF patients are living longer.[81] They may affect potential for transplant. Of particular concern to CF care-providers, there is a decrease in pulmonary function and BMI in the 2 to 4 years preceding the diagnosis of CFRD, and the development of CFRD has been found to accelerate the decline in pulmonary function and overall clinical status—and possibly increase mortality.[82-85]

There is a strong association between exocrine pancreatic dysfunction and risk of developing CFRD as insulin secretion and end organ response is intact in most pancreatic-sufficient patients.[86,87] The pathophysiology of CFRD likely involves many factors. Histologic examination of pancreatic tissue from CFRD patients demonstrates a significant reduction in the proportion of beta-cells in pancreatic islets owing to progressive fibrosis.[88,89] This structural abnormality is accompanied by functional changes. A 41% reduction in peak plasma insulin concentration along with a delayed time to reach peak levels after oral glucose challenge indicates a dual dysfunction of insulin secretion by CFRD patients.[90] Finally, patients with CFRD have evidence of target organ resistance to insulin.[91] Therefore, CFRD is characterized by hyperglycemia caused by a combination of poor insulin secretion and target organ insulin insensitivity. CF patients are at risk for complications from diabetes, therefore yearly screening is indicated after age 10 years. Additionally, glucose intolerance or diabetes should be investigated in a patient demonstrating one of the following: abnormal random blood glucose, abnormal HbA1c, weight loss, or symptoms of hyperglycemia. Symptoms include polyuria, polydipsia, poor weight gain or growth velocity, decline in pulmonary function, or delayed puberty.[85]

Symptom control and risk reduction of later complications are aims of treatment which includes maintenance of optimal nutritional status and healthy glycemic control. Oral hypoglycemics such as Repaglinide are used in some centers, although further investigation and evidence is required before such therapies can be part of national guidelines. Initiation of insulin therapy reversed the deterioration in body mass and pulmonary function in patients with CFRD.[92] All patients with CFRD should be screened annually for microvascular complications, with a dilated eye evaluation and a urinalysis for microalbumin measurement.[80]

BONE DENSITY

In 1979, Hahn and Mischler separately reported that the bones of CF patients were demineralized as compared to non-CF controls.[93,94] This finding seemed to be of academic interest; however, because patient survival has improved steadily and consistently over the last 40 years, we are begin-

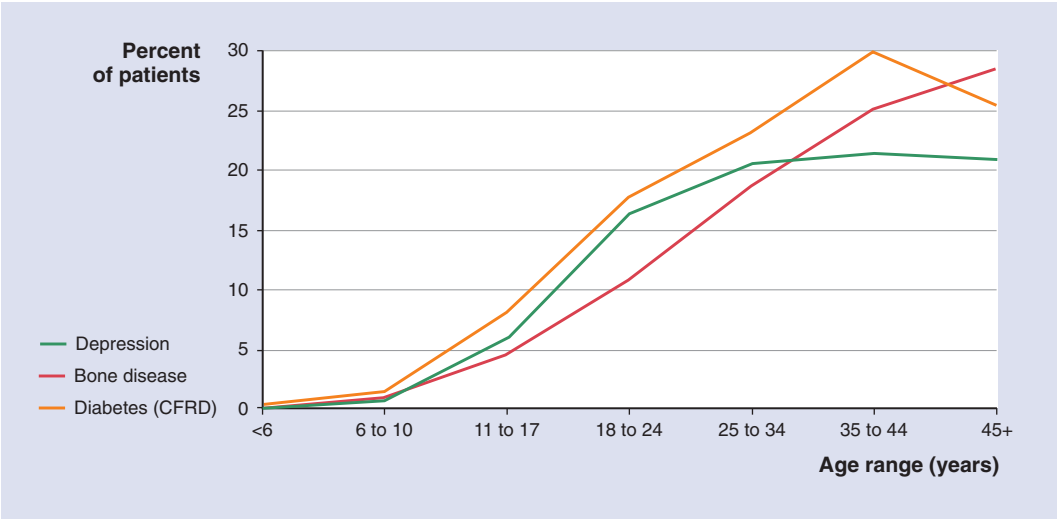

Figure 60-6 Complications versus age. CFRD, cystic fibrosis–related diabetes. (Redrawn from Cystic Fibrosis Foundation, 2006 Patient Registry, Bethesda, MD.)

ning to see long-term problems associated with the disease that were heretofore unknown. Decreased bone density, fractures, and kyphosis occur earlier in CF patients than in healthy controls.[95-97] Although CF bone disease is present in 10.3% of CF patients older than 18 years of age (see Fig. 60-6), good bone health starts in the early adolescent years.[1] In 1996, Henderson and Madsen reported that children affected with CF achieve a lower peak bone mass than their non-CF counterparts.[97] To make matters worse, adults with CF tend to lose bone mineral density 3 to 5 times faster than non-CF controls.[98]

The term *CF bone disease* is purposely nondescript because the exact pathophysiology of the problem is, at this point, unknown.[98] Because the disease begins near or during the growth spurt, there is a failure to achieve optimal "banking" of minerals in the bone and there is a loss of mineral reserves. Contributing factors include delayed pubertal maturation, physical inactivity, poor overall nutritional status, specific vitamin D malabsorption, hypogonadism, and glucocorticoid therapy. The expert committee on bone health reached a consensus that CF patients have inadequate absorption of vitamins D, K, and calcium. Additionally, chronic pulmonary infection increases bone resorption while suppressing bone formation.[95,97,99-104] The state of the art in bone disease is in flux presently as many centers are investigating this relatively new problem. Recently, ΔF508, male sex, poorer nutritional status, and more severe lung disease were found in one study to be independently associated with reduced bone mineral density. The mechanism of action of ΔF508 in reducing bone density in cystic fibrosis remains to be elucidated.[105]

Taken together, data suggest that bone disease begins near or during the growth spurt and is characteristically more pronounced in patients with more pulmonary disease.[98] Recently, bone health has become a priority in CF care. In 2004, the U.S. CF Foundation convened an expert panel to provide guidelines for bone health and identified patients who require screening and subsequent investigations and therapy for patients with CF bone disease.[98]

EMERGING PATHOGENS AND INFECTION CONTROL

In 2004, pediatric CF patients in the United States were most commonly culture positive for *P. aeruginosa*, *S. aureus* and *Haemophilus influenzae*. *P. aeruginosa* is the most significant pathogen in CF, found on positive culture in 57.3% of all patients and approximately in 80% of patients in the 25- to 34-year age range (Fig. 60-7). Historically, acquisition of *P. aeruginosa* at a young age presented an adverse factor in terms of morbidity and mortality.[106] Early and aggressive anti-*Pseudomonas* eradication programs targeting children demonstrating intermittent positive cultures have been so successful that in 2001, no Danish CF patient younger than 14 years of age was chronically infected with *P. aeruginosa*.[107] Eradication of nonmucoid *P. aeruginosa* in children with CF is possible and can delay infection from noneradicable mucoid strains.[108] Aside from these usual suspects, there are other organisms notable for wide-spectrum antibiotic resistance. *Stenotrophomonas maltophilia*, *Achromobacter xylosoxidans*, and *Burkholderia* spp demonstrate resistance to multiple antibiotics with variable impact on infected patients. Additionally, nontuberculous mycobacteria are being found in a significant number of CF patients.

Stenotrophomonas maltophilia

S. maltophilia is an opportunistic nosocomial pathogen that has been isolated from chronically ill or immunocompromised patients on wide-spectrum antibiotics or on ventilatory support. In 2004, 11.6% of CF patients grew *S. maltophilia* on one occasion.[1] During a course of 6 months, 30% of subjects enrolled in the tobramycin solution for inhalation trial grew *S. maltophilia* on one occasion.[109] *S. maltophilia* is soil based and can be found in moist areas including sinks and faucets. The virulence of *S. maltophilia* in the setting of CF is not presently clear. A retrospective review in 2002 concluded that the acquisition of *S. maltophilia* occurs in the setting of more severe disease but does not in itself lessen survival. Although independent association with decreased

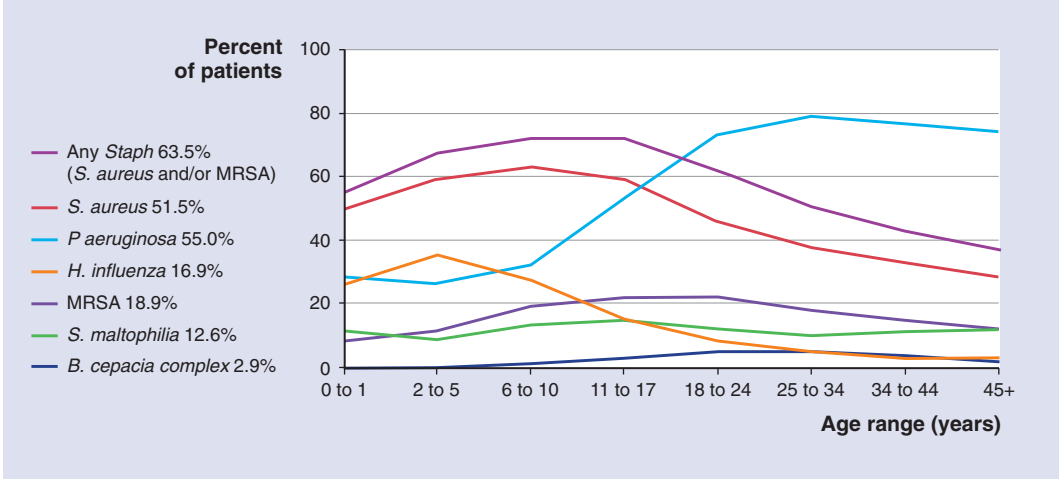

Figure 60-7 Respiratory infections versus age. MRSA, methicillin-resistant *Staphylococcus aureus*. (Redrawn from Cystic Fibrosis Foundation, 2006 Patient Registry, Bethesda, MD.)

survival with *S. maltophilia* infection is not presently evident, many CF teams will treat patients demonstrating positive cultures and symptom progression not attributable to other causes. Treatment is difficult owing to antibiotic resistance and, unlike *Burkholderia* spp and multidrug resistant *P. aeruginosa*, studies of combination testing are lacking. Cross-infectivity has not been identified as a problem, although universal precautions are appropriate.[110]

Achromobacter xylosoxidans

Like *S. maltophilia*, *A. xylosoxidans* also infects severely ill hospitalized patients and the virulent potential of this bacterium in CF is not fully understood. No deterioration in clinical status was noticed in 13 CF patients chronically infected with *A. xylosoxidans* over 2 years as compared to 544 controls.[111] Presently, treatment is case specific and multiple antibiotics are sometimes necessary.[112] Patient cohorting is not presently recommended.[113]

Burkholderia cepacia Complex

The genus *Burkholderia* has been found to chronically infect CF patients. The *Burkholderia cepacia* complex (Bcc) contains at least nine phylogenetically closely related yet distinct species, previously known as *genomovars*.[114] The difficulty in accurately identifying the proper species has required the services of specialized laboratories. Only 3% of CF patients in the United States are infected with a *B. cepacia* complex organism and infection has been found to be typically of one strain.[1,115] The prevalence may be misleading as most infections are in adults, making it a significant pathogen in adult CF centers. The ability of Bcc species to cross-infect patients makes it an important issue in some centers. Bcc is an infection control issue because some strains within certain species have an ability to spread easily between CF patients.[116]

Another issue with infection control is that virulence is variable within a species, indicating that cohorting of "C*epacia* patients" should not supersede universal precautions and that unrestricted contact between such patients should be avoided.[117] Certainly, Bcc infection has been associated with pulmonary decline[118] and pretransplant infection with certain strains of Bcc has been associated with poorer outcome post-lung transplantation.[119-121] However, phenotypic response does vary and there is variability in virulence. Local laboratories in the United States, Canada, and Europe can be found through the International *Burkholderia cepacia* Working Group website at http://go.to/cepacia.

Nontuberculous Mycobacteria

Aside from the emergence of typically resistant bacteria, a significant number of CF patients are infected with nontuberculous mycobacteria (NTM). Historically, patients considered immunodeficient presented with disseminated disease, however, *Mycobacterium avium-intracellulare* complex (MAC), a group of NTM, are rapidly becoming a significant cause of pulmonary disease in immunocompetent patients.[122] NTM are found in soil and drinking water and there is little evidence for person-to-person transmission.[123] In CF patients, infection may be due to a number of reasons including abnormal anatomy, such as cavitary lesions or bronchiectasis, as well as selective pressure from wide-spectrum antibiotics.[124] Unlike tuberculosis, NTM infection is not a reportable disease, therefore, overall prevalence is unknown. Additionally, diagnosis can be difficult in regular sputum samples because bacterial overgrowth and decontamination procedures decrease the yield for NTM. Laboratories are continually improving culture techniques for NTM.[125,126]

The American Thoracic Society (ATS) guidelines suggest disease is present if (1) there are clinical signs and symptoms of cough, fever, fatigue, weight loss, hemoptysis, and dyspnea, with exclusion of other disease; (2) there are radiographic findings on chest radiography (infiltrates, nodules, or cavitation) or high-resolution computed tomography (HRCT) of chest abnormalities (nodules and/or multifocal bronchiectasis); and (3) there is bacteriologic isolation of the NTM organism on sputum/bronchial washings or tissue biopsy. Confirmation of infection by ATS bacteriologic standards requires either one positive smear with two positive cultures, or in the event of smear-negative samples, three positive cultures. If only a washing is available, a high level of AFB on smear can suffice.[127]

Age-related prevalence and distribution of NTM species among 385 CF patients aged 1 to 24 years was determined by a French multicenter prospective study.[128] Overall prevalence was 8.1% and the mean age of first culture was 14.6 years, with a range from 1 to 22 years. *Mycobacterium abscessus* was found in 39% of positive patients, whereas MAC was found in 21%, followed by *Mycobacterium gordonae* and others. Of considerable interest, all of the patients with MAC were older than 15 years of age, whereas *M. abscessus* was found in all ages up to 22 years. In the United States, a multicenter study of patients older than 10 years found an overall prevalence rate of 13% with considerable variation between centers, ranging from 7% to 24%.[129] Of the positive cultures, 20% of patients demonstrated criteria positive for pulmonary disease. In contrast to the French data, MAC was the most common NTM (72%), followed by *M. abscessus* (16%). Other NTM such as *Mycobacterium gordonae*, *M. kansasii*, *M. lentiflavum*, and *M. peregrinum* were rarer. For pediatricians, the French data are unsettling because rapidly growing mycobacteria, such as the difficult to eradicate *M. abscessus*, may be of more importance in children than slow-growing NTM.[130,131]

Therapy involves multiple medications because macrolide monotherapy can lead to resistance. In 2004, 49% of CF patients in the United States were prescribed a macrolide at least once and although there was no NTM emergence during the macrolide trials in CF, induced sputum for NTM should be performed in all patients before and yearly after the initiation of chronic macrolide therapy. Additional testing should occur in a setting of symptoms. NTM infections are also common after lung transplantation (6.5%, 17 of 261 patients.)[132]

SYNERGY AND MULTIPLE-COMBINATION BACTERICIDAL TESTING

A multiresistant isolate is resistant to all antibiotic agents from at least two of the three following classes: the beta-lactams, the aminoglycosides, or the quinolones.[1] Researchers have investigated the in vitro effects of synergy testing,

namely the activity of two antibiotic combinations against such multiresistant pathogens. Multiple-combination bactericidal testing (MCBT) is a further innovation allowing simultaneous synergy testing of three or four drug combinations.[133] Although successful combinations can be found for both multiresistant isolates of *P. aeruginosa* and *B. cepacia* complex, studies evaluating clinical effect have been lacking. A randomized double-blinded control trial enrolled 251 CF patients chronically infected with multiresistant gram-negative bacteria. Upon developing a pulmonary exacerbation, patients were randomized to receive either a 14-day course of antibiotics determined by MCBT or by conventional sensitivity testing. The time to next pulmonary exacerbation was not prolonged in the MCBT-treated group and there was no difference between the groups with respect to rate of treatment failure, changes in lung function, dyspnea score, and sputum bacterial density.[134] One possible contributing factor was the delay from initial MCBT to exacerbation. In the study, MCBT orders were based on sputum results within the 3 months before the patient's actual exacerbation. In nearly 25% of cases, MCBT-directed drug combinations were no longer bactericidal against all of the bacterial isolates recovered during the exacerbation. The study was not sufficiently powered for subgroup analysis; therefore, MCBT may have a role in a specific subset of patients and further investigation is required.

CANCER

Improved survival in CF has allowed the emergence of competing life-threatening illness such as cancer. Spurred by case reports of gastrointestinal and biliary cancers, Neglia and colleagues performed an interesting retrospective study using the registry data from the United States and Canada.[135-138] Although they found no overall increase in cancer risk in CF patients, they did find an increased risk of cancer concerning the biliary tract, small bowel, colon, liver, and pancreas. Similar results were found by Schoni in 1996 using the European registry.[139] Maisonneuve reported similar findings over 10 years but also documented increased risk of cancer in post-lung transplant patients.[140] As in the case of CFBD and CFRD, the exact etiology of this problem is not known, although patients homozygous for ΔF508 seem to be at the highest risk.[141] It is suggested that primary prevention such as smoking cessation and healthy diet choices, including antioxidants, be encouraged in CF patients. Secondary measures also should be initiated, such as occult blood screening of stool, although no evidence presently exists defining frequency and the age appropriate for initiation of testing. There is a need for the development of screening measures in this growing population.[80]

HORMONE DYSREGULATION

Aggressive nutritional programs, effective pancreatic enzyme replacement, regular exercise, and adequate blood glucose regulation have resulted in an impressive increase in the growth parameters of CF patients. Despite these interventions, a significant proportion of CF patients demonstrate poor linear growth. The 2004 Patient Registry noted that there are 16.3% of patients with stature below the 5th percentile. Often in CF children, this deficit is not corrected during puberty and patients tend to reach lower average adult heights. In addition to the obvious psychosocial impact, there has been a documented association between poor linear growth and subsequent deterioration in pulmonary function.[142,143] Although short stature in CF can occur independently of adequate weight gain, groups have investigated the role of human recombinant growth hormone (rGH) in CF patients.[144] Prepubertal children given daily rGH therapy demonstrated significantly higher height and weight Z-scores and growth velocities. A significant decrease in hospitalizations was also noted from the previous year in GH-treated children.[145] Treatment with rGH during overnight gastrostomy-tube feedings produced a significant improvement in weight and height velocity, FVC, and FEV_1 over 1 year.[146]

Schibler performed exercise testing on CF patients assigned to rGH treatment and placebo. Both $\dot{V}O_2$max and maximal workload were significantly improved after 6 months in the rGH group but unchanged in the placebo group.[147] Glucose intolerance, a theoretical concern of GH use that requires prudence, has been encountered in only two patients in the recent randomized controlled trials. Evidence indicates growth hormone provides modest benefit in prepubertal CF patients, although cost and concern over use of hormone therapy in patients without long-term data in CF has limited its use.

ISSUES FOR INFANTS AND YOUNG CHILDREN

Two issues have arisen for children with CF. Centers have recently advocated use of regular chest computed tomography scan (chest CT) every 2 years to document progression of pulmonary disease. Proponents of regular chest CT suggest that pulmonary function testing underestimates mild and moderate lung disease.[148] Presently, there is no evidence that routine chest CT improves overall outcome.[149] Additionally, a computational model developed to calculate cumulative cancer mortality from biennial chest CT radiation estimated a cumulative cancer mortality of 1% and 6.5% at ages 40 and 65 years, respectively.[150] Low radiation dose CT is being developed. Given the uncertain benefit and possible risks, more information regarding the efficacy and safety of routine chest CT is necessary before guidelines are changed.

Evidence is also accumulating regarding use of flexible bronchoscopy for organism recovery in CF patients. Baughman published the results of 28 bronchoscopies in 11 adult patients who were not improving after 10 days of antibiotics. Bronchoalveolar lavage fluid (BALF) microbiological results changed therapy in 13 of the 28 exacerbations.[151] The group proposed that bronchoalveolar lavage (BAL) was a useful diagnostic tool in CF in patients in whom empirical therapy failed. In stable adult patients, sputum collection provided equal information to bronchoscopy for characterizing the genotype and antibiotic susceptibility of chronic *P. aeruginosa* infection.[152]

Jung and colleagues evaluated oropharyngeal, sputum, and bronchoalveolar lavage samples from 38 stable CF patients. They determined the sensitivity, negative and positive predictive values, and specificity to detect *P. aeruginosa* were

35.7, 73.5, 83.3, and 96.2% for oropharyngeal cultures in nonexpectorating patients and 91.7, 94.1, 100, and 100% for sputum cultures from expectorating patients, respectively.[153]

Data specific to children with CF is sparse. In 1999, Rosenfeld and colleagues investigated difference between oropharyngeal and BALF in children with CF younger than 5 years of age. The specificity and negative predictive value of OP cultures for *P. aeruginosa* were high, whereas the sensitivity and positive predictive values are poor. They submitted that a negative oropharyngeal culture is fairly good evidence for lack of infection; however, a positive culture does not reliably indicate infection in the lower respiratory tract with *P. aeruginosa*. Specificity for *S. aureus* was lower, whereas results were similar for *H. influenza*. Further studies are justified. Presently, routine screening of pediatric patients with oropharyngeal culture is adequate; however, bronchoscopy has a place in determination of bacterial conditions in patients who cannot provide adequate sputum and in whom empirical treatment is failing.

FINAL NOTE

The CF model of cooperative clinical care and research has proved overwhelmingly effective over the last 50 years. Despite a mid-20th century median survival age of less than 10 years, presently there are as many adults as children with CF. We must sustain this progress despite scarce healthcare resources and actively encourage trainees to continue the legacy. From Dorothy Andersen to Lap-Chi Tsui, from Paul di Sant'Agnese to Leo Matthews, the motto of the venerable Montréal Canadiens' Hockey Club, taken from "In Flanders Fields" by Lt. Col. John McCrae, MD, is representative of the history and future of CF care: "*Nos bras meutris vous tendent le flambeau. A vous, toujours, de le porter bien haut.*" Translated: "To you with failing hands we throw the torch. Be yours to hold it high."

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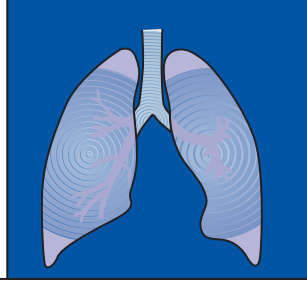


CHAPTER 61 Genetics and Disease Mechanisms

Charles R. Esther, Jr., and Margaret W. Leigh

TEACHING POINTS

- Cystic fibrosis is caused by defects in the cystic fibrosis transmembrane conductance regulator (CFTR).
- CFTR functions both as a chloride channel and as a regulator of other transporters.
- There are more than 1400 mutations in CFTR that can cause CF, but by far the most common is ΔF508.
- Genotype predicts certain aspects of CF disease severity, but other factors such as overall genetic background and the environment, play a large role in the impact of lung disease.
- The basic pathophysiologic defect in CF is altered ion transport across the membrane, which causes dehydration of extracellular fluids in most tissues affected in CF.

Our understanding of the pathophysiology of cystic fibrosis (CF) has undergone extraordinary changes over the past half century. Early studies focused on the thick, sticky mucus produced by patients with CF, reflected in the fact that CF was once known as "mucoviscidosis," a term still in use in some European countries. In the 1950s, Dr. Paul di Sant'Agnese discovered the elevated salt content in sweat from individuals with CF,[1] prompting a focus on ion permeability. Altered ion conductances in CF were shown by Dr. Quinton in ductal tissues of the sweat gland,[2] which were recognized to be essentially impermeable to chloride. Later studies in respiratory epithelia by Drs. Boucher and Knowles confirmed the decreased chloride conductance and also demonstrated an increase in sodium permeability in those with CF.[3,4] These studies and others suggested that the basic defect in CF was lack of a low-conductance, cyclic AMP (cAMP) regulated chloride channel. Surprisingly, when the gene responsible for CF was cloned in 1989 by Drs. Tsui, Collins, and Riordan, the predicted protein had characteristics more similar to a membrane transporter than the predicted channel (which are biophysically very different).[5] The gene was therefore named the cystic fibrosis transmembrane conductance regulator (CFTR), reflecting uncertainty as to whether the encoded protein acted as an ion channel or a regulator of other channels. Subsequent study of CFTR confirmed that it does function as a chloride channel, but that it also has an important role in regulating other membrane channels and transporters. The most recent studies of CF have focused on how the defects in ion transport in epithelial cells lead to the respiratory and gastrointestinal manifestations of CF, with recognition that CF epithelia have dehydration of extracellular fluids and consequent poor clearance of secretions. Our growing understanding of the pathophysiology of CF has led to novel therapeutic strategies targeted to the basic defects in ion conductances and the consequences.

CFTR GENE AND PROTEIN

Structure

The CFTR gene is located on the long arm of chromosome 7. It is a relatively large gene, with 27 exons spread over almost 250 kb of genomic DNA (Fig. 61-1A).[5] The gene is transcribed to a 6.5 kb long mRNA which can be detected in many organs affected by CF including the lung, pancreas, intestine, and sweat gland (see Fig. 61-1B). The translated CFTR protein is 1480 amino acids long. Unlike some other genes, there are few splice variants or other alternative transcripts that encode functional protein.

The CFTR protein has several structural elements that contribute to its function. The protein contains two large transmembrane domains, each of which has six hydrophobic transmembrane spanning segments (see Fig. 61-1C). Each transmembrane domain is followed by a nucleotide binding domain that contains motifs (called *Walker domains*) preserved among ATP binding proteins. CFTR also has a large hydrophilic domain between the first nucleotide binding fold and the second transmembrane domain. This region is called the *regulatory* or *R-domain*, reflecting the presence of multiple consensus phosphorylation sites that play a role in regulation of CFTR function. The C terminal end of CFTR is notable for the presence of four amino acids (DTRL) that form a consensus PDZ-binding motif.[6] The PDZ-binding motif in CFTR mediates binding with other proteins that play roles in its localization and regulation.

The pattern of two transmembrane domains each followed by a nucleotide binding fold places CFTR within a superfamily of membrane transporters called *ABC* (ATP binding cassette) *transporters*. Indeed, low resolution crystal structures suggest that the transmembrane domains of CFTR form a central pore similar to that of other ABC superfamily members.[7] CFTR differs from other ABC superfamily members both functionally (acting as an ion channel) and by the presence of the R-domain, which is unique to CFTR.

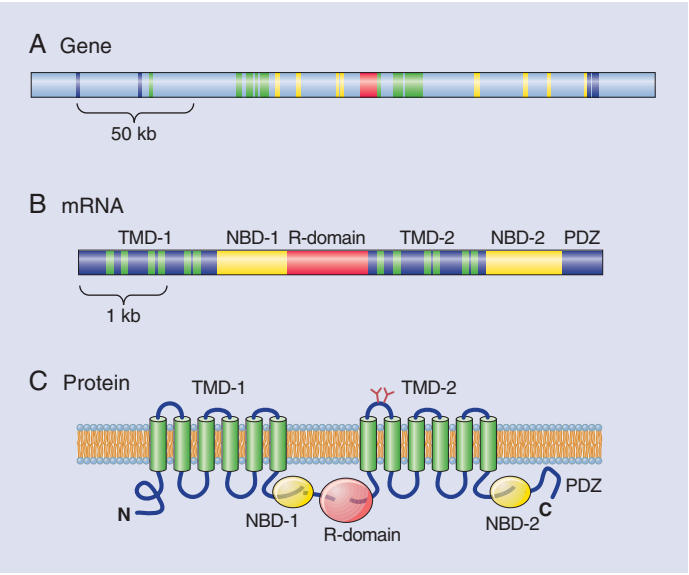


Figure 61-1 Gene, mRNA, and protein structures of CFTR. A, The CFTR gene is composed of 27 exons spanning nearly 250 kB of DNA. **B,** The CFTR mRNA is 6.5 kB long. Sequences predicted to encode the transmembrane domains (TMD), nucleotide binding folds (NBD), the regulatory domain (R-domain), and the PDZ-binding motif are shown. Each TMD is predicted to encode six transmembrane spanning segments (*green*). **C,** The primary structure of the CFTR protein is shown in orientation to the plasma membrane. The extracellular loop between the first and second transmembrane spanning regions of TMD-2 is glycosylated (*red pitchforks*). CFTR, cystic fibrosis transmembrane conductance regulator.

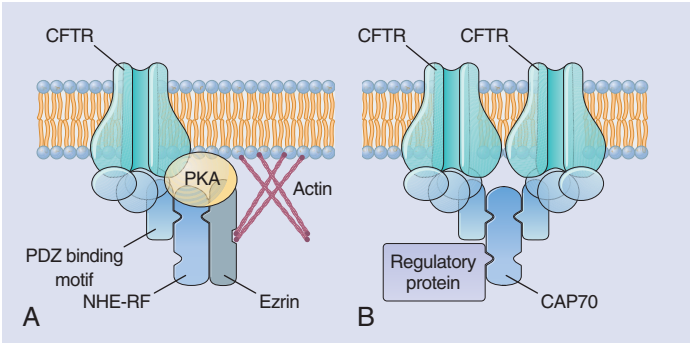


Figure 61-2 Interactions of CFTR with PDZ domain adapter proteins. A, CFTR can bind the adapter protein NHE-RF via the C terminal four amino acids (DTRL) that form a PDZ binding motif. NHE-RF interacts with ezrin which links CFTR to the actin cytoskeleton and facilitates interaction with the regulatory protein kinase A (PKA). **B,** CFTR may form dimeric structures through interaction with PDZ domain adapter proteins. In this example, the PDZ domain protein CAP70 is shown, although similar interactions have been demonstrated with other PDZ domain proteins. CFTR, cystic fibrosis transmembrane conductance regulator.

Like other transmembrane proteins, CFTR is translated and processed in the endoplasmic reticulum (ER), passes through the Golgi apparatus, then to the apical plasma membrane in epithelial cells.[8-10] CFTR undergoes its initial folding steps and core glycosylation in the ER. Folding of a large, multidomain protein such as CFTR is a complex task that requires the assistance of molecular chaperones such as Hsc70/Hsp70[11] and Hsp90.[12] These chaperone proteins interact with co-chaperones such as DnaJ homologs[13,14] and the glycoprotein binding protein calnexin[15] to form the cellular error-checking machinery that distinguishes correctly folded from incorrectly folded CFTR. This error-checking process forms an important check point in CFTR maturation. Whereas correctly folded CFTR migrates to the Golgi apparatus for further processing, misfolded CFTR is recognized as abnormal, complexed with ubiquitin, and targeted to the proteosome for degradation.[16] The maturation process is surprisingly inefficient, and as much as 75% of normal CFTR is misfolded and degraded.[17] CFTR that does successfully pass to the Golgi undergoes further modification and is then targeted to the plasma membrane in secretory vesicles. To aid this process, the N terminal end of CFTR interacts with proteins called *SNARES* (e.g., syntaxins 1a and 8),[18,19] which are part of the secretory machinery that promote targeting and fusion of secretory vesicles to the plasma membrane. CFTR at the cell surface is recovered in endosomes with a half-life of 4 to 6 hours. Some of this endosomal CFTR is recycled back to the plasma membrane and the rest is degraded.[20,21]

At the plasma membrane, CFTR is bound into a network of proteins via interaction with the multi PDZ domain adapter proteins NHE-RF/EBP-50[6] and CAP70.[22] These PDZ adapter proteins bind to the C terminal PDZ-binding motif of CFTR and act as molecular scaffolds to facilitate interactions with other PDZ domain proteins. For example, CFTR is linked to the actin cytoskeleton via the PDZ domain ezrin, and this interaction plays a significant role in targeting of CFTR to the apical plasma membrane (Fig. 61-2).[23] The PDZ adapters also bring CFTR into macromolecular complexes that involve regulatory proteins such as protein kinase A (PKA)[24] and protein kinase C (PKC).[25] There is also evidence that PDZ adapters may link CFTR to itself in a multimeric network[22] or to other biologically active proteins such as the beta-adrenergic receptor.[24] The relevance of these multimeric complexes is currently unclear, with conflicting evidence as to whether CFTR functions as a monomer or a dimer in vivo.[26]

Function

The exact functional role of CFTR remained controversial well after the cloning of the gene. Although much evidence suggested that CFTR should function as a chloride channel, all other members of the ABC transporter superfamily act as membrane transporters and not ion channels. Therefore, several investigators hypothesized that CFTR actually functioned as a channel regulator. Extensive investigation has now shown that CFTR actually has both roles: a chloride channel that regulates other channels and transporters.

ION CHANNEL

Expression of CFTR cDNA in cell systems that lack native CFTR leads to the appearance of a low conductance, cAMP-regulated chloride channel similar to the one missing in patients with CF.[27,28] Furthermore, mutations in putative pore-forming regions of CFTR lead to alterations in ion conductivity when the altered protein is expressed.[29] Perhaps most compelling, purified CFTR protein acts as a cAMP-

regulated chloride channel when reconstituted in lipid bilayers.[30] These experiments clearly demonstrate that CFTR is a cAMP-regulated chloride channel.

Under physiologic conditions, the channel formed by CFTR is highly selective for anions over cations (>10 : 1). The single channel conductance, a measure of the ability of the channel to permit passage of ions per unit time, is relatively low with a value of ~7 to 10 picosiemens (pS). CFTR conducts anions equally well in both directions (i.e., it does not rectify the current). Although generally described as a chloride channel, CFTR is capable of conducting other anions as well. The most physiologically relevant is bicarbonate, which has a conductance of about one-fourth that of chloride.

CHANNEL AND TRANSPORTER REGULATOR

In addition to its role as a chloride channel, CFTR has also been implicated in the regulation of many proteins involved in transport across the plasma membrane. These proteins include channels for sodium,[31] chloride,[32] potassium,[33] calcium,[34] and water;[35] and both the sodium/hydrogen[36,37] and chloride/bicarbonate exchangers.[38] The mechanisms and physiologic relevance of many of these interactions remain unclear, and may reflect changes in membrane potential and/or chloride flux mediated by CFTR rather than a direct regulatory interaction. Two of the more physiologically relevant and best studied regulatory interactions are discussed in more detail subsequently.

REGULATION OF THE SODIUM CHANNEL, ENaC

One of the cardinal biophysical features of CF is hyperabsorption of sodium by epithelial tissues.[39] This hyperabsorption can be blocked by the drug amiloride, indicating that it is mediated via the abundant apical membrane sodium channel called *ENa*C.[31] These observations suggest that ENaC activity is decreased in cells with active CFTR, a hypothesis that has been confirmed in studies on several cell types including frog oocytes[40] and cultured epithelial cells.[31]

The mechanisms by which CFTR mediates downregulation of ENaC are not clear. There is currently no evidence of a physical interaction between CFTR and ENaC. Several studies have suggested that changes in chloride flux or intracellular chloride concentration mediated by CFTR may be sufficient to explain the regulatory effect on ENaC.[41] In support of this hypothesis, expression of an unrelated chloride channel CLC-0 can also downregulate ENaC.[42,43] An alternative hypothesis is that the network of proteins that bind to CFTR via the C terminal PDZ domain may include regulatory elements that can influence ENaC activity. However, there is currently little experimental support for this mechanism.

REGULATION OF THE CHLORIDE CHANNEL, ORCC

Another channel regulated by CFTR is the outwardly rectifying chloride channel (ORCC), which is of historical interest because it was the initial channel identified as being abnormal in CF airway epithelia.[44,45] While detailed study clearly demonstrated that ORCC was not directly responsible for CF, other investigations showed that the presence of CFTR conferred PKC/ATP regulation on the ORCC.[32,46] The precise mechanism and the physiologic role of ORCC are unknown, although recent studies suggest that ORCC may regulate basolateral transport of chloride in epithelial cells.[47]

TRANSPORTER

The similarity of CFTR to the ABC transporter superfamily has led to speculation that the protein may serve as a transporter as well as an ion channel. Although some evidence exists that CFTR may transport certain molecules such as ATP[48] and glutathione,[49] these findings remain controversial. As noted earlier, CFTR may alter the transport properties of other molecules making a direct transport by CFTR difficult to distinguish from a regulatory interaction (see Pitfalls and Controversies box).

Regulation

CFTR is involved in highly regulated processes that control ion and water flux across the membrane. As a result, the activity of CFTR is controlled at multiple levels. The primary regulation of CFTR involves phosphorylation by various kinases, although binding and hydrolysis of ATP also plays a significant role.

cAMP/PHOSPHORYLATION

A characteristic feature of the CFTR channel is its regulation by cAMP, with increasing cAMP levels leading to increased chloride channel activity.[5] This regulation is mediated via phosphorylation of CFTR by the cAMP-responsive protein kinase A (PKA). Under normal circumstances, phosphorylation by PKA is obligatory for activation of chloride channel activity. Furthermore, as previously noted there is evidence that CFTR is structurally coupled to PKA within the plasma membrane via proteins that interact with the C terminal PDZ binding sequence.[23] Although there is still some uncertainty, it appears that nearly all of the physiologically relevant phosphorylation in mammalian cells occurs at 10 PKA sites located within the R-domain.[50] Indeed, deletion of the R-domain yields a chloride channel that is no longer dependent on PKA phosphorylation for activity.[51,52]

Other protein kinases play a role in regulation of CFTR as well. Phosphorylation by the receptor activated protein kinase C regulates CFTR-mediated chloride secretion,[53,54] and seven potential PKC phosphorylation sites are also located in this R-domain.[55] The metabolic sensor AMPK is associated with CFTR.[56]

ATP BINDING

Like all ABC transporters, CFTR contains two nucleotide binding domains that bind ATP. In most ABC transporters, the energy of ATP binding and hydrolysis is used to actively transport substances across the cell membrane. However, CFTR appears to use this energy to control chloride channel activity. The exact mechanism by which this occurs is unclear. The current working model suggests that ATP binding leads to dimerization of the two nucleotide binding folds, inducing a conformational change in CFTR that permits chloride transport (assuming appropriate phosphorylation of the R-domain).[26] ATP binding at one site is relatively stable, but ATP can be hydrolyzed at the second site, which may be involved in channel closing.[57]

Genetics of Cystic Fibrosis

CF is an autosomal recessive disorder, which means that both copies of CFTR must be mutant to manifest the disorder. Individuals who carry only one mutant copy of CFTR are called carriers and are essentially asymptomatic. A child of two carriers has a 1 in 4 chance of inheriting the mutant CFTR allele from each parent and, therefore, of having CF. CF is most common in whites of Northern European descent in whom the carrier rate is ~1 in 20, and 1 in 2500 newborns are affected.[58,59] CF occurs with much less frequency in African-American (1 in 17,000) and Asian (<1 in 100,000) populations.

Over 1400 different disease-causing mutations have been described in CFTR (http://www.genet.sickkids.on.ca/cftr/). By far the most common is a three base pair deletion called ΔF508. The mutation results in deletion of the phenylalanine residue at position 508, which is found on the exterior surface of NBD-1 in high resolution crystal structures of this domain.[60] This mutation is found in ~70% of CF chromosomes worldwide, and its presence leads to defective processing of CFTR and reduced activity of the little CFTR that reaches the cell surface. It is thought that ΔF508 mutation first occurred more than 52,000 years ago and spread through Europe in a heterogeneous time frame.[61] This spread may have been aided by heterozygote advantage (i.e., a survival benefit to CF gene carriers). Several hypotheses have been proposed to explain the heterozygote advantage, of which the best known is that CF gene carriers may be partially protected against life-threatening childhood diarrheal syndromes mediated through the CFTR chloride channel secretory pathway.[62,63] Other hypotheses include suggestions that reduced levels of CFTR protect against *Salmonella typhi* infection or bronchial asthma.[64]

In addition to ΔF508, about 15 mutations are common among whites, and account for up to 15% of the CF alleles within white populations.[65,66] Although many of these mutations occur in other ethnic groups, their frequencies may vary considerably.[59,67,68] The ΔF508 mutation occurs with less frequency in individuals of Southern European extraction (50% of chromosomes),[59,69] Ashkenazi Jewish extraction (30% of chromosomes),[70] African Americans (45% of chromosomes),[71] and Native Americans (<5% of chromosomes).[72] Perhaps the most striking example is in the Ashkenazi Jewish population, in whom the W1282X mutation accounts for 50% of the mutations in CFTR.[70] Furthermore, both Hispanic and African-American populations have distinct patterns of CFTR mutation frequencies (Table 61-1).[66,68] Regardless of ethnic group, most mutations in CFTR are rare.

The large number of mutations in CFTR leads to a bewildering number of genotypes associated with cystic fibrosis. To provide some clarity, a simple classification of five types of CFTR mutations has been proposed, with each class representing a specific mechanism regarding production and routing of CFTR protein to the plasma membrane (Fig. 61-3).[73] Class I mutations lead to no production of CFTR. These are often abnormalities in initiation of transcription (promoters), problems in splicing the mature transcript, premature truncation of the protein by a stop cordon (nonsense mutation), or frameshift mutations that result in nonsensical protein sequences. Class II mutations reflect problems in CFTR protein processing, primarily in the endoplasmic reticulum (ER), which ultimately lead to proteins being recognized as abnormal and targeted for degradation. The common ΔF508 mutation is a class II mutation. These mutations typically reflect single amino acid (missense) mutations. Class III mutations reflect altered function of the mature CFTR that has successfully transited to the plasma membrane. These mutations result from abnormalities in activating the CFTR via intracellular messengers and are often clustered in the nucleotide binding folds or the R domain. Class IV mutations also alter function of the mature CFTR, causing abnormalities in the conduction properties of the CFTR protein. These mutations are typically caused by mutations in the transmembrane spanning regions. Class V mutations result in decreased abundance of an otherwise normal CFTR protein.

In general, class I, II, and III mutations produce the most severe biophysical abnormalities, with little chloride conduction measured in cell culture systems or by nasal potential difference measurements in affected subjects.[74,75] In contrast, class IV and V mutations often preserve a degree of CFTR-mediated chloride conductance. However, these biophysical differences do not always translate into differences in an individual's phenotype.[76]

Recent advances in potential therapies have added new emphasis to understanding of the nature of CFTR mutations. Several studies have demonstrated that application of aminoglycoside antibiotics such as gentamicin can cause "read through" and permit functional expression of CFTR from certain class I stop mutations such as G542X.[77,78] Furthermore, several large-scale projects are attempting to identify compounds that enhance the ability of class II mutations (particularly ΔF508) to transit successfully through the ER. These compounds are termed "correctors" and some may soon reach clinical trials.[79] Because ΔF508 that reaches the cell surface does not exhibit wild type activity (and could therefore be classified as a class III mutation as well), the hunt is also on for "potentiators" that enhance the chloride channel properties of ΔF508 CFTR. As these potential therapies and others are developed, knowledge of the specific CFTR mutations present in an affected individual will take on greater importance.

Genotype-Phenotype Relationship

Cystic fibrosis is a monogenic disorder; it is caused by mutations in one gene, CFTR. However, its phenotypic expression is dependent on a number of factors including CFTR genotype, overall genetic background, and environmental influences. As a result, severity of any particular phenotype (lung disease, malabsorption, etc.) is related to the relative contribution of each of these factors and results in a varying degree of genotype-phenotype correlation.

CFTR GENOTYPE

The large number and variety of mutations found in CFTR led to early speculation that the CFTR genotype could be used to predict phenotypic consequences. The relationship between genotype and phenotype has been most extensively studied with the ΔF508 mutation, which was the first discovered and by far the most common. Studies on ΔF508 homozygotes

Table 61-1
Mutations in CFTR*

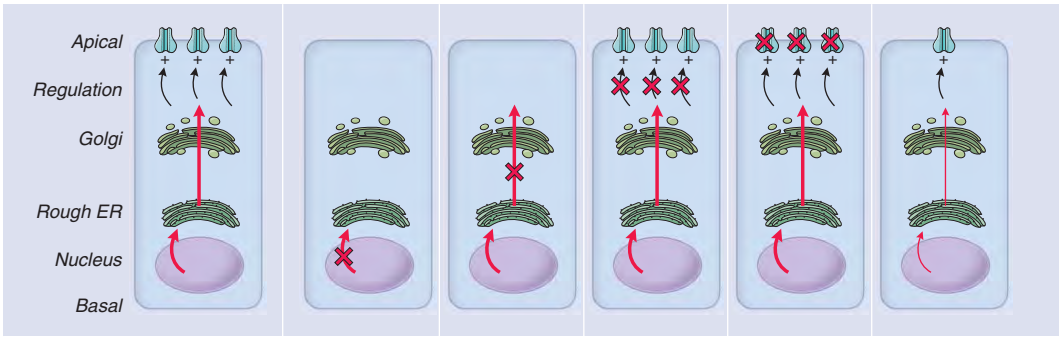
Percent of All Alleles	Non-Hispanic White	Hispanic White	African American	Asian American	Ashkenazi Jewish
>30	ΔF508	ΔF508	ΔF508	ΔF508	W1282X ΔF508
1-30	G542X	L206W	3120 + 1 G > T	3849 + 10 kbC > T	G542X
	G551D	G542X	R553X	S549N	3849 + 10 kbC > T
	621 > 1G > T	R553X	D1152H	G551D	N1303K
	W1282X	R1066C	ΔI507	R347H	
	N1303K	R334W	G542X		
		N1303K	A559T		
		3849 + 10kbC > T	G551D		
		406-1 G > A	621 + 1G > T		
0.1-1	ΔI507	ΔI507	S549N	V520F	1717-1G > T
	R553X	S549N	R1158X	R553X	ΔI507
	R117H	W1282X	2307insA	N1303K	G551D
	3849 + 10 kbC > T	R1162X	R1162X		3120 + 1G > T
	1717-1G > T	G551D	G330X		711 + 1G > T
	2789 + 5G > A	W1089X	R334W		2789 + 5G > A
	R347P	3876ΔA	1812-1G > A		
	711 + 1G > T	1717-1G > T	1717-1G > T		
	R560T	621 + 1G > T	N1303K		
	3569ΔC	Y1092X	405 + 3A > C		
	A455E	D1270N	W1282X		
	G85E	711 + 1G > T	3849 + 10kbC > T		
	R1162X	G85E	R560T		
	Q493X	Q890X	2184ΔA		
	2184ΔA	3120 + 1G > T	Y1092X		
	1898 + 1G > A	2789 + 5G > A	D1270N		
	R334W	R347P	G85E		
	3905insT	R1158X			
	E60X	3569ΔC			
	Y1092X	R117H			
	2183ΔAA-G	E60X			
		D1152H			

*Mutations that occur at a frequency of ≥0.1% of all mutations within a population are shown, stratified by how frequent alleles appear within the population. The order reflects relative frequency, although exact frequencies can vary considerably within subpopulations.
CFTR, cystic fibrosis transmembrane conductance regulator.
Data are a synthesis of the following studies: Watson MS, Cutting GR, Desnick RJ, et al: Cystic fibrosis population carrier screening: 2004 Revision of American College of Medical Genetics mutation panel. Genet Med 6(5):387-391, 2004; Sugarman EA, Rohlfs EM, Silverman LM, Allitto BA: CFTR mutation distribution among U.S. Hispanic and African American individuals: Evaluation in cystic fibrosis patient and carrier screening populations. Genet Med 6(5):392-399, 2004; and Schrijver I, Ramalingam S, Sankaran R, et al: Diagnostic testing by CFTR gene mutation analysis in a large group of Hispanics: Novel mutations and assessment of a population-specific mutation spectrum. J Mol Diagn 7(2):289-299, 2005.

clearly establish a link between genotype and pancreatic exocrine function; 99% of patients homozygous for ΔF508 have pancreatic exocrine insufficiency, although a few had adequate pancreatic exocrine function to prevent malabsorption in early childhood. These patients also have uniformly elevated sweat chloride values (diagnostic for CF when performed in a qualified laboratory), and more than 99% of the adult males are infertile with obstructive azoospermia attributable to congenital bilateral absence of the vas deferens (CBAVD).[80] However, lung function is quite variable within ΔF508 homozygote populations, with some individuals succumbing to lung disease in early childhood, whereas others have relatively normal lung function well into adulthood. Therefore, although the ΔF508 homozygous genotype accurately predicts some gastrointestinal, reproductive, and sweat gland phenotypes, it is a poor predictor of lung disease.

The relation between genotype and phenotype has been explored in other CF genotypes. In general, patients who are homozygous for any class I, II, or III mutation have a very high probability of pancreatic exocrine insufficiency, elevated sweat chloride, and obstructive azoospermia.[73] As a result, most class I, II, or III mutations are called "severe." In contrast, individuals with at least one type IV or V mutation are much more likely to have pancreatic sufficiency and often have lower sweat chloride values. The type IV and V mutations are therefore considered "mild." Other phenotypic consequences of CF have varying correlations to genotype. Meconium ileus and obstructive liver disease occur in ~15% to 20% and ~4% of patients with severe mutations, respectively, but are rare in those that carry a mild mutation.[81] With regard to respiratory manifestations, several studies have shown that patients homozygous for severe mutations have greater decline in lung function over time than those with at least one mild mutation.[82] However, on the individual level, these findings do not apply, and genotype cannot be used to predict severity of lung disease.

There are other variations in the CFTR gene that can influence its expression but do not sufficiently impair expres-



Normal	Class I	Class II	Class III	Class IV	Class V
	621–1G→T 711+1G→T 1717–1G→A 1078ΔT 3659ΔC E60X Q493X G542X R553X Y1092X R1162X W1282X	ΔF508 ΔI507 S549N N1303K	G551D R560T	G85E R117H R334W R347P	2789+5G→A 3849+10Kb C→T A455E

Figure 61-3 Genetic classes of CFTR mutations. A schematic that outlines production of functional CFTR in epithelial cells is shown on the left. CFTR DNA is transcribed in the nucleus and translated in the rough ER, the translated protein undergoes processing through the rough ER to the Golgi, and the mature CFTR gene product reaches the apical cell surface where it acts as a chloride channel, which is subject to regulation (*black arrows*). Mutations in CFTR can be classified based on their impact on this process, as shown in the schematics labeled Class I through Class V. Class I mutations result in aberrant transcription or translation of CFTR. Class II mutations result in ineffective processing of CFTR. Class III mutations result in a CFTR protein that cannot be activated by regulatory mechanisms. Class IV mutations lead to CFTR with decreased ion conductance, and Class V mutations lead to decreased production of an otherwise normal CFTR protein. A list of common (>0.1% of all CFTR mutations) mutations for each class are shown below. CFTR, cystic fibrosis transmembrane conductance regulator.

sion to cause CF. These variations are therefore referred to as polymorphisms rather than mutations, and many can be found at relatively high frequency in unaffected populations. Although polymorphisms in isolation do not cause CF, they can influence gene expression in conjunction with other CFTR mutations sufficiently to impact the CF phenotype. One well described example is the 5T/7T/9T polymorphism found in intron 8 of CFTR. Alleles with the 5T polymorphism have aberrant splicing, which results in deletion of exon 9 in most CFTR transcripts, leading to nonfunctional protein.

In an otherwise normal CFTR gene, this altered splicing has little consequence and the 5T variant can be found in the ~5% of otherwise healthy individuals.[83] However, when the 5T polymorphism occurs in conjunction with the mild mutation R117H, the result is a more severe impairment in functional CFTR expression from this allele. As a result, individuals who are heterozygous for ΔF508 and R117H with the 5T polymorphism have fairly classic manifestations of CF. In contrast, individuals heterozygous for ΔF508 and R117H in conjunction with the 7T polymorphism (which does not express the splicing defect) are often phenotypically normal or have CBAVD with no respiratory or GI disease. More than 200 polymorphisms have been described, though not all have a significant impaction CFTR expression (*http://www.genet.sickkids.on.ca/cftr/*).[81]

A growing recognition of CF as a disease entity and increased sophistication in diagnostic testing has led to identification of many patients who have mutations in both CFTR alleles but lack the classic features of pancreatic insufficiency and progressive lung disease that characterize CF. These patients often have normal or borderline sweat chloride values and mild gastrointestinal or lung disease. Such individuals have been characterized as having "atypical CF." Further complicating this issue, many men have been described who have CBAVD, mutations in CFTR, but absolutely no pancreatic or lung abnormalities. Controversy has developed over whether such individuals should be labeled as having cystic fibrosis or another term such as "CFTR related disease." In a further extension of the CFTR-deficient phenotype, the carrier state is no longer regarded as asymptomatic, as previously thought. Patients with one CFTR mutation have increased rates of pancreatitis[84] and sinusitis.[85] Therefore, it is now clear that there is a spectrum of disease related to mutations in CFTR, of which the most severe is classified as cystic fibrosis.

Characterization of the many different CFTR mutations at the molecular level has permitted examination of the rela-

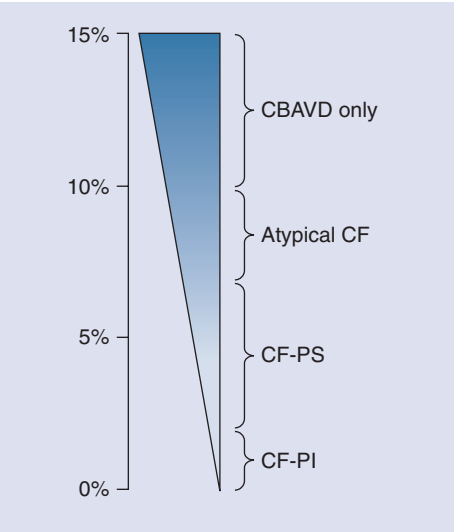


Figure 61-4 Relation between the level of expression of CFTR and clinical disease. Increasing levels of CFTR expression lead to progressively milder manifestations of CF. CBAVD, congenital bilateral absence of the vas deferens; CFTR, cystic fibrosis transmembrane conductance regulator; PI, pancreatic insufficient, PS, pancreatic sufficient.

tionship between expression of functional CFTR and the CF phenotype. Overall, there appears to be a rough correlation between the level of expression of functional CFTR and severity of illness (Fig. 61-4). Preservation of at least 10% of normal CFTR expression is generally sufficient to avoid the typical respiratory and GI manifestations of CF, although it may be insufficient to prevent CBAVD.[86] Lesser levels of expression are associated with more severe disease, with the classic features of pancreatic insufficiency and progressive respiratory decline seen when expression levels are less than 2% to 3% of normal. However, as discussed in more detail subsequently, correlations between expression of CFTR and phenotype are not exact and are influenced by other factors such as genetic background and environment.

GENETIC BACKGROUND AND MODIFIER GENES

The impacts of genetic background and the environment can be difficult to distinguish because individuals who share the same genes (e.g., siblings) often share the same environment. However, twin studies have suggested that genetic background does influence CF phenotype. Monozygotic twins, who share the same environment and 100% of their genes, have a greater concordance of disease severity than dizygotic twins, who share the same environment but only 50% of genes.[87] This finding strongly suggests that genetic factors other than CFTR play a significant role in determining CF phenotype. These data have been supplemented by results of animal studies, which have demonstrated a linkage between a region on mouse chromosome 7 and intestinal obstruction.[88] This region corresponds to human chromosome 19q13, and sibling studies have identified a locus within that region that is linked to meconium ileus.[89] The putative gene involved has been named CFM-1 although it has not yet been identified.

The recognition that genetic background can influence CF phenotype has led to significant effort to elucidate the identity of specific modifier genes. Much of this effort has focused on candidate genes which fit two criteria: (1) a biologically plausible mechanism to impact disease phenotype, and (2) presence of one or more polymorphisms within the population that can then be studied to determine linkage to phenotype.[90] Several potential candidates have been identified in small studies, including alpha$_1$-antitrypsin,[91,92] tumor necrosis factor-alpha,[93] and others. However, many initial associations are not confirmed in further investigations,[94] emphasizing the need for study of larger populations. One potential gene modifier that has been linked to CF phenotype in a larger study is MBL2. This gene encodes mannose binding lectin, a serum protein involved in innate defense.[95] Several polymorphisms in MBL2 lead to lower levels of expression, and these low-expression polymorphisms have been associated with decreased lung function in multiple studies[96] including one that included nearly 600 individuals with CF.[97]

One of the largest studies to date searching for modifier genes is the Gene Modifier Study in the United States.[98] This study enrolled more than 800 individuals all homozygous for ΔF508 (to minimize the impact of CFTR genotype) who had either mild or severe lung disease. Polymorphisms in 14 genes previously identified in smaller studies were examined for linkage to severity of lung disease. Two polymorphisms in transforming growth factor beta (TGF-β) were found to be more common in those with severe lung disease in this study, and the association was confirmed in evaluation of a separate group of 498 CF patients. No other significant associations with disease severity were found with polymorphisms in any other genes, including MBL2. Further study is ongoing to find new modifier genes and clarify the discrepancies between the various studies.

ENVIRONMENT

Environmental influences clearly play a role in the development and progression of lung disease and other manifestations in CF. This is most clearly demonstrated with the association of lower SES and poorer outcomes in CF.[99] However, specific environmental influences have proved more difficult to identify. Some studies have demonstrated a link between passive smoking and lung function,[100] although others have not.[101] Higher levels of exercise may also be associated with better lung function.[102]

Genetic Testing

The use of genetic testing has proved invaluable in the diagnosis of cystic fibrosis, particularly in clinical situations when the diagnosis is unclear with atypical pulmonary disease, normal pancreatic exocrine function, and/or nondiagnostic sweat-chloride tests. If disease-associated mutations can be defined on each allele of CFTR, the diagnosis of CF is confirmed. However, because of the large number of mutations present on CFTR, even large panels (including commercially available panels of 25 to 87 mutations) identify only 80% to 85% of all mutant CFTR chromosomes, with decreased frequency in different ethnic groups.[103] Screening for additional mutants typically adds little to the sensitivity because each novel mutation is found in a very small portion of the population.[66] Newer testing protocols that include sequencing and other methods for identifying novel mutations are now commercially available and have been reported to have

a sensitivity of 99% or greater in detecting CFTR mutations.[104] However, it is still important to recognize that even with new methods, diagnosis of CF cannot be completely ruled out on the basis of negative genetic tests because a mutation in any individual may be unique and not detectable by current assays. Furthermore, not all alterations in CFTR that can be detected with highly sensitive genetic assays are associated with disease. Therefore, genetic testing must be used with caution to avoid inappropriate inclusion or exclusion of CF as a clinical diagnosis.

POPULATION CARRIER SCREENING AND NEWBORN SCREENING

The last decade has seen a significant change in the recommendations regarding population screening. The change has been spurred in large part by the results of studies from populations that were early adopters of newborn screening for CF. The Wisconsin Cystic Fibrosis Neonatal Screening Project was a randomized, controlled trial that demonstrated that early identification of CF by newborn screening resulted in long-term improvements in nutritional parameters, although no measurable changes in lung function.[105] The data have been confirmed in other studies from the United Kingdom[106] and Australia.[107]

Based on the results of the Wisconsin study and others, a growing number of states have added neonatal CF testing to newborn screening panels. After a thorough review of the evidence, the CDC concluded in 2004 that "the magnitude of health benefits from screening for CF is sufficient that states should consider including routine newborn screening for CF."[108] Screening paradigms vary, but generally involve an initial evaluation for elevated levels of immunoreactive trypsinogen (IRT) in blood spots obtained during routine newborn screening. Newborns with elevated IRT levels are then referred to a secondary screen which involves either repeat testing of IRT from a second sample or a genetic screen for a panel of CF mutations on the original blood spot. Current screening methodologies report sensitivities of 94% to 99% but have false-positive to true-positive ratios of 9.5 to 25.[108] This is, however, in the acceptable range of tests for other diseases tested by newborn screening.

In addition to newborn screening, the American College of Obstetricians and Gynecologists and the American College of Medical Genetics issued a joint recommendation in 2001 that all women considering pregnancy be offered prenatal screening for cystic fibrosis using a genetic panel of 25 most common CFTR mutations,[109] and the genetic panel was updated in 2005.[110] If the pregnant woman is identified as a CF carrier, then the father is offered genetic testing and, if indicated, prenatal genetic testing can be performed on the fetus via amniocentesis or chorionic villus sampling.

Disease Mechanisms

CFTR has been detected in many organs including the lung, pancreas, sweat glands, liver, and colon.[5] Therefore, it is not surprising that cystic fibrosis is a multiorgan disease, with manifestations in several organ systems. It is becoming clear that much of the pathophysiology observed in CF can be linked to inadequate hydration of epithelial fluids caused by a lack of CFTR.

RESPIRATORY

Progressive obstructive airway disease leading to bronchiectasis and respiratory failure accounts for the majority of severe morbidity and mortality from CF.[111] Lung disease is known to develop after birth because the airways of infants who die with CF in the first days of life appear normal with no evidence of infection, inflammation, or significant mucus plugging.[112] Over time, the typical features of CF lung disease develop including mucus plugging of the airways, hypertrophy and hyperplasia of the secretory elements, and chronic infection, primarily with *Pseudomonas aeruginosa* and *Staphylococcus aureus*. These features generally begin in the small bronchioles and progress to the larger airways.[113] Basic pathophysiologic mechanisms that contribute to these outcomes occur at multiple levels including the airway epithelia, submucosal glands, and the response to infection and inflammation.

AIRWAY EPITHELIA

Although early studies localized CFTR predominantly to the submucosal gland,[114] more recent experiments with sensitive antibodies have clearly demonstrated that CFTR is found on the apical membrane throughout the ciliated airway epithelium, although not in alveolar cells.[115] There are also scattered cells in the airway epithelium that exhibit very high levels of CFTR, although the function of these cells is not yet understood. The role of the apically localized CFTR has been delineated by several studies on well-differentiated cultures of respiratory epithelia.[116-118] Lack of CFTR leads to a depletion of the airway surface liquid, a thin layer of fluid that lines the apical membrane of the airway epithelia.[119] The airway surface liquid is divided into two phases: an overlying mucus gel phase that sits on top of a periciliary liquid (PCL) phase that surrounds the cilia. The respiratory cilia require a sufficient depth of PCL (~7 μm) for proper function, and studies of well differentiated respiratory epithelial cultures demonstrate that healthy cells regulate apical fluid flow to maintain sufficient PCL (Fig. 61-5A). In contrast, CF respiratory epithelial cultures fail to maintain sufficient PCL, resulting in compression of cilia and a severe reduction in mucociliary transport (see Fig. 61-5B).[116]

To understand how lack of CFTR leads to depletion of the PCL, it is necessary to explore the physiologic pathways that control fluid balance in airway epithelia. The healthy airway epithelial cell generates electrochemical gradients via the sodium/potassium pump, potassium channels, and $Na^+/K^+/Cl^-$ cotransporters located on the basolateral surface of the cell (Fig. 61-6).[119] On the apical membrane, these gradients tend to favor net influx of sodium ions into the cell through the ENaC sodium channel and efflux of chloride ions out of the cell primarily through CFTR and, to a lesser extent, via calcium-activated chloride channels (CaCC). Ions can also travel through paracellular pathways to maintain electrical neutrality. Because osmotic forces favor flow of water through cellular and paracellular pathways, net influx of sodium ions leads to fluid absorption, whereas net efflux of chloride ions leads to fluid secretion. Ion transport is tightly regulated in healthy airway epithelia, balancing absorption and secretion to maintain the appropriate level of PCL. In vivo, the airway

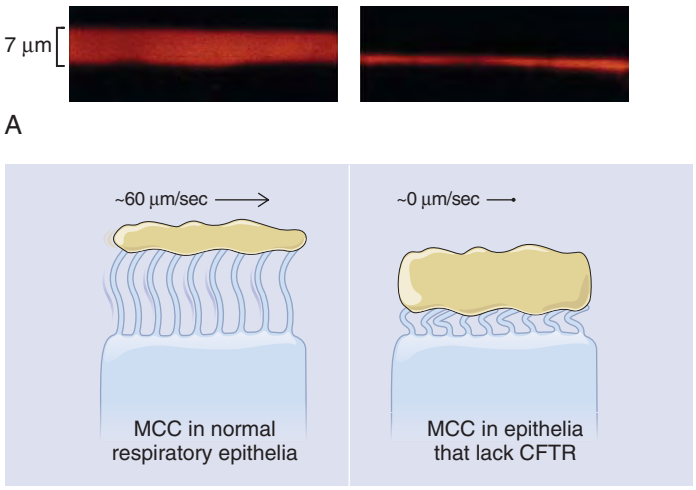


Figure 61-5 Defective airway surface liquid and mucociliary clearance in CF. A, Confocal image respiratory epithelia that express normal (*left*) or mutant (*right*) CFTR. The ASL is stained with fluorescent dye for visualization, and is notably decreased in the epithelia expressing mutant CFTR. **B,** Schematic of ciliated airway epithelial cells expressing normal (*left*) and mutant (*right*) CFTR. The normal cell has fully extended cilia and an overlying mucus layer showing typical mucociliary clearance rate of 60 μm per second (*left*). The epithelial cell with mutant CFTR has compressed cilia with increased mucus and essentially no mucociliary clearance. ASL, airway surface liquid; CFTR, cystic fibrosis transmembrane conductance regulator; MCC, mucociliary clearance. (**A,** courtesy of Brian Button, Ph.D., University of North Carolina at Chapel Hill.)

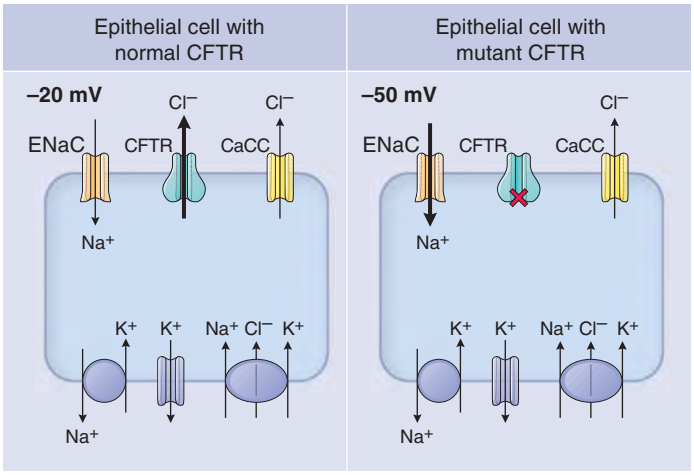


Figure 61-6 Electrochemical gradients in epithelia. Schematic of the channels and transporters responsible for regulation of ion transport in epithelial cells expressing either normal (*left*) or mutant (*right*) CFTR. In normal cells, electrochemical gradients favoring influx of sodium and efflux of chloride are generated by the actions of the basolateral sodium/potassium pump, potassium channels, and $Na^+/K^+/Cl^+$ contransporters. Chloride secretion is mediated by CFTR and, to a lesser extent, CaCC. Sodium absorption occurs through ENaC and is moderated by CFTR, and total potential difference at the apical membrane is –20 mV. Paracellular pathways for sodium and chloride (*not shown*) allow ionic balance. Cells with mutant CFTR have reduced chloride secretion and greater activity of EnaC, which increases sodium absorption. This leads to a lower potential difference of –50 mV at the apical membrane. CFTR, cystic fibrosis transmembrane conductance regulator.

epithelia is primarily absorptive, reflecting the need to absorb the bulk flow of fluid from the large surface area of the most distal airways.[120,121]

Airway epithelia that lack CFTR therefore lack the main chloride efflux pathway that leads to fluid secretion. Perhaps more significant, these cells also have upregulation of the sodium channel and therefore increased fluid absorption.[4,31] The net result is depletion of the apical fluid and hence the PCL. Depletion of the PCL results in compressed cilia and near complete loss of ciliary transport. A dehydrated mucus builds up in the airway and adheres to the epithelial surface because the normal lubricating function of the PCL is absent.[122]

The alternate chloride secretion pathway through CaCC is intact in CFTR-deficient cells, and chloride secretion through CaCC can compensate for lack of CFTR-mediated chloride secretion to some extent. These channels can be activated by the purinergic signaling pathway which involves activation of purinergic receptors by extracellular compounds such as ATP.[123] Recent evidence suggests that CaCC-mediated chloride secretion stimulated by purinergic receptors may be more active in vivo than previously believed and could account for the observation that young children with CF preserve a greater degree of mucociliary clearance than would be predicted from cell culture studies.[117] This observation is supported by promising early results from a clinical trial of an inhaled purinergic agonist.[124] However, the role of the purinergic pathway and chloride secretion through CaCC in both the pathophysiology of CF and as a treatment modality awaits confirmation from further studies.

SUBMUCOSAL GLANDS AND GOBLET CELLS

Increased mucus production is common in the CF patient, and this mucus is derived from both goblet cells and submucosal glands. Goblet cells are mucus-secreting cells that line the respiratory epithelium and typically account for ~15% of the cells. In CF, goblet cells undergo both hyperplasia (increase in cell number) and metaplasia (extension of goblet cells into the bronchioles where they do not usually occur). Similarly, submucosal glands also hypertrophy in CF. Early studies on CF focused on the abnormally thick and viscous sputum produced by patients. Although it is now understood that dehydration of extracellular fluid layers better describes the pathophysiology of CF, there are differences in mucus that may contribute to the disease phenotype. Mucus from CF patients has altered glycosylation patterns and increased sulfation.[125,126] However, these changes may reflect the presence of chronic inflammation and infection and correlate with disease severity.[127] Evaluation of mucus from cultured CF cells (presumably free from inflammation) has provided conflicting results, with increased sulfation noted in some studies but no changes in others.[128]

One of the earliest detectable abnormalities is dilation of the submucosal gland ducts in the absence of inflammation,[112] suggesting that alterations in gland secretions occur before infection and inflammation. Presumably, this dilation results from either increased gland secretion or "plugging" of the gland duct by viscous mucus secretions. Immunocytochemical studies have identified that the highest levels of CFTR expression in the lung are in the serous acini of the submucosal glands of the proximal airways (Fig. 61-7).[114]

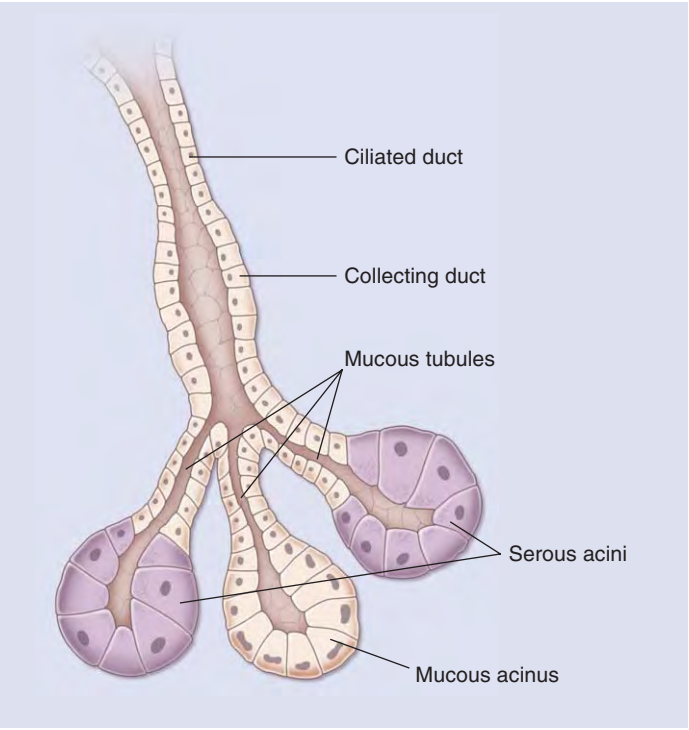


Figure 61-7 Schematic of the submucosal gland. CFTR is highly expressed in the serous acini of the gland, which aids secretion of fluid that helps flush mucus from the tubules into the collecting duct and ciliated duct. CFTR, cystic fibrosis transmembrane conductance regulator.

The serous cell secretes salt and water, and because it is located in the pole of the gland, the secreted liquid flushes mucins secreted in the mucous tubules to the gland orifice and hence to the airway surface. The electrochemical gradients that drive secretion fluid are similar to those of the airway epithelium. However, chloride secretion is mediated entirely through CFTR and is highly dependent on alteration of intracellular membrane potential by activation of basolateral membrane potassium channels. These basolateral membrane potassium channels are activated by regulatory agents such as acetylcholine that are involved in stimulation of gland secretion.[129]

Studies of gland secretions have been made possible by evolution of microanalytic techniques that permit evaluation of the secretions from a single submucosal gland. These studies demonstrate that CF gland secretions are of lower volume and higher viscosity than normal gland secretions.[130] It is currently unclear whether this represents alterations in flow from the serous cell, changes in the mucus secreted from gland goblet cells, or absorption of fluid by the glandular collecting duct or surrounding airway epithelia. Furthermore, the proximal duct of the gland contains ciliated epithelia and may experience the defects in mucociliary transport from decreases in PCL that are seen in airway epithelia. It is likely that a combination of these mechanisms accounts for the altered gland secretions seen in CF.

AIRWAY INFECTION AND INFLAMMATION

Chronic respiratory infection and elevated levels of inflammation are hallmarks of CF lung disease. The deficient secretion in airway epithelia and submucosal glands undoubtedly contributes to the infection by preventing effective clearance of bacteria out of the respiratory tract. Some studies have suggested that the salt content of the airway surface liquid is elevated in CF, which could inactivate innate defenses to bacterial infection.[131,132] However, altered ASL salt concentrations have not been demonstrated in CF patients[133] or animal models of CF.[134] There are several other factors that have been identified in CFTR-deficient respiratory epithelia that may contribute to the chronic infection and inflammation.

Patients with CF almost invariably have elevated levels of inflammatory markers such as interleukin-8,[135,136] interleukin-6, tumor necrosis factor-alpha,[137] and leukotrienes[138] in the airway. Although this is explained, in part, by the presence of chronic bacterial infection, the inflammatory response in CF is exaggerated with higher levels of proinflammatory cytokines than in non-CF patients with similar burdens of pathogens.[136] Indeed, CF epithelial cell lines produce greater amounts of IL-8 when exposed to the pathogen *Pseudomonas* than non-CF epithelia.[139] The mechanisms that underlie this greater inflammatory response are unknown. Interestingly, a transgenic mouse model that overexpresses ENaC also exhibits an increased inflammatory response,[140] suggesting that defects in ion transport may play a role in this phenomenon.

Several studies have demonstrated interactions between CF epithelia and *P. aeruginosa*, which may favor the chronic infection with this organism that occurs in most CF patients. CF epithelial cells exhibit a greater adherence to certain strains of *Pseudomonas*, which can be reduced by expression of normal CFTR.[141] CFTR may also serve as a receptor for *Pseudomonas*, permitting effective internalization and killing of this bacteria by normal, but not CF, epithelia.[142] A similar role for CFTR in the internalization of *Salmonella typhi* in intestinal epithelia has been demonstrated[143]; this may explain the high frequency of CF mutations in certain populations because internalization of *S. typhi* leads to infection and would be reduced in CFTR mutation gene carriers.[64]

Gastrointestinal

Gastrointestinal (GI) manifestations are common in CF, and pancreatic insufficiency is a nearly universal feature of the most severely affected patients.[80] In general, the pathophysiology in the GI tract is similar to that of the airway: dehydration of secretions due to lack of chloride secretion leading to build-up of thick, inspissated secretions.

PANCREAS

CFTR can be readily detected in the pancreas and has been localized to the apical membrane of the intralobular pancreatic duct.[144] The pancreas is one of the few organs in CF that is often affected at birth, with obstruction of the pancreatic duct and ductules with inspissated secretions. In fact, the eventual development of cystic changes and fibrosis in the pancreas are actually responsible for the name of the disease, which is more fully rendered as cystic fibrosis of the pancreas.[113] In addition to the blocked pancreatic ducts, the fluid secreted from the CF pancreas is not as alkaline as in healthy individuals.

The pathophysiology of pancreatic dysfunction in CF is in many ways similar to that of airway epithelia. As in the

airway, normal CFTR permits net secretion of fluid into the extracellular space based on gradients established by the sodium/potassium pump, $Na^+/K^+/Cl^-$ transporter, and potassium channels. However, a major difference between the pancreas and airway epithelia is that the predominant secreted anion is bicarbonate rather than chloride. CFTR is involved in bicarbonate secretion via two mechanisms. First, the apical surface of the pancreatic duct contains a chloride/bicarbonate anion exchanger that transports chloride secreted by CFTR into the cell in exchange for bicarbonate, leading to a net transport of bicarbonate.[38] More recent evidence suggests that CFTR itself transports significant quantities of bicarbonate under certain circumstances.[145]

Lack of CFTR leads to decreased secretion of an inadequately alkalinized fluid, dehydration of secretions, and eventual blockage of the pancreatic ducts in most patients.[80] Digestive enzymes released by the pancreas remain in the ducts, leading to inadequate digestion of intestinal nutrients and eventual destruction of the pancreatic structures causing the pathognomonic cystic and fibrotic changes. Over time, the destructive influence of the pancreatic enzymes can affect the pancreatic islet cells, leading to reduced ability to secrete insulin and CF-related diabetes,[146] which is associated with more severe pulmonary disease.[147]

INTESTINES

CFTR is found in the apical membrane throughout the small and large intestines, and is localized predominantly to the crypt cells. As with other epithelia, the fundamental defect in the CF intestine is the inability to secrete chloride ions via a cAMP-regulated mechanism. The electrochemical gradients that drive chloride secretion are similar to those in airway epithelia, but like the submucosal gland, the intestine lacks the alternative chloride efflux pathway through CaCC. In another similarity to respiratory epithelia, CFTR in the intestine appears to downregulate the activity of the sodium channel ENaC.[148] The biophysical defect of altered chloride secretion is present in colonic epithelia and can be measured in rectal biopsies using specialized equipment. Such measurements can be used to establish a diagnosis of CF, and measures of residual chloride current correlate well with phenotypic manifestations of disease.[149]

Lack of CFTR in the intestine leads to dehydration of fecal contents and intestinal obstruction. Intestinal mucus secretion is also enhanced in CF, although the mechanism is not clear. In the newborn, the thick fecal contents can block the terminal small bowel, leading to meconium ileus, a pathology that is found almost exclusively in CF. Similar pathophysiology is thought to contribute to the distal intestinal obstructive syndrome (DIOS) seen frequently in older individuals—once called "meconium ileus equivalent."

Recent evidence suggests that the CF intestine may experience enhanced inflammation and bacterial overgrowth similar to that of the airway. Increased inflammatory markers have been detected in the intestines of both CFTR-deficient mice[150] and humans.[151-153] Furthermore, evaluation of CFTR-deficient mice detected a 40-fold overgrowth of intestinal bacteria relative to controls.[154] The potential contribution of intestinal inflammation and infection to the malabsorption phenotype of CF is intriguing, but remains to be explored.

LIVER

CFTR can be detected in the biliary ducts and is thought to mediate chloride and fluid secretion. In many patients with CF, the biliary ducts are obstructed with thick secretions. As a consequence of this obstruction, a subset of CF patients develop hepatobiliary disease of varying severity ranging from asymptomatic elevation of liver enzymes to multilobular cirrhosis and portal hypertension. The factors that predispose certain patients to liver disease but leave others unaffected are currently unknown, but are under investigation.

Reproductive Tract

With few exceptions, CF males are sterile with obstructive azoospermia. The anatomic defect is absence, atrophy, or obstruction of the vas deferens as well as the tail and body of the epididymis and can be detected at birth in many infants.[155] The pathophysiologic basis for these changes is unclear. One proposed mechanism for atrophy of the vas deferens and epididymis is prenatal failure of the CF epididymis epithelium to secrete ions and water that dilate the lumens of these structures. However, a study of 12 to 18 week (gestational age) aborted CF fetuses found structurally normal vas deferens, although with some mucus accumulation in the lumen.[156] Alternatively, CFTR itself may be important for maturation of the epididymis.

Females also have decreased fertility. CFTR is expressed in the uterine epithelium, and expression in this region appears to be menstrual cycle dependent.[157] Cervical mucus in CF women is thickened. Typically, cervical submucosal glands and the endocervical canal are dilated and obstructed by mucus plugs. This viscous cervical mucus impedes sperm migration, leading to decreased fertility. Another potential mechanism is altered salt and water secretion by the oviduct epithelium. The resulting dehydration of oviduct fluid may impair migration of sperm and eggs through the oviduct.

Sweat Gland

The sweat gland is a complex structure with an acinar region that secretes an isotonic liquid and a ductal region that is functionally designed to absorb salt but not water.[158] The net effect is to deposit a dilute watery solution on the skin surface for evaporative water loss and cooling. The physiology of secretion from the acinar region is similar to that of other cells: electrochemical gradients favor secretion of chloride through the apical membrane; sodium and water follow. Both CaCC and CFTR chloride channels are present in the acinus, and these cells exhibit a secretory response to both acetylcholine (which stimulates increased intracellular calcium that activates CaCC) and, to a lesser extent, beta agonists (which stimulate increased intracellular cAMP that activates CFTR). As expected, the CFTR-mediated secretion is absent in patients with CF,[159] but total sweat volume is relatively well preserved owing to the remaining secretion through CaCC.

The sweat duct expresses significant quantities of CFTR, but differs from all previously discussed tissues of the respiratory and gastrointestinal tract in that it selectively absorbs salt but not water from the lumen (Fig. 61-8). This can be accomplished because the tight junctions of the sweat duct are not leaky as they are in other tissues, and they create a barrier to passage of ions or water through paracellular routes.

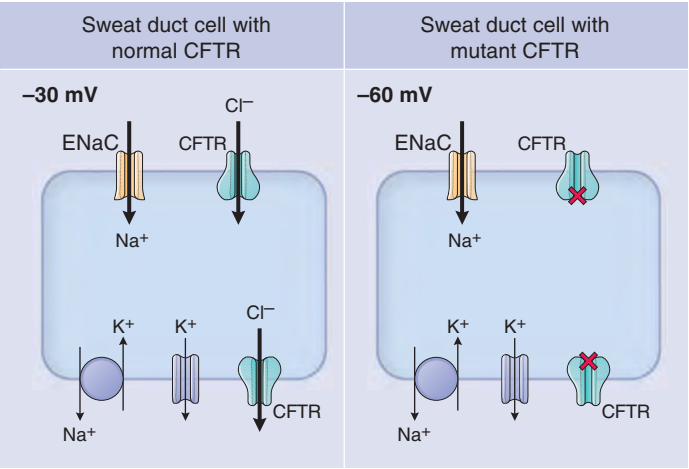


Figure 61-8 Electrochemical gradients in the sweat duct. Schematic of the sweat gland collecting duct expressing normal (*left*) or mutant (*right*) CFTR. In the normal sweat duct, the sodium/potassium pump and potassium channels generate an electrochemical gradient that favors absorption of sodium through ENaC. Chloride follows due to electrochemical forces. The lack of chloride transport in the sweat duct with mutant CFTR prevents absorption of both sodium and chloride and results in the abnormal elevations of salt in the sweat of patients with CF. CFTR, cystic fibrosis transmembrane conductance regulator.

Sodium is absorbed through ENaC in the apical membrane and is exported from the cell via a basolaterally located sodium/potassium pump. Because ductal cells lack the $Na^+/K^+/Cl^-$ cotransporters found in respiratory and gastrointestinal epithelia, there is no driving force for chloride secretion. Therefore, the active removal of sodium ions from the lumen and intracellular regions of the cell creates an electrochemical driving force for transcellular passage of chloride out of the lumen through both apical and basolateral CFTR channels. There may be an additional contribution from active absorption of chloride through the chloride/bicarbonate exchanger. In the absence of functional CFTR, chloride can no longer be absorbed from the sweat duct lumen. In addition, unlike other cell types, absence of functional CFTR leads to a *decrease* in ENaC activity, further reducing the absorption of salt from the lumen.[160] The result is a sweat content that is increased in sodium and chloride compared to that in healthy individuals.

Under usual circumstances, the increase in salt content of sweat has little physiologic consequence. However, under conditions of severe heat stress, individuals with CF are at risk for dehydration owing to excessive loss of salt and water in the sweat. Dehydration in CF infants was observed by Dr. Paul di Sant' Agnese during a heat wave in New York in the 1950s, and served as the initial recognition that sweat content may be abnormal in CF.[1] His astute observation eventually led to the development of the sweat chloride test, which continues to serve as the main diagnostic procedure for CF.

SUMMARY

Over the past half century, study of CF has elucidated significant insights into the basic physiology of epithelia and the pathophysiology of disease. More importantly, a better understanding of the genetics and disease mechanisms of CF has led to important clinical initiatives such as newborn screening programs and clinical trials of new therapeutic agents aimed at addressing basic cellular defects. Further study will no doubt elicit more scientific breakthroughs that can be translated into longer, higher quality lives for those who have CF.

PITFALLS AND CONTROVERSIES

CFTR is a member of the ABC family of membrane transporters, suggesting that it may have a transport function as well as acting as an ion channel. An ABC transporter uses energy from hydrolysis of ATP to pump a substance across the plasma membrane; in contrast, a channel serves as a pore through which substances pass due to their electrochemical gradients. Early studies suggested that CFTR may transport ATP across the plasma membrane, where it could act on purinergic receptors to regulate epithelial physiology.[48] Others have proposed that CFTR transports glutathione, which would suggest that the airways of patients with CF may have decreased tolerance to the oxidative damage normally mitigated by extracellular glutathione.[49] These findings remain controversial and not all laboratories demonstrate physiologically relevant transport activities with CFTR. Furthermore, the regulatory actions of CFTR make it difficult to distinguish a transport activity of CFTR from that of an interacting protein.

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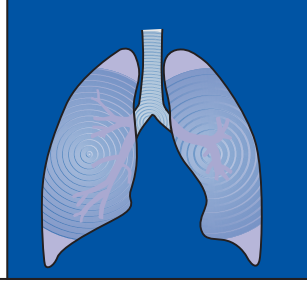

CHAPTER 62 Respiratory Manifestations

Harm A. W. M. Tiddens and Margaret Rosenfeld

TEACHING POINTS

- Structural lung damage is due primarily to a vicious cycle of bacterial infection and the host inflammatory response.
- Structural damage begins early in life, generally in the peripheral airways.
- Most structural lung damage is irreversible (what is lost is lost).
- Cystic fibrosis (CF) lung disease is the sum of the present and the past.
- Lung function measurements are relatively insensitive to structural abnormalities.
- CF care is center care.
- Cross infection of microorganisms between patients should be prevented.

Cystic fibrosis, affecting all races, is well known as the most common life-shortening inherited disease in whites. Although lung disease is still the cause of death in >80% of CF patients, survival has improved dramatically around the world over the past 3 decades: in the United States median survival increased from 14 years in 1969 to 36.8 years in 2005.

The marked improvement in CF quality of life and survival is due to improvements in nutritional management, the increasing provision of care through multidisciplinary specialized CF care centers, more aggressive use of antibiotics, and new therapeutics such as inhaled antibiotics and mucolytic agents. The adoption of newborn screening for CF by a growing number of regions is likely to add to this improving picture, as are collaborative quality improvement projects and the active investigation of many new drugs now in the CF "research pipeline."

PATHOPHYSIOLOGY OF CF LUNG DISEASE

Since the identification and cloning of the cystic fibrosis transmembrane conductance regulator (CFTR) gene in 1989,[1] great progress has been made in elucidating the pathophysiologic cascade responsible for CF lung disease. However, controversies and questions remain in our understanding of how defective or absent CFTR function promotes the chronic endobronchial infection and vigorous neutrophilic inflammation that cause the progressive structural airway damage of CF lung disease (Fig. 62-1).

The ciliated respiratory epithelium of the airways is lined with airway surface liquid (ASL), which consists of two layers, a periciliary liquid layer adjacent to the epithelial surface in which the cilia beat, and an overlying mucus layer that can be propelled by the cilia. In the normal lung, the periciliary liquid layer height and volume are tightly regulated to provide for optimal mucociliary clearance, a critical primary innate airway defense. Maintenance of an adequate periciliary liquid layer enables normal ciliary function and lubricates the high molecular weight mucins in the gel layer, whose properties are altered by water content, ion concentrations, and pH.

In the CF lung, the first step in the pathophysiologic cascade is abnormal regulation of periciliary liquid volume and possibly of ionic content caused by absent or defective CFTR function (Fig. 62-2).[2,3] Decreased periciliary liquid volume reduces mucociliary clearance by hindering ciliary beat and promoting interactions between gel layer mucins with cell-surface mucins that inhibit particle clearance.[4] Altered viscosity and regulation of submucosal gland secretion may further impair host defense. Reduced mucociliary clearance may overwhelm innate antimicrobial peptides and promote the initial endobronchial infection in CF as well as the chronic infection.

The link between the abnormal composition and mechanical properties of airway secretions in the CF lung and its propensity for chronic endobronchial bacterial infection is incompletely understood. CFTR has been proposed to be a receptor for *Pseudomonas aeruginosa* internalization.[5] Reduced *P. aeruginosa* binding to mutant CFTR could result in decreased ability of the CF lung to clear this organism, and allow for initiation of endobronchial infection. In addition, CF epithelial cells in vitro appear to have decreased sialylation of apical receptors, which may promote adherence of *P. aeruginosa* to the CF airway[6]; the in vivo relevance of this observation is unknown.

Because CFTR is expressed primarily in the airways, with particularly high expression in submucosal glands, CF lung disease is localized primarily to the airways and submucosal glands. The alveoli and interstitium are spared until the late stages of the disease. The lungs in CF patients appear histologically normal at birth.[7,8] However, endobronchial bacterial infection and the accompanying vigorous neutrophilic inflammatory response begin in infancy, often in the first several months of life.[9] Lower airway inflammation can be seen in bronchoalveolar lavage (BAL) fluid from which bacterial pathogens are simultaneously isolated or not.[10] Although inflammation in the apparent absence of infection may be due, at least in part, to regional heterogeneity of infection,

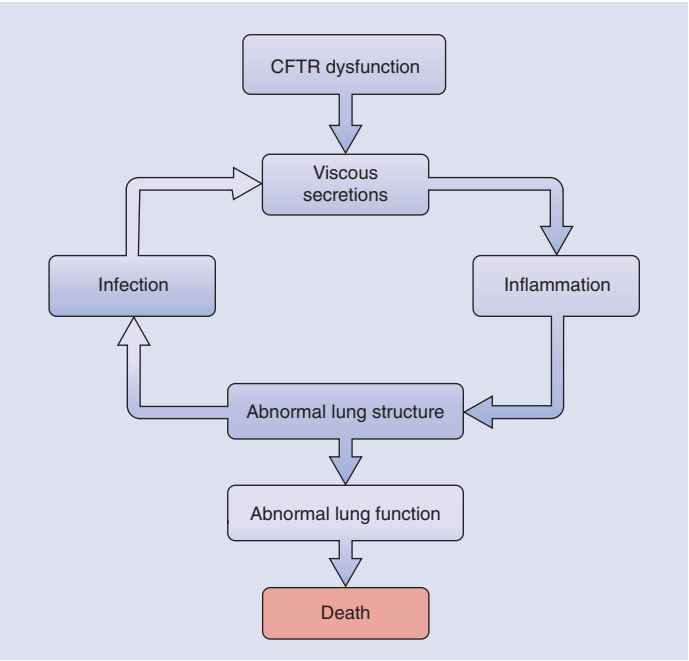

Figure 62-1 This general scheme shows the pathway from abnormalities in the CFTR protein to damage of lung tissue, which leads to impaired lung function and premature death in many patients. Note that abnormalities of lung structure are present before abnormalities in lung function are detected.

debate continues as to whether the CF respiratory epithelium may be intrinsically proinflammatory.[11] In addition, the role of viral infections in promoting airway inflammation is incompletely understood.

Neutrophils are the primary culprit in the pathogenesis of CF lung disease, releasing massive amounts of elastase and other proteases that overwhelm local host defenses including α_1-antitrypsin and secretory leukocyte protease inhibitor (SLPI) and inflicting structural airway damage.[12] This damage further impairs mucociliary transport and facilitates the attachment and growth of bacteria, particularly *Pseudomonas aeruginosa*, thus reinforcing the vicious cycle.[13-15] Dying neutrophils release large amounts of DNA that increase the viscosity of the endobronchial secretions, further reducing mucociliary clearance and promoting further bacterial infection. Interleukin-8 (IL-8), produced by epithelial cells, macrophages, and neutrophils, appears to be the critical neutrophil chemoattractant in the CF airway.[16] IL-1β, tumor necrosis factor-α, neutrophil elastase, and leukotriene B_4 also play important roles in heightening and maintaining neutrophil influx.

Chronic infection and inflammation result in airway wall thickening and plugging of bronchioles with purulent secretions, a process that appears to begin in the peripheral airways. As the disease progresses, airways become irreversibly dilated and bronchiectatic. Airway damage can display striking regional heterogeneity, with regions of advanced bronchiectasis adjacent to regions of relatively normal lung (Fig. 62-3). With advanced bronchiectasis, the lung parenchyma can become atelectatic or infected, impairing gas exchange. Chronic hypoxia may lead to pulmonary hypertension. Hypertrophy of the bronchial circulation may lead to recurrent hemoptysis.

CLINICAL PRESENTATION OF CF LUNG DISEASE

The clinical manifestations of CF lung disease are highly variable in onset, rate of progression, and severity. Within the first 6 months of life many infants develop cough, tachypnea or wheeze, often triggered or worsened by intercurrent viral respiratory infections.[17] Cough, while intermittent early in the course of the disease, eventually becomes a prominent, daily symptom, generally accompanied by expectoration of sputum beginning in early school age. CF lung disease is characterized by intermittent, recurrent episodes of increased cough and sputum production, often accompanied by a decline in pulmonary function and systemic symptoms such as anorexia and fatigue, termed a *pulmonary exacerbation.*[18] These episodes require more intensive antibiotic therapy, including intravenous therapy, if the response to oral or inhaled antibiotics is inadequate or the exacerbation is severe. Recurrent sinusitis is nearly universal and is a major source of symptoms in some patients; nasal polyposis is also a frequent finding. As disease severity progresses, patients develop progressive exercise intolerance and are at increased risk for sleep-disordered breathing. Recurrent hemoptysis may develop. As lung disease becomes severe, the burden of the daily medical regimen increases—as does the frequency of hospitalizations and intravenous antibiotics. Patients with advanced lung disease may require supplemental oxygen, particularly with sleep. Lung transplantation may be considered in patients with end-stage lung disease to potentially improve survival and quality of life. In the United States, there are about 150 lung transplantations and about 420 deaths in CF patients annually.[19]

CF RESPIRATORY MICROBIOLOGY

Early Pathogens

CF-related lung disease is characterized by a unique set of bacterial pathogens that are acquired in an age-dependent fashion (Fig. 62-4).[19] At a very early stage *Staphylococcus aureus* and *Haemophilus influenzae* are the most frequently isolated organisms. *P. aeruginosa*, the most significant pathogen in CF lung disease, is also frequently acquired in the first several years of life. In a prospective study of 40 infants from the time of diagnosis through 3 years, sequential specimens from oropharyngeal swabs and BAL fluid yielded cultures positive for *P. aeruginosa* in one third of patients by two years, and combined microbiological and serologic evidence of exposure was seen in 97.5% of patients by 3 years.[20]

The ascertainment of initial *P. aeruginosa* respiratory tract infection in CF is difficult because of the limitations of current techniques. Children younger than about 6 years of age can rarely expectorate sputum for culture. Oropharyngeal cultures are widely used as a surrogate for lower airway cultures in these patients, but have poor sensitivity and positive predictive value for lower airway *P. aeruginosa* infection.[9,21] BAL, while sampling the lower respiratory tract, is invasive and may produce false-negative results owing to regional heterogeneity of infection[22] and dilution. Measurement of serum antibodies against *P. aeruginosa* may be used to identify *P. aeruginosa* infection at an early stage.[17,23] Initially

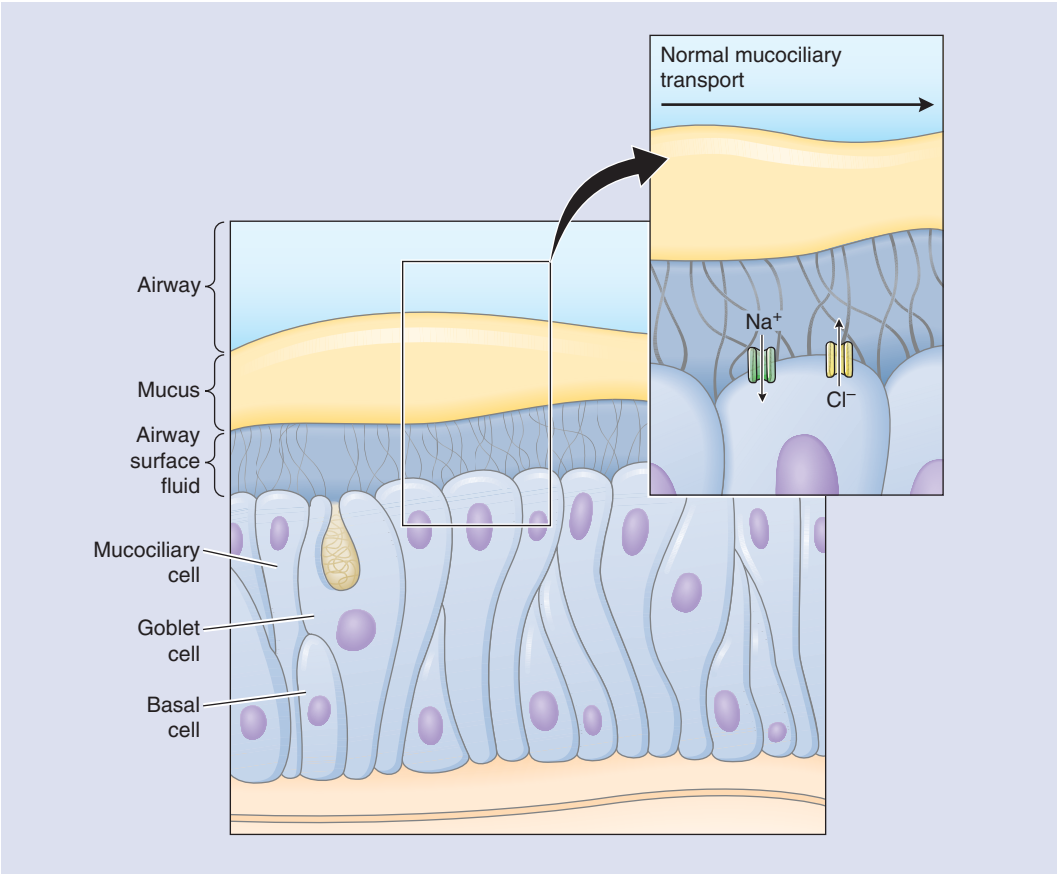

Figure 62-2 Mucociliary transport in the healthy lung: A fluid layer is maintained through a balance of chloride secretion through the CFTR channel and sodium absorption. This fluid layer covers the surface of airway epithelial cells and supports a thin mucus layer produced by mucosal secretory glands. The mucus layer is transported by respiratory cilia from the lower airways to the central airways. A defective chloride channel leads to depletion of the fluid layer and an impaired mucociliary transport. (With permission from Ratjen F: N Engl J Med 354:291-293, 2006.)

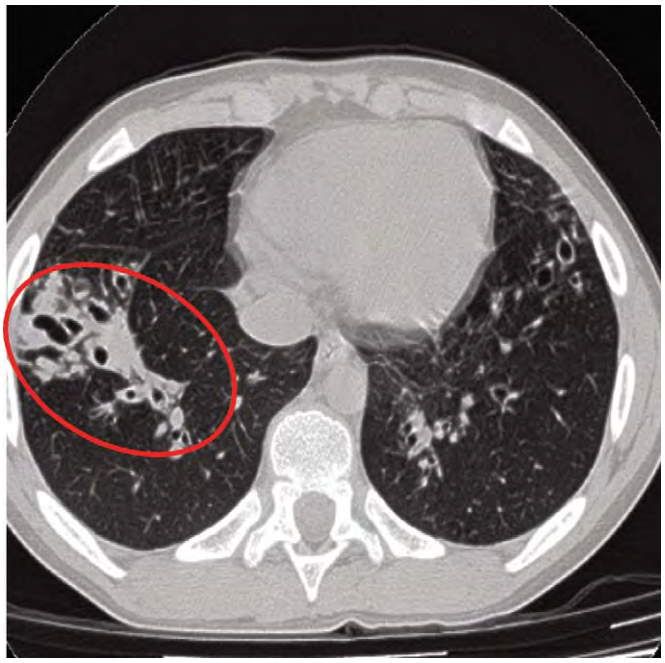

Figure 62-3 This high resolution CT image clearly shows the heterogeneity of cystic fibrosis lung disease. An area of localized end-stage lung disease (*red ellipse*) can be seen next to areas that are apparently normal.

P. aeruginosa is nonmucoid and highly antibiotic sensitive in most patients.[20] There is a window of opportunity for suppression and possible eradication of initial nonmucoid *P. aeruginosa*.[24,25] Because chronic *P. aeruginosa* infection is associated with more morbidity and a worse prognosis,[17,26-28] aggressive early *P. aeruginosa* eradication regimens have been adopted at most CF care centers. When infection persists, *P. aeruginosa* changes to a mucoid phenotype that cannot be eradicated with current treatment options.

Late Pathogens

With progression of the lung disease, antibiotic treatment in general becomes more intensive. As a result, resistant pathogens such as *Burkholderia cepacia* complex, *Stenotrophomonas maltophilia*, *Achromobacter xylosoxidans*, methicillin-resistant *S. aureus*, *Aspergillus fumigatus*, and nontuberculous mycobacteria are progressively selected.[4] The prevalence of *B. cepacia* complex varies considerably between centers.[23] Epidemic strains have been described. Some genomic species of *B. cepacia* complex are associated with the *B. cepacia* syndrome, characterized by high fever, bacteremia, and rapid progression to severe necrotizing pneumonia and high risk of death.[29] Cohort studies have not demonstrated an association between isolation of *S. maltophilia* or *A. xylosoxidans*

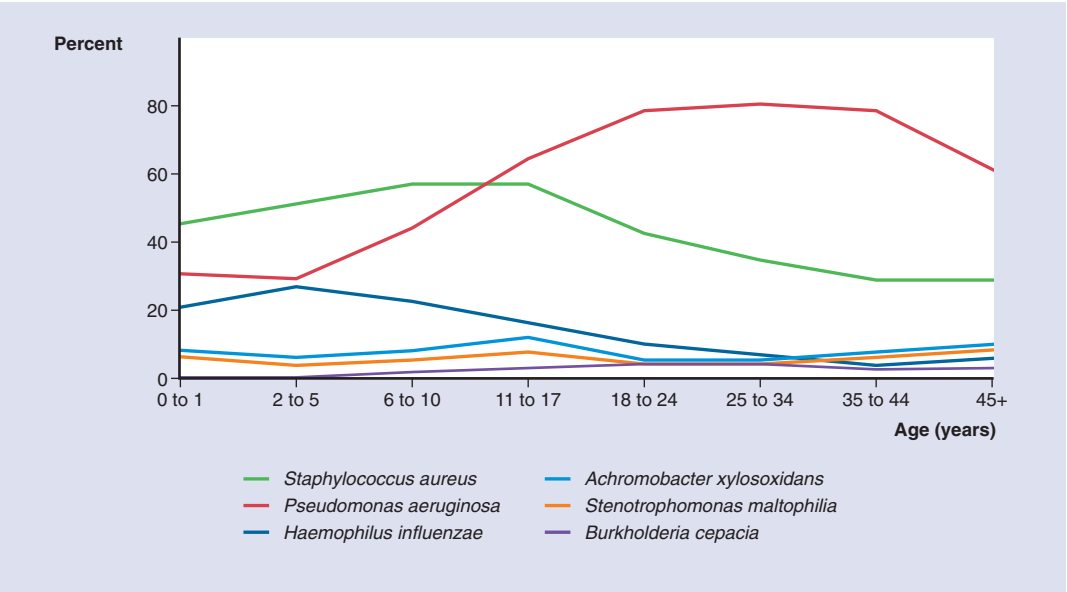

Figure 62-4 Age-specific prevalence of airway infections in patients with cystic fibrosis. Organisms reported to the U.S. Cystic Fibrosis Patient Registry, 2001. Overall percentage of patients (all ages) who had at least one respiratory tract culture (sputum, bronchoscopy, oropharyngeal, or nasal) performed in 2001 that was positive for the following organisms: *Pseudomonas aeruginosa* (*red line*), 58.7%; *Staphylococcus aureus* (*green line*), 48.0%; *Haemophilus influenzae* (*dark blue line*), 15.9%; *Stenotrophomonas maltophilia* (*orange line*), 8.4%; *Achromobacter xylosoxidans* (*light blue line*), 4.4%; *Burkholderia cepacia* (*purple line*), 3.1%. (From the Cystic Fibrosis Foundation.)

from respiratory cultures and decline in lung function.[30,31] However, in individual patients these microorganisms may contribute to the progression of lung disease.

The prevalence of *A. fumigatus* in respiratory cultures varies from 2% to 57%.[32-35] There is emerging evidence that *A. fumigatus* contributes to structural lung damage,[36] although no consensus exists to routinely treat this organism.

Some CF patients develop a specific allergic immunologic response to *A. fumigatus*, termed allergic bronchopulmonary aspergillosis (ABPA).[32,34,35] The diagnosis of ABPA is difficult in CF because many of the diagnostic criteria overlap with common manifestations of CF. The U.S. CF Foundation recently adopted a standard set of diagnostic criteria for ABPA (Box 62-1),[37] and recommended routine annual screening for ABPA through assessment of serum IgE. ABPA should be considered in the setting of an acute or subacute clinical deterioration not responsive to appropriate antibiotic therapy.

Nontuberculous mycobacteria (NTM) are environmental organisms found in soil and dust, and can be isolated from the sputum of CF patients utilizing culture techniques that inhibit overgrowth by *P. aeruginosa*. In a large, multicenter study, the overall prevalence of NTM in a pediatric and adult CF population was estimated to be 13%.[38,39] Risk factors for NTM colonization included older age and better-preserved lung function.[38,39] Allergic bronchopulmonary aspergillosis and systemic steroids also appear to be risk factors.[40] Approximately 20% of CF patients from whom NTM is cultured meet ATS microbiological criteria for NTM infection as opposed to colonization. Diagnostic criteria for NTM infection in CF include: multiple positive respiratory cultures for NTM; clinical or lung function deterioration not responsive to conventional antibiotic therapy; and CT findings of peripheral nodules of "tree in bud" appearance and/or cavitating disease.[41] Individuals with NTM infection require aggressive antimycobacterial therapy, typically with three antibiotics and often for prolonged periods. Relapse is common.

BOX 62-1 Criteria for the Diagnosis of Allergic Bronchopulmonary Aspergillosis (ABPA)

Classic criteria
- Clinical deterioration
- Immediate positive skin test or positive RAST
- IgE > 1000 kU/L
- *Aspergillus fumigatus*–positive precipitins or presence of anti–*A. fumigatus* IgG
- Altered chest radiograph

Consensus of the Cystic Fibrosis Foundation for the diagnosis of ABPA. (From Stevens DA, Moss RB, Kurup VP, et al: Allergic bronchopulmonary aspergillosis in cystic fibrosis—state of the art: Cystic Fibrosis Foundation Consensus Conference. Clin Infect Dis 37 Suppl 3:S225-S264, 2003.)

ORGANIZATION OF CF CARE

One of the major advances in CF care over the past several decades has been the development of specialized CF care centers throughout Europe, Australia, the United States, Canada, and parts of South America. The regular monitoring

and aggressive treatment that can be provided by these centers has been associated with improved outcomes.[42,43] At these centers, CF care is provided by an experienced multidisciplinary team that includes pulmonologists, nurses, social workers, nutritionists, and respiratory therapists. Other providers involved in CF center care may include a gastroenterologist, endocrinologist, otorhinolaryngologist, microbiologist, pharmacist, radiologist, and psychologist. The microbiology laboratory affiliated with each CF center is specialized in the analysis of CF respiratory specimens. Centers generally maintain a patient database for clinical care, quality improvement projects, and to identify potentially eligible research subjects for clinical trials. With the increasing life span of CF patients, separate adult care centers have now been established, to which patients transition generally between 16 and 21 years of age.

Although most *Pseudomonas aeruginosa* isolates are environmentally acquired, cross infection in the hospital is a serious risk. Outbreaks of epidemic strains of highly virulent, multidrug-resistant *P. aeruginosa* and several *Burkholderia* species have caused fatalities and rapid decline in lung function at a number of CF centers around the world.[44,45] Thus, strict infection-control policies must be maintained at centers caring for CF patients.[46,47] Infection-control policies and cohort segregation seem to be effective to reduce the spread of epidemic strains.[45] One of the most important issues is implementation of proper hand cleaning procedures and cough hygiene for all members of the CF team and for the patients.

Some clinics segregate cohorts of patients by bacterial strain. This makes the organization of the clinic complex and it does not exclude cross infection of newly acquired but undetected strains or viruses within a cohort. Other clinics have the policy of minimizing or preventing contact between patients. Clearly, these infection control policies have an important emotional impact on the lives of CF patients. Despite these negative effects, the majority of patients are in favor of infection control measures to reduce the risks of cross infection.[45]

MONITORING OF LUNG DISEASE

A standardized approach to the monitoring of CF lung disease is critical to effective treatment. Through serial respiratory cultures, lung function tests, and imaging studies, disease progression is assessed at multiple levels of the pathophysiologic cascade (Fig. 62-5). This monitoring process should ideally start at diagnosis, so that abnormalities can be detected and treated early, potentially before they become irreversible. However, monitoring is particularly challenging in infants and young children. Symptoms lag behind structural damage. Children younger than about 6 years of age generally cannot expectorate sputum for culture. Lung function tests are difficult to perform in the youngest children and are insensitive to localized or early damage.[56,57] However, infant lung function tests have shown that airway function is diminished soon after diagnosis and does not catch up during infancy and early childhood.[61,62] Imaging techniques such as CT scans are currently the most sensitive method with which to detect early structural changes, but they also carry inherent risks.

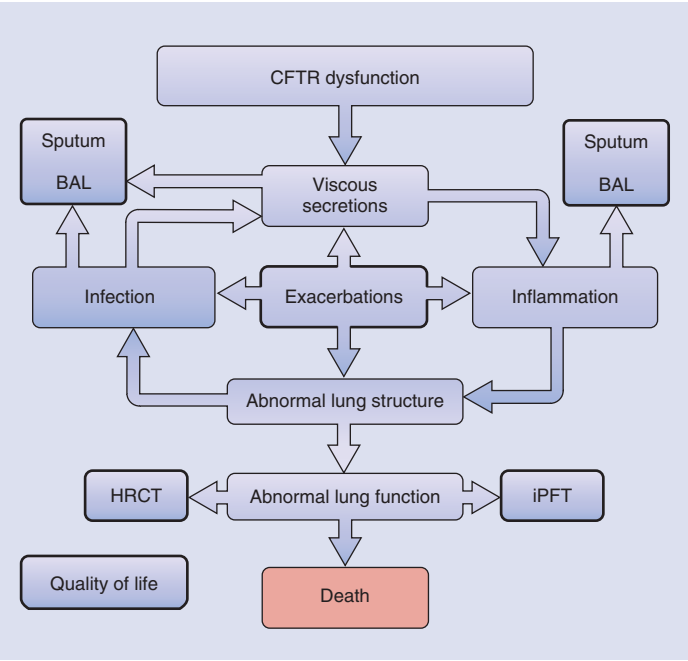

Figure 62-5 Methods to monitor cystic-fibrosis-related lung disease for clinical management. BAL, bronchoalveolar lavage; CFTR, cystic fibrosis transmembrane conductance regulator; HRCT, high-resolution computed tomography; iPFT, infant pulmonary function tests.

LUNG MICROBIOLOGY

Regular monitoring of respiratory tract cultures is needed to guide antibiotic treatment. In patients able to spontaneously expectorate, sputum serves as an adequate proxy for lower airway secretions. In pre-expectorating children, oropharyngeal cultures are often used to screen for the presence of *P. aeruginosa* and other pathogens. These cultures have good specificity but low sensitivity for lower airway *P. aeruginosa*.[48] Hence, a negative oropharyngeal culture makes lower airway infection with *P. aeruginosa* less likely, but a positive culture is not sufficient to establish the diagnosis of lower airway *P. aeruginosa* infection. Endolaryngeal suction and cough plates[49] are alternative methods for obtaining upper respiratory tract cultures but their diagnostic accuracy for lower airway organisms is unknown. Sputum induction with 6% to 7% hypertonic saline has been safely used in adults and older children with CF, but is generally not successful in children younger than 8 years of age.[50] BAL, while allowing direct sampling of lower airway secretions, is an invasive procedure that cannot be repeated frequently. Hence, as a method to detect early *P. aeruginosa* infection, it is of limited use. A diagnostic bronchoscopy should be considered in non-expectorating patients with newly acquired auscultatory findings and/or symptoms that persist despite antibiotic treatment.

LUNG FUNCTION

Lung function has been considered the standard for monitoring the pulmonary condition of CF patients for decades. Spirometry repeated at each outpatient visit is valuable to identify trends, detect acute changes in lung function, and monitor response to therapy (Fig. 62-6). From 6 years of age, most children are able to perform a flow-volume maneuver

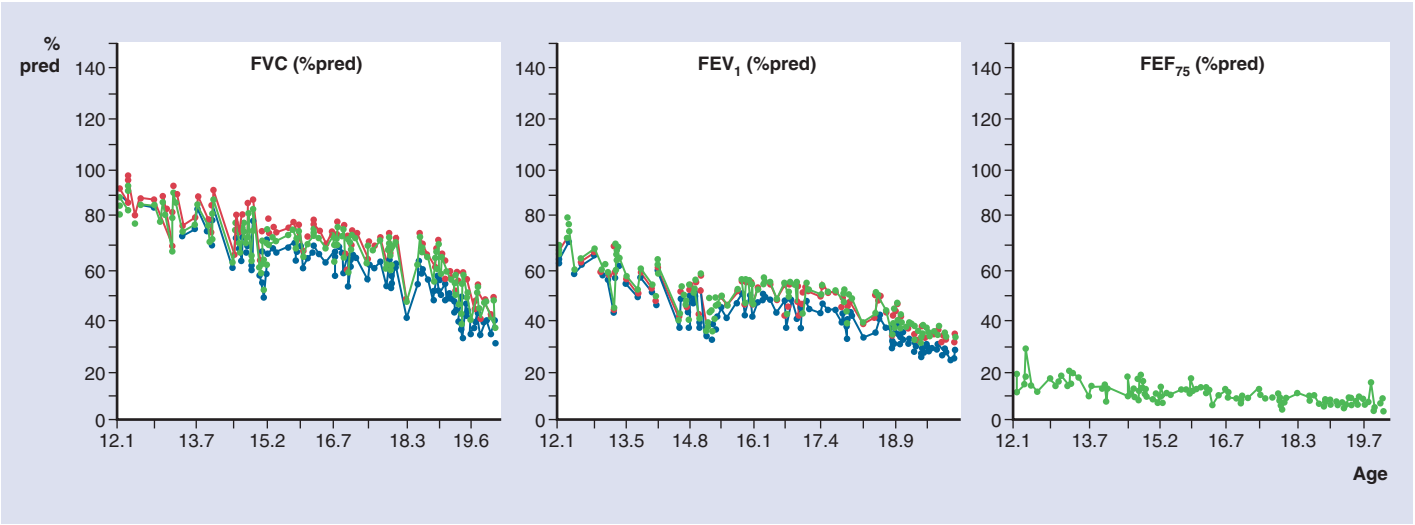

Figure 62-6 Longitudinal plot of FVC, FEV_1 and FEF_{75}% predicted versus age of a cystic fibrosis patient who progressed to end stage lung disease for three commonly used sets of reference equations.[182-184] At the age of 12 years the FEF_{75}% predicted is substantially and consistently reduced, whereas FVC is still in the lower normal range and FEV_1 is in the intermediate range. These curves are indicative of early and irreversible abnormalities in the peripheral airways that precede more central airway changes. In addition, note the negative trend of the FVC, FEV_1 curves that reflect progressive deterioration of the lungs. Also note the more frequent data points (clinic visits) and dips in the curves related to pulmonary exacerbations that required extra antibiotic treatment. FEF, forced expiratory flow; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity.

in a reproducible fashion. At that age, dynamic flow-volume parameters such as FVC and FEV_1 are mostly in the normal range. The first changes that can be observed in lung function are reduced peripheral flows such as the FEF_{25-75}, FEF_{50}, and FEF_{75} (Fig. 62-7).[51] These peripheral flows are more variable than FEV_1 and FVC because they are influenced by a large number of small airways.[52,53] The importance of peripheral airway involvement in CF was supported by cross-sectional data from the European Epidemiologic Registry of Cystic Fibrosis, which showed that the FEF_{25-75} is the first lung function parameter to decline with age and parallels the decline in FEV_1 and FVC in patients with or without a history of *P. aeruginosa* isolation.[51] Many CF patients show bronchodilator responsiveness of FEV_1 and the peripheral flows. This finding of airway hyperreactivity in a CF patient does not necessarily equal the diagnosis of asthma. Such improved flows can be explained by smooth muscle relaxation in combination with thickening of the airway walls.

Routine monitoring of lung function would ideally begin in infancy. Unfortunately, lung function measurements in children younger than 5 to 6 years of age remain problematic. In infants younger than 3 years of age, adult-type spirometry and lung volume measurements can now be obtained,[54,55] but they require sedation, expensive specialized equipment and training, and are time consuming.[56,57] In children 3 to 6 years of age, too old for sedated infant lung function testing yet too young to cooperate with spirometry, the best method for monitoring airway obstruction is not established. Specific airway resistance measured with a body plethysmograph may be most sensitive to early changes in CF but again requires specialized equipment and training.[58] Spirometry can be successfully performed by the majority of preschool children using modified acceptability criteria,[59,60] but the sensitivity of these measurements to early CF lung disease is not known. For these reasons, lung function measurements in young children are not done routinely in most CF centers.

Repeated lung function testing in young children with CF shows persistent decreased flows.[61,62] Hence, airway function is diminished soon after diagnosis in infants with CF and does not catch up during infancy and early childhood. More recently, gas washout techniques have been used in CF to determine the homogeneity of ventilation distribution. Substantial inhomogeneity was observed in the majority of young children with CF even in the presence of normal lung function as judged by spirometry.[63,64] Multiple-breath inert gas washout was considered of greater value than spirometry to detect early cystic fibrosis lung disease . Although gas washout techniques appear promising for the detection and monitoring of early CF lung disease, currently no standardized, com-

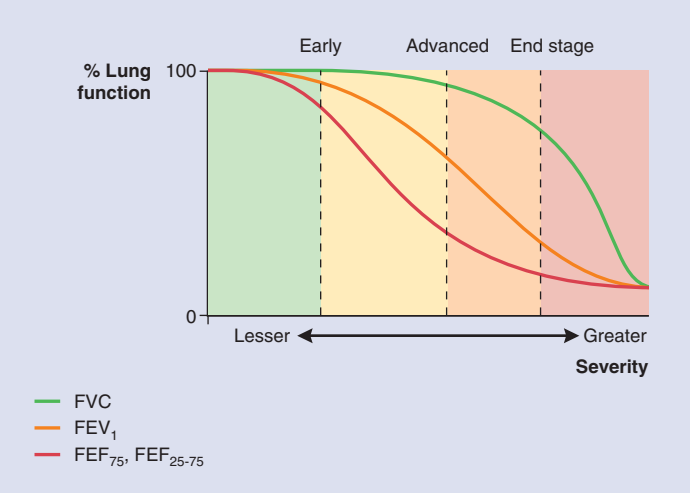

Figure 62-7 This theoretical plot shows the relation between various lung function parameters on the vertical axis and disease severity on the horizontal axis. (Based on Tiddens HAWM: Detecting early structural lung damage in cystic fibrosis. Pediatr Pulmonol Suppl 34:228-231, 2002.)

mercially available device exists with which to perform these measurements.

In the late 1980s, lung function parameters such as the FEV_1 and FVC were sensitive parameters to monitor CF-related lung disease because the annual loss in lung function was high.[65] With improved therapy, the rate of decline in lung function has steadily improved in many centers and now approaches 1% per year for FEV_1 in many cohorts.[36,66] This low annual rate of decline in lung function combined with the variability of flow volume parameters implies that lung function has become a relatively insensitive tool to monitor CF lung disease.

For clinical management it is important to realize that there can be a considerable discrepancy between lung function and structure (Fig. 62-8), the most striking being structural damage in lungs of patients with normal lung function. Such patients can have mild, moderate, and even severe structural lung disease. About one third of the patients with an FEV_1 above 85% in a Dutch cohort followed longitudinally showed substantial damage on the CT scan.[36] With disease progression, eventually structural lung changes will result in functional abnormalities.

Lung function testing has the major advantage that it is readily available, relatively inexpensive, and that it does not require radiation. It will remain an important tool as long as one realizes that it does not give the complete picture of lung abnormalities.

LUNG STRUCTURE

The result of the vicious circle of infection, inflammation, and viscous pulmonary secretions is structural lung damage. The most sensitive technique to monitor structural changes in CF is chest CT.[67] In patients 6 years and older it has been estimated that CT is about 10 times as sensitive as lung function parameters for detecting progression of CF lung disease.[68] On chest radiographs, it is often not possible to identify the nature of increased markings. Furthermore, chest radiographs are relatively insensitive for detecting important structural changes such as bronchiectasis. The identification of structural abnormalities on CT is, in general, straightforward and often the nature of the structural abnormality can be readily identified. The two CT techniques that can be used for the evaluation of CF lung disease are high-resolution CT (HRCT)

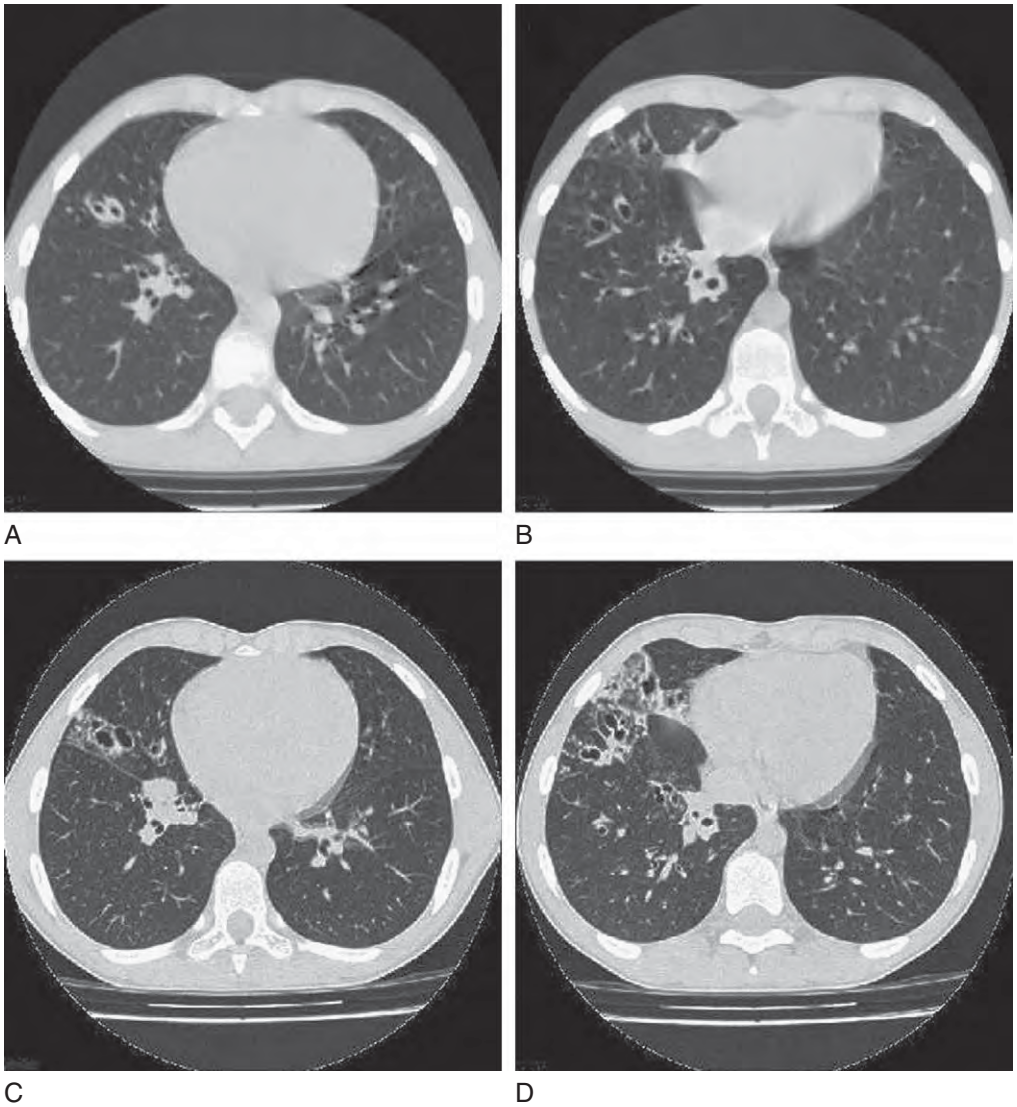

Figure 62-8 Patient with cystic fibrosis with improvement of lung function but deterioration of lung structure. The top panels (**A** and **B**) show high-resolution computed tomography (HRCT) scan in a patient of 10 years of age. Lung function (% predicted) is as follows: forced expiratory volume in 1 second (FEV_1) of 86, forced vital capacity (FVC) of 93, forced mid-expiratory flow (FEF_{25-75}) of 80, and FEV_1/FVC of 80. The lower panels (**C** and **D**) show HRCT images at 13 years of age. Lung function (% predicted) at time of CT was: FEV_1 96, FVC 91, FEF_{25-75} 105, and FEV_1/FVC 90. Note the inhomogeneity of the lung abnormalities. (Reprinted with permission from de Jong PA, Nakano Y, Lequin MH, et al: Progressive damage on high-resolution computed tomography despite stable lung function in CF. Eur Respir J 23:93-97, 2004.)

and volumetric, or spiral, CT. HRCT uses thin sections (<2 mm) obtained at intervals through the lungs, which limits the radiation exposure of the patient.[62] A volumetric CT images the whole lung and is considered the optimal technique for longitudinal evaluation and for quantitative analysis such as the airway wall thickness. Furthermore, a volumetric CT is faster than HRCT but it exposes the patient to more radiation. The most striking structural abnormality in the CF lung is bronchiectasis, which is an irreversible change that can be observed early in life (Fig. 62-9). In longitudinal studies that followed the pulmonary status of CF patients with computed tomography (CT), bronchiectasis was generally irreversible (Fig. 62-10).[68] The lungs of CF patients with end-stage lung disease contain a large number of bronchiectatic airways, reflecting the sum of structural damage that occurred in previous years. Bronchiectatic airways are reservoirs of large quantities of bacteria, inflammatory mediators, and DNA released from the nuclei of decomposed neutrophils. The presence of bronchiectasis is likely to result in damage to adjacent healthy areas of the lung. In patients with

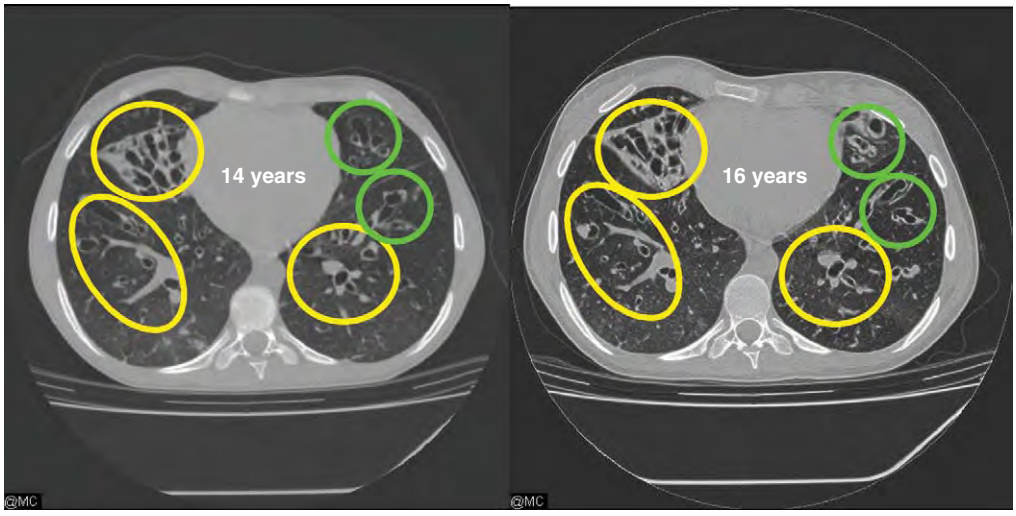

Figure 62-9 These CT scans are of a girl with cystic fibrosis (ΔF508, ΔF508 mutation) and advanced lung disease who was 14 years old when the first CT was made and 16 when the second CT was made. FEV_1 and FVC were 53% and 56% at time of first CT and 58% and 74% at time of second CT. Note that most of the bronchiectatic airways in the *yellow circles* visible on the 1st CT are still present on the 2nd CT. The areas enclosed by the *green circles* have progressed slightly. FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity.

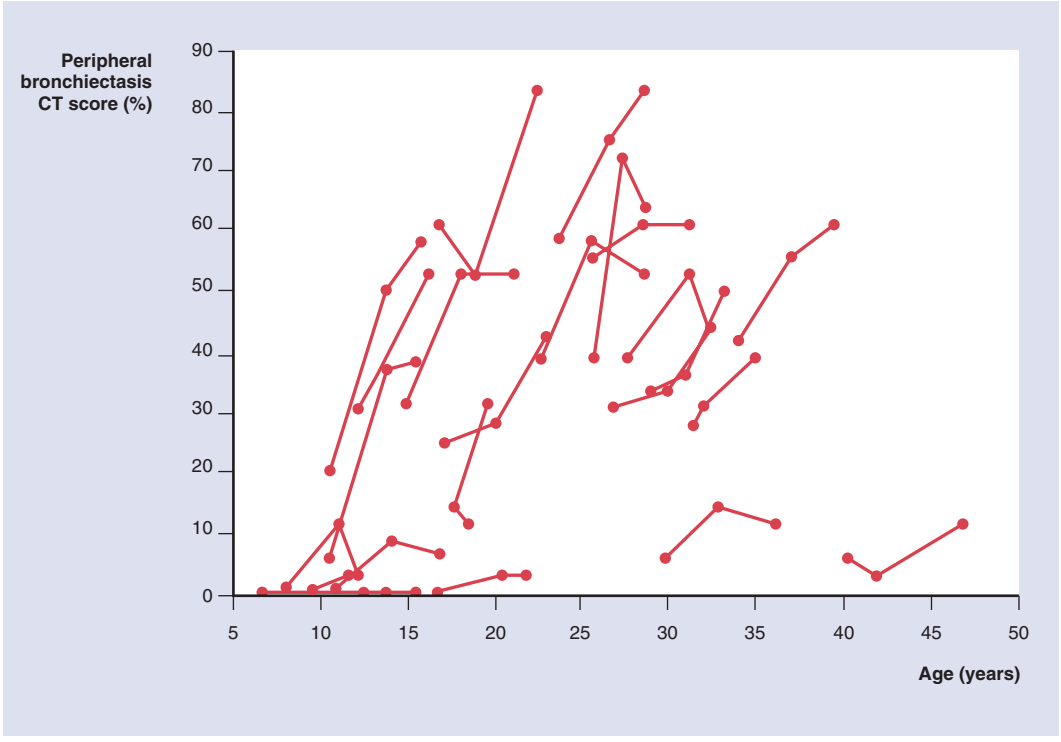

Figure 62-10 Changes in the peripheral bronchiectasis CT score over 6 years in 24 patients who had three CT evaluations. Most of the 24 patients had a stable FEV_1 over the 6 years, whereas the peripheral bronchiectasis CT score showed the expected disease progression. FEV_1, forced expiratory volume in 1 second. (Reprinted from de Jong PA, Lindblad A, Rubin L, et al: Progression of lung disease on computed tomography and pulmonary function tests in children and adults with cystic fibrosis. Thorax 61:80-85, 2006.)

chronic obstructive pulmonary disease (COPD), the presence of bronchiectasis correlates with quality of life. It is likely the same is true for CF.

Another important structural change in CF detectable by CT is airway wall thickening. This thickening is present early in the disease process and more severe in the peripheral airways. In lung tissue obtained from CF patients undergoing pneumectomy for lung transplantation, airways were up to threefold thicker relative to airways of smokers undergoing lobectomy for a lung tumor. Importantly, in both groups of patients but particularly in CF, the inflammatory process and geometric changes were more severe in the peripheral than in the central airways.[14] Indeed, airway wall thickening in CF patients with end-stage lung disease is as severe as in asthma patients who died from acute status asthmaticus.[69] In other pulmonary diseases such as COPD and asthma, airway wall thickening is proportional to the severity of the airway inflammation.[70] Clearly, airway wall thickening is an important feature of lung disease in CF.

Thickened central airways can be identified on CT scans. Thickening of peripheral airways smaller than 1 mm cannot be directly identified. However, on expiratory scans, trapped air can be observed as darkened areas (Fig. 62-11). Because of airway wall thickening and mucus impaction, small airways close at a volume above residual volume. Airway wall thickening and areas of trapped air can be observed early in the disease process and seem to be reproducible over time, suggesting irreversibility of the structural changes causing the defects.[71,72]

CT studies reveal that the lung pathology in CF is inhomogeneous. Normal areas can be adjacent to areas with end-stage lung disease (see Figs. 62-3 and 62-8). Although CT is a sensitive technique to identify structural lung abnormalities and to monitor disease progression, it must be used judiciously because of radiation exposure and expense. The cancer risks associated with radiation exposure are cumulative, so lifelong exposure should be limited to the technical minimum. The radiation exposure for each study should be minimized by utilizing settings adapted to the size of the child. The number of lifelong examinations should be monitored and minimized. In a number of CF centers, a CT scan is performed every second or third year to monitor disease progression.[68] The radiation burden of this strategy is considered to be acceptable.[73] It is likely that the radiation dose used for chest CT can be further reduced in the near future and that magnetic resonance imaging will, at some point, allow further reduction of the number of CT scans.

Because many children show considerable structural abnormalities by the age of 4 to 5 years, it seems to be appropriate to perform the first CT scan at an earlier age. This can be done under sedation using the controlled ventilation technique.[74] With this technique the radiation dose can be reduced and the development of atelectasis can be avoided. Alternatively, in slightly older children with modern scanners, a CT scan of the lung can be made during spontaneous respiration. To reduce the radiation dose, some investigators have reduced the number of images to 4 to 6 at predefined anatomic positions.[74] This approach could be important

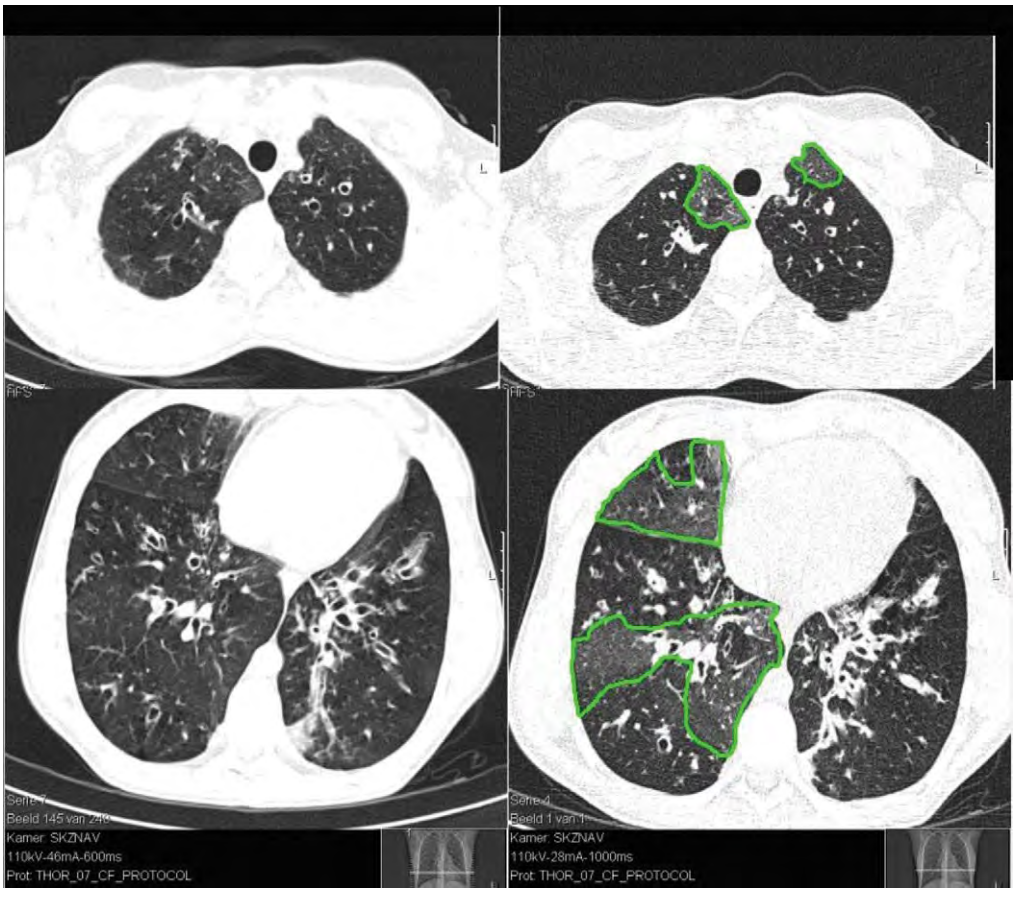

Figure 62-11 The left two images are selected from a volumetric chest CT examination in inspiration. The two images on the right are taken at identical levels after exhalation. The areas encircled in *green* show an increased density relative to the inflation images. Most of the other areas show near identical density indicating trapped air. Note in addition a barrel-shaped chest. The large anterior posterior diameter is larger relative to the side-to-side diameter.

especially for young children who are known to be more sensitive to radiation. A disadvantage of this approach is that it substantially reduces the sensitivity of CT to detect localized structural abnormalities.[73] In young children substantial abnormalities can be observed, such as thickened airway walls, narrowed airway lumens, bronchiectasis, and air trapping.[71]

Modern imaging techniques such as CT can play an important role in estimating the severity of CF lung disease starting at an early stage of the disease. Unfortunately its use is limited by radiation exposure. Newer tools such as MRI can hopefully be developed to visualize relevant structural changes with sufficient precision.

TREATMENT OF CF LUNG DISEASE

The primary aim of therapy is to preserve the normal architecture of the lung and to prevent any damage from occurring. This is important because most structural lung damage, such as bronchiectasis, is irreversible and cannot be restored. Because chronic airway inflammation and infection start in infancy, treatment should ideally start at that age. Unfortunately, many CF therapies have not been tested in infants and young children, so their safety and efficacy in this age range is unknown. Treatment must be lifelong, and ensuring lifelong adherence to the often burdensome treatment regimen is the major challenge of the CF team and the patient.

Therapy can be directed at various levels of the disease process (see Fig. 62-1). Some of these therapies are in active clinical use, whereas others are in development. Gene therapy is the most rational form of therapy; unfortunately, it is also the most challenging.[75-77] In the field of gene therapy an increased understanding of vector biology and host interaction has led to the development of novel strategies to enhance the efficiency and selectivity of gene delivery to the lung. Although significant challenges remain, there is now a realistic prospect of a clinically effective treatment in the next 10 years. For today's treatment, it is key to keep in mind that gene therapy will not be able to reverse structural abnormalities such as bronchiectasis. Hence, even if at some point a cure for the basic defect in CF becomes available, a patient with bronchiectasis will remain a bronchiectasis patient for life.

The next level of therapies is directed toward restoring normal tonicity and ion content of airway surface liquid and improving impaired mucociliary clearance. Potentiator and corrector therapies aimed at partially restoring CFTR function are in the drug discovery pipeline—as are therapies aimed at decreasing sodium absorption through the epithelial sodium channel (ENaC) or increasing chloride efflux through alternate chloride channels. Recombinant human DNase is a mainstay of CF therapies, and hypertonic saline is coming into more widespread use.

At the next level, chronic airway infection and inflammation are major challenges. Fortunately, major steps forward have been made in the understanding of antibiotic treatment strategies in CF. In contrast anti-inflammatory treatment is largely unexplored territory. Only a few studies have been performed on the effect of anti-inflammatory treatment on relevant end points. The various therapeutic modalities will be addressed subsequently.

Antibiotics

Antibiotic treatment in CF is prescribed for four general indications: to prevent the infection by a certain microorganism; to eradicate a microorganism at an early stage of an infection; to suppress the growth of a microorganism that is chronically present in the airways; or to treat a pulmonary exacerbation.

The antibiotics can be administered orally, by inhalation, or intravenously. The oral route offers the advantages of ease of administration and systemic absorption, allowing the drug to reach poorly ventilated areas of the lung that may not be reached by the inhaled route. However, the oral route also introduces some disadvantages, the most important of which is the unpredictable gastrointestinal absorption of some drugs in CF and interaction with food.[78] A second disadvantage is that the maximal dose is often limited by gastrointestinal side effects. When tissue levels are below the minimal inhibitory concentration (MIC), resistance is more likely to occur. Exposure of the GI tract to the antibiotic changes the composition of gut flora and may induce antibiotic resistance in intestinal organisms. In addition, adherence to oral antibiotic regimens may be challenging for drugs that require exact timing in relation to meals or, in young children, for drugs that have an unpleasant taste. Many patients develop symptoms such as diarrhea and growth of *Candida*.

Although more time-consuming than oral administration, inhalation of antibiotics allows delivery of high concentrations to the site of infection with minimal systemic absorption. When antibiotics are nebulized, a filter on the expiration port of the nebulizer is needed to prevent contamination of the environment by the exhaled antibiotic. An inhaled antibiotic should be delivered with the nebulizer and compressor with which use of the drug has been approved. An alternative nebulizer should be used only when approved by the regulatory agencies after proper registration studies.

Patients with CF frequently require intravenous (IV) antibiotics for treatment of pulmonary exacerbations, which are episodic increases in respiratory signs and symptoms characterized by increased cough, increased sputum production, poor appetite, reduced exercise tolerance, and a decline in lung function parameters.[79] The doses of antibiotics that can be given through the IV route are in general much higher compared to the oral route.

In patients requiring frequent courses of IV antibiotics, placement of a totally implantable venous access device (TIVAD) should be considered. Up to one third of the total population of adult CF patients has a TIVAD at some time in their lives.[80] The average lifetime of a TIVAD ranges from 440 to 1429 days.[80-83] TIVAD-related complications occur in 1 in 1065 to 2059 catheter days and in up to one third of the patients with a TIVAD, and can range from minor to severe (Table 62-1).[80] The most common complication is thrombosis—either surrounding the catheter or adherent to the vein.

Prophylactic Antibiotics

The effect of prophylactic treatment has primarily been investigated for anti-staphylococcal treatment early in life in a limited number of randomized controlled studies.[105] Anti-

Table 62-1
Complications of Totally Implantable Venous Access Device

Variables	Number of Complications	Catheter Use Complications/Days
Thrombosis	0.185/1000 catheter days	1/5405
Infection	0.119/1000 catheter days	1/ 8403
Mechanical problem	0.079/1000 catheter days	1/12658
Superior vena cava syndrome	0.026/1000 catheter days	1/38461
Air embolism	0.013/1000 catheter days	1/76923
Pneumothorax	3.4% of catheter placements	—

Adapted from Aitken ML, Tonelli MR: Complications of indwelling catheters in cystic fibrosis: A 10-year review. Chest 118(6):1598-1602, 2000.

staphylococcal antibiotic treatment leads to fewer children having isolates of *Staphylococcus aureus*, when commenced early in infancy and continued up to 6 years of age. Whether this strategy leads to improved outcome is unclear. In addition, whether long-term anti-staphylococcal prophylactic treatment leads to increased acquisition of *P. aeruginosa* infection is still a matter of debate. It has been suggested that anti-staphylococcal treatment from diagnosis up to the age of 3 years is effective and safe.[105]

P. AERUGINOSA, FIRST INFECTION

Initial *P. aeruginosa* isolates are generally nonmucoid, highly susceptible to antibiotics, and present at low density.[84] These features suggest a "window of opportunity" for early intervention with antipseudomonal antibiotics in an attempt to delay or prevent chronic *P. aeruginosa* infection. Over time, the distinct microenvironment in the CF airways allows selection of *P. aeruginosa* uniquely adapted for chronic, persistent infection. These organisms are mucoid, become increasingly antibiotic-resistant, are present at high density, and are virtually impossible to eradicate. Chronic *P. aeruginosa* infection is clearly associated with poorer clinical outcomes among CF patients.[28,85-88] Thus, early eradication regimens have gained widespread acceptance. Clinical trials have demonstrated a clear microbiologic treatment effect of antipseudomonal therapy at the time of early *P. aeruginosa* infection,[24,25,89,90] but there has been minimal evaluation of clinical outcomes or emergence of resistant *P. aeruginosa* or new pathogens associated with aggressive early intervention.

The ideal regimen for eradication needs to be further established. In studies of limited size, it has been shown that nebulization of 300 mg tobramycin for inhalation twice daily was highly effective in eradicating *P. aeruginosa*.[25] Alternatively nebulization of 80 mg tobramycin twice daily for 1 year or 3 weeks or 3 months of oral ciprofloxacin combined with nebulized colistin seems to be effective as well.[24,89,91]

P. AERUGINOSA, CHRONIC INFECTION

Nebulized antibiotics have become the cornerstone of treatment of chronic *P. aeruginosa* infection. Intermittent maintenance therapy with 300 mg tobramycin for inhalation twice daily for patients with chronic *Pseudomonas* infection has been shown to be an efficacious and safe strategy to improve lung function, reduce exacerbation rate, and improve quality of life.[92-94] Importantly, this strategy does not seem to induce major resistance problems.[95] An increase in fungal organisms (*Candida albicans* and *Aspergillus* species) during prolonged intermittent treatment with tobramycin for inhalation was observed. The improvement in FEV_1 during tobramycin for inhalation treatment was slightly less for patients where *Aspergillus* was present in their sputum.[20] Tobramycin inhalation is labeled to be nebulized by a Pari LC Plus nebulizer combined with a Pulmo Aide or comparable compressor.

Colistin is another nebulized antibiotic that is frequently prescribed for maintenance therapy against *Pseudomonas*.[91] Limited comparative data suggest that colistin is less effective than tobramycin for inhalation in preserving lung function of patients chronically infected with *P. aeruginosa*.[96,97]

The effectiveness of long-term maintenance therapy with colistin in relation to a specific aerosol delivery system has been less well documented.[98,99] Because of the lack of proper registration studies, colistin is not registered for nebulization in CF in many countries. Technically colistin can be nebulized using a Pari LC star or Hudson updraft II.[100] There have been reports of airflow obstruction and chest tightness with colistin inhalation both in adults and children.[101,102] Symptoms can be reduced by inhaling a bronchodilator prior to the colistin inhalation.

EXACERBATIONS

Clinically, CF lung disease is characterized by episodic increases in respiratory symptoms such as cough and sputum production, often accompanied by systemic symptoms such as weight loss, anorexia, and fatigue.[18] Pulmonary exacerbations are changes in respiratory signs and symptoms from the patient's baseline necessitating treatment. Although pulmonary exacerbations are a prominent feature of CF lung disease, no standardized definition exists, so the presence of an exacerbation remains essentially a clinical diagnosis. Table 62-2 shows the odds ratio for the association of clinical characteristics with the presence of a pulmonary exacerbation in a large cohort of CF-patients.[79] Treatment of a pulmonary exacerbation generally includes antibiotics and increased airway clearance. Antibiotics are generally chosen based on the antimicrobial susceptibility pattern of isolates from a recent respiratory culture.

Patients chronically infected with *P. aeruginosa* with a mild pulmonary exacerbation may be treated with a course of oral ciprofloxacin. It possesses excellent bactericidal activity against *P. aeruginosa* and may be additive when used in combination with aminoglycosides such as tobramycin for inhalation. In addition, it has an excellent oral absorption and

Table 62-2
Odds Ratio for Association of Clinical Characteristics with the Presence of a Pulmonary Exacerbation*

Characteristics	Odds Ratio
PATIENT HISTORY	
Increased cough	24.5
Increased sputum production or chest congestion	24.5
Decreased exercise tolerance or dyspnea with exertion	22.4
Increased fatigue	15.2
Decreased appetite	15.2
Increased respiratory rate or dyspnea at rest	14.1
Change in sputum appearance	11.4
Fever	5.9
School or work absenteeism	5.6
Increased nasal congestion or drainage	4.6
PHYSICAL FINDINGS AND PULMONARY FUNCTION	
Retractions or use of accessory muscles	12.9
Pharyngitis	5.8
Cyanosis	4.7
Wheeze, crackles, or ronchi on auscultation	4.3
Rhinitis	2.4
Weight loss ≥1 kg over past month	2.1
Decline in FEV_1 > 10% over past month	2.7

*In univariate analyses among 246 cystic fibrosis patients.
FEV_1, forced expiratory volume in 1 second.
Data from Rosenfeld M, Emerson J, Williams-Warren J, et al: Defining a pulmonary exacerbation in cystic fibrosis. J Pediatr 139(3):359-365, 2001.

bioavailability in airway secretions. Early clinical studies of ciprofloxacin monotherapy in adults with CF experiencing pulmonary exacerbations demonstrated improved pulmonary function in some cases comparable with intravenous antibiotics.[103] Emergence of *P. aeruginosa* and *S. aureus* resistant to ciprofloxacin and other quinolones is a concern and is associated with monotherapy for more than 3 to 4 weeks.

More severe pulmonary exacerbations in chronically *P. aeruginosa*–infected patients are generally treated with a combination of an aminoglycoside and a beta-lactam antibiotic to achieve synergistic antibacterial activity.[104] Once-daily aminoglycoside dosing appears to provide equivalent efficacy and safety in CF patients compared to three times daily dosing, and even decreased risk of nephrotoxicity in young children.[105] Because CF patients have more rapid clearance of many antibiotics, particularly aminoglycosides,[106] drug levels must be carefully monitored. It must be emphasized that antibiotic therapy for a pulmonary exacerbation in patients chronically infected with *P. aeruginosa* decreases the endobronchial burden of *P. aeruginosa* but cannot completely eradicate the organism. Unfortunately, there is a poor correlation, if any, between the choice of antibiotic based on antimicrobial susceptibility patterns and clinical response.[107,108] The value of susceptibility testing in the selection process for antibiotics is, therefore, not clear but currently our best option.

The effect of treatment can be evaluated using serial lung function testing, oxygen saturation profile, weight gain, sputum volume, and feeling of well-being by the patient. The aim of therapy is to recover the lung function to the personal best in the year before the admission. Typically, patients are treated with intravenous antibiotics for 2 to 3 weeks, which in the majority of patients is the time after which a plateau in improvement in lung function is observed.[109] In patients failing to respond to appropriate antibiotics, additional pathogens such as nontuberculous mycobacteria should be considered, screening should be undertaken for allergic bronchopulmonary aspergillosis, and complications such as atelectasis or pneumothorax should be evaluated.

With increasing use of long intravenous catheters coupled with greater availability of drug delivery services, greater numbers of CF patients are treated with intravenous antibiotics at home. A few small studies have compared the efficacy of treating exacerbations at home versus treatment by hospitalization, with conflicting results.[110,111] However, most studies have found significant cost savings and important psychosocial benefits for the patients and the family when treated at home.[112] Of course, careful patient selection is of prime importance.

Improving Mucociliary Clearance

Mucociliary clearance is severely impaired in CF owing to abnormal tonicity and composition of the epithelial lining fluid and the presence of large quantities of free DNA. Therapeutic options to improve mucociliary clearance are airway clearance techniques and various inhaled therapies.

AIRWAY CLEARANCE TECHNIQUES

Airway clearance techniques aimed at augmenting clearance of viscous lower airway secretions is a cornerstone of CF care at all ages. A range of techniques is employed, including passive techniques requiring the assistance of a second individual (manual percussion, postural drainage, autogenic drainage) and active and passive techniques providing patients more autonomy (positive expiratory pressure [PEP] mask, Flutter, Acapella, and high frequency chest wall oscillating vests). Although airway clearance techniques have been demonstrated in small studies to have short-term effects on increasing mucus transport and lung function,[113] there is surprisingly little evidence from randomized controlled trials regarding longer-term clinical efficacy.[114-116] Furthermore, it is unclear which technique is most effective because well-designed comparative studies are lacking.[115-117] Therefore, the selection of the most appropriate technique can be determined primarily by the preference of the patient. Clearly, the patient is most likely to adhere to a technique that fits best in his or her daily life. In general, patients prefer self-administered airway clearance techniques. A small pilot study demonstrated equivalent short-term efficacy of high frequency chest wall oscillation and conventional percussion with postural drainage,[118] but published larger controlled studies are lacking. Physical exercise is thought to be an effective form of physiotherapy that may be equally effective as other physiotherapy techniques.

RhDNase

Bronchiectatic airways in lungs of CF patients are reservoirs of large quantities of bacteria, inflammatory mediators, and DNA released from the nuclei of decomposed neutrophils. Bronchoalveolar lavage fluid from CF infants has increased free elastase, elevated neutrophil counts, and interleukin-8 levels and elevated DNA concentrations.[9] DNA levels are 3 to 5 times higher than in subjects without CF and tend to be higher in older patients. Recombinant human RhDNase I

(RhDNase) improves mucociliary clearance by hydrolyzing extracellular DNA present in elevated levels in lower airway secretions.[119] Large multicenter placebo-controlled trials have shown that maintenance treatment with nebulized RhDNase delivered by Pulmo-Aide or Portaneb compressor and Hudson T-Updraft II or Sidestream nebulizer improves lung function, and reduces the exacerbation rate.[120,121] In a large-scale 2-year placebo-controlled study in children between 6 and 10 years of age with well-preserved lung function (mean FEV_1 96% predicted and mean FEF_{25-75}, 85% predicted), FEV_1 improved by 3% and FEF_{25-75} by 8% compared to placebo. This study was the first to demonstrate the importance of the peripheral airways in CF.

RhDNase should be delivered to the patient with a jet-nebulizer as used in these studies. There are indications that administration of RhDNase by a compressor-nebulizer combination that delivers a high output rate and low medium particle size is more effective.[122] However, this should be further investigated in well-designed studies of sufficient size. RhDNase should not be mixed in the nebulizer with any other drugs. As many patients nebulize RhDNase before physiotherapy as followed by physiotherapy.[123] However, there are studies that suggest that nebulization of RhDNase followed by physiotherapy improves efficacy.[124,125] The optimal relation between inhalation of RhDNase and physiotherapy should be discussed with each patient.

Bronchoscopic instillation of RhDNase has been advocated for the treatment of lobar atelectasis that persists after intravenous antibiotics and physiotherapy.[126,127] Persistent atelectasis is associated with a poorer prognosis and, thus, every attempt should be made to reverse the atelectasis. Direct instillation of 2.5 mg RhDNase in 10 mL normal saline has effectively been used to mobilize large quantities of mucopurulent secretions from the obstructed bronchus and to expand the atelectatic lobe.[126,127]

Hypertonic Saline

Through osmotic forces, hypertonic saline may increase the volume of airway surface liquid, restore mucus clearance, and improve lung function. In patients with cystic fibrosis, inhalation of hypertonic saline produced a sustained acceleration of mucus clearance and improved lung function. This treatment may protect the lung from insults that reduce mucus clearance and produce lung disease.[128-130] In addition, it has been shown in a large randomized controlled study of 48 weeks' duration that nebulization twice daily of 4 mL NaCl 7% after inhalation of a bronchodilator resulted in a moderate improvement of lung function (FVC, and FEV1) and in a reduced exacerbation rate.[131] Importantly, this effect was in addition to the effect of RhDNase, which was used by 36% of study subjects. In a cross-over study, it was shown that hypertonic saline was inferior to RhDNase in terms of improving lung function.[132] The nebulizer system used in this trial was a Pari Proneb Turbo compressor and PariLC plus nebulizer.

Other Mucolytics

In some countries mucolytics such as *N*-acetylcysteine are still used on a large scale. The effectiveness in relation to a specific delivery system of inhaled *N*-acetylcysteine for CF patients has not been investigated in sufficiently large trials with relevant end points.[133] Hence, at present there is no evidence supporting the use of mucolytics such as *N*-acetylcysteine in cystic fibrosis. Other mucolytics, such as mannitol and heparin, are in development to be used in CF.[134,135]

Anti-inflammatory Therapy

Airway disease in CF is characterized by a continuous cycle of chronic infection and inflammation dominated by a neutrophilic infiltrate. This inflammation, which starts early in life, is characterized by the increased production of proinflammatory cytokines in the airways.[9,21,136] The relation between the abnormal CFTR gene product and the development of inflammation and progression of lung disease in CF is not fully understood.[137] The exaggerated immune response is the rationale for treatment with anti-inflammatory agents. However, it is unclear how far the inflammatory response can be dampened without progressing toward serious infection. The most important trials to date with anti-inflammatory agents were done with orally administered drugs such as prednisone, ibuprofen, and azithromycin.[138-140] Interestingly, treatment with these drugs improved lung function in CF. However, oral treatment with prednisone was associated with severe side effects. Oral treatment with ibuprofen is effective at slowing decline in lung function but is considered to be burdensome by some patients because blood levels need to be monitored regularly and consistent timing of doses is required. Short term (6-month) studies with azithromycin showed improvement in lung function and a decline in the rate of pulmonary exacerbations.[140] It is not clear whether the observed improvements are primarily the result of anti-inflammatory, antibiotic, or of a more systemic effect. However, in general, it is thought that long-term data are needed to determine the safety and effectiveness of azithromycin when used chronically for more than 6 months. The use of azithromycin is associated with a substantial increase in resistance to *Staphylococcus aureus* and *Haemophilus influenzae*.[141] Inhalation of corticosteroids is a popular alternative for anti-inflammatory therapy in CF.[123] Unfortunately, there is no evidence to support the widespread prescription of inhaled corticosteroids because conclusive long-term studies on the efficacy of inhaled corticosteroids are lacking.[142] A recent large-scale study demonstrated that in most CF patients receiving maintenance inhaled corticosteroids, this medication could be withdrawn without significant changes in lung function or exacerbation rate.[143]

Clearly, inhaled corticosteroids should be prescribed in patients who suffer from asthma-like symptoms, although the diagnosis of asthma is difficult to make in CF. When treatment of inhaled corticosteroids is indicated, this can best be prescribed by pressurized metered dose inhaler (pMDI)–spacer or with a breath actuated pMDI. Most available dry powder inhalers (DPIs) used for inhaled corticosteroids show flow dependency of aerosol characteristics for inspiratory flows between 30 and 60 L/minute. Many CF patients are not able to generate inspiratory flows of 60 L/minute or higher.[144] Suboptimal flows not only reduce the output of drug from the DPI but also increase particle size. This is

not desirable because larger particles have a low probability of reaching the peripheral airways, where most pathology is localized in CF. When inhaled corticosteroids are prescribed, they should be inhaled after chest physiotherapy to limit impaction in the central airways and avoid immediate clearance from the lungs by the clearance techniques. After inhalation, the patient should rinse his/her mouth to reduce the risk of oral candidiasis. New anti-inflammatory drugs are being tested in clinical trials and might open this therapeutic area.

Bronchodilators

Many CF patients are routinely treated with bronchodilators.[123] However, similar to inhaled corticosteroids, there is very little evidence to support this widespread use.[145] Some studies have shown that lung function of CF patients improves after inhalation of bronchodilators.[146] Furthermore, it has been suggested in a limited study that the daily use of salbutamol reduces the number of exacerbations and the decline in lung function.[147] However, some CF patients experience a paradoxical drop in lung function after inhalation of bronchodilators.[148,149] This might be caused by a reduced stability of central airways during a forced expiration.[150] Furthermore, the use of β_2-sympathomimetics increases the metabolic rate.[151,152] Based on the limited data on the effectiveness of bronchodilators on relevant end points and their possible negative effects in CF, it seems wise to restrict their use.[145] Bronchodilators can be used for those patients who show substantial reversibility of airflow obstruction after inhalation of bronchodilators and who report relief of symptoms after inhalation. In addition, bronchodilators are used prior to the inhalation of drugs such as colistin and hypertonic saline that are known to cause bronchial obstruction. This kind of obstruction can be the result of bronchial smooth muscle shortening but also of inflammatory changes of the airway wall. For CF patients who need bronchodilators, it makes sense to prescribe long-acting β_2-sympathomimetics.[153] The delivery device of first choice is a pMDI-spacer or a breath-actuated pMDI for reasons discussed earlier.

MANAGING THE THERAPEUTIC PACKAGE

Fortunately, many new treatment modalities are currently in development. With new treatments, however, comes the need to make future choices between modalities. Ideally these decisions would be based on the results of comparative studies, but it is unlikely that such studies will be conducted because of their considerable expense. Nonetheless, new therapies cannot be endlessly added to the existing therapeutic package. The more complicated and time-consuming daily therapies are for a CF patient, the more likely it is that adherence will decrease and mistakes will be made . The total therapeutic package of a CF patient should be critically evaluated at least annually. The aim should be to select a therapeutic package that is acceptable for the patient and that will obtain a maximal short- and long-term effect. The selection of drugs in this package should first of all be based on evidence-based medicine. Fortunately, the number of high quality studies of sufficient sample size and correct design is

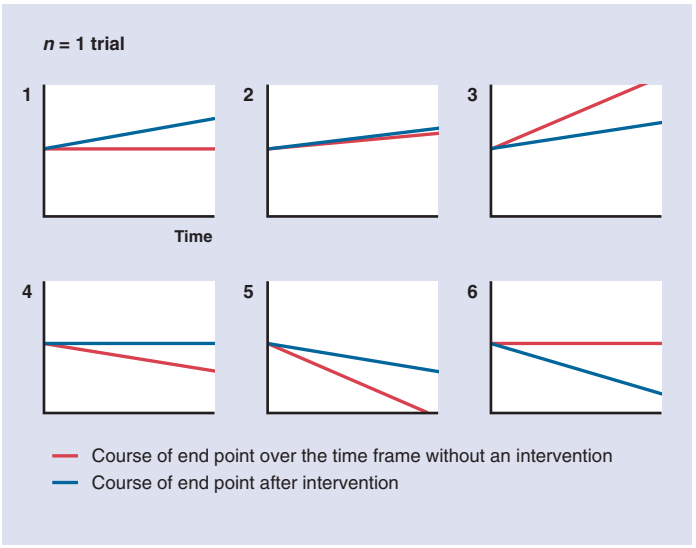

Figure 62-12 The *red line* represents the natural course of an end point (such as lung function) over the time frame of a hypothetical intervention. The *blue line* represents the course of the end point after the hypothetical intervention. In reality, the natural course of the disease for an individual patient over the time frame of the intervention is unknown. In panels 1, 2, and 3 the clinician might have concluded that there was a positive response to the intervention, whereas in panels 4, 5, and 6 the response would have been interpreted as poor or even negative. In reality, the response in panels 1, 4, and 5 is positive, whereas for panels 2, 3, and 6 the response is poor or even negative.

on the rise.[154,155] Some physicians use the $n = 1$ study to determine the effect of a new treatment modality in a single patient. The usefulness of this approach is limited because it can only be used when the natural course of the disease is known for the observational period. Unfortunately, for CF this will seldom be the case because the natural course of disease is highly variable (Fig. 62-12).

CF therapies are time-consuming. The most time-consuming treatments are nebulized medications. A patient treated with daily nebulization of RhDNase, and twice-daily tobramycin for inhalation is spending up to 60 minutes a day on nebulizer therapy. The use of these systems should, therefore, be restricted to drugs with proven efficacy. Regular maintenance of nebulizer devices and critical evaluation of the technical skills of the patients is crucial to optimize efficacy, to reduce the risks of aerosol therapy, and to avoid waste of patient time and resources. For each drug and each administration, the time relation between inhalation of the drug and physiotherapy should be reviewed with the patient on a regular basis.[123]

ADVANCED LUNG DISEASE

CF patients generally slowly progress to more advanced lung disease (see Fig. 62-6). Lungs of such patients are highly abnormal (Fig. 62-13). The damage that can be observed represents the sum of lifelong chronic infection and inflammation and of recurrent exacerbations. Most of the structural abnormalities that can be observed on the CT scan of such patients are irreversible. The clinical condition of such patients is in general characterized by increased work of breathing, expectoration of large quantities of sputum, weight

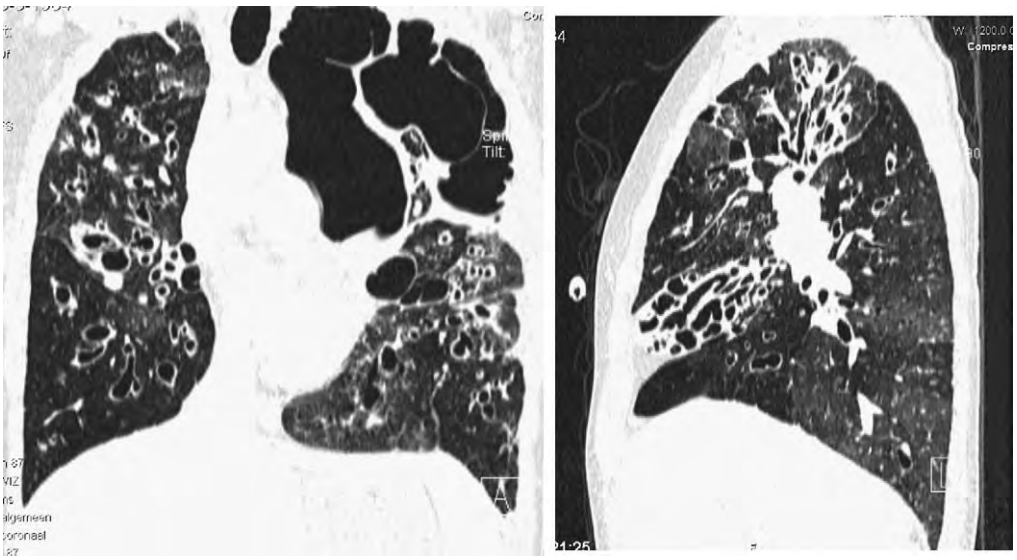

Figure 62-13 End-stage lung disease in a 23-year-old patient. Hardly any normal tissue is available. Note the large bullae in the left upper lobe. Note the extensive areas with bronchiectasis. In the right lower lobe, dark areas are visible compressing the rest of the left lung. These areas are hypoperfused and contain trapped air.

loss, and reduced exercise tolerance. These patients are at increased risk of complications such as hemoptysis and pneumothorax. Therapy in these patients becomes more intensive because any worsening of the pulmonary condition leads to noticeable reduction in ability to conduct activities of daily living.

Hemoptysis

Hemoptysis is defined as expectoration of blood in sputum. Mild hemoptysis, characterized by blood-tinged sputum, is not uncommon when infection and inflammation in a patient becomes more severe, and generally responds to antibiotics. In a large retrospective observational cohort study it was estimated that the annual incidence of hemoptysis was 0.87% and occurred in 4.1% of patients overall. Moderate or massive hemoptysis was more prevalent in older patients with a mean age of around 24 years.[156] In addition, it was more prevalent in patients with a FEV_1 below 40% predicted. Other principal risk factors associated with an increased occurrence of moderate to severe hemoptysis included the presence of *S. aureus* in sputum cultures, and diabetes. Following moderate to severe hemoptysis there is an increased morbidity and an increased 2-year mortality rate. Most cases of hemoptysis can be handled conservatively.[156] In the case of massive life-threatening hemoptysis, bronchial artery embolization should be considered. This procedure has a high success rate for short-term control of bleeding. However, more than one half of the patients require repeated embolization during long-term follow-up.[157]

Pneumothorax

Pneumothorax is a serious complication in CF patients. Spontaneous pneumothorax is a complication that is reported commonly in older patients with CF. In a large retrospective observational cohort study it was estimated that the annual incidence was in the order of 0.64% and in 3.4% of patients overall. Pneumothorax was more prevalent in older patients with a mean age of 21.9 years. In addition, it was more prevalent in patients with severe pulmonary impairment. Almost 75% of pneumothoraces occurred in patients with FEV_1 of below 40% predicted. Other risk factors that were associated with an increased occurrence of pneumothorax were the presence of *P. aeruginosa*, *Burkholderia cepacia*, or *Aspergillus*, enteral tube feeding, pancreatic insufficiency, allergic bronchopulmonary aspergillosis, and massive hemoptysis. Following pneumothorax, there is an increased morbidity and an increased 2-year mortality rate.[158]

MANAGEMENT OF ADVANCED LUNG DISEASE

Oxygen

Hypoxia during sleep and exercise may occur in CF patients with more advanced lung disease. These patients are likely to have reduced exercise tolerance, poor sleep quality, reduced quality of life, and eventually may develop pulmonary hypertension. It seems logical to treat these patients with oxygen therapy. Unfortunately, only a few studies have evaluated the effectiveness of various forms of oxygen therapy.[159,160] Only one randomized controlled trial evaluated the effect of nocturnal oxygen therapy on clinical end points.[161] The authors concluded that nocturnal oxygen treatment in CF did not appear to affect mortality rates, frequency of hospitalizations, or the progression of disease. However, school and work attendance was maintained in the oxygen group but deteriorated in the placebo group. They recommended that oxygen use should be instituted only after the development of symptoms of hypoxia.

There is no clear-cut definition of hypoxia in CF.[159] It is well recognized that patients with a resting awake SaO_2 below 93% have significant nocturnal desaturation. However, one third of patients with a SaO_2 above 93% became hypoxic at night.[162] One of the definitions used to define sleep hypoxia is when a nocturnal SaO_2 is observed below 93% for more than 25% of the study time. Other studies have selected a mean SaO_2 of below 95%. Exercise-induced arterial hypoxia

in children has been defined as a fall in SaO_2 during exercise of 4% or over from baseline. Hypoxia is reported to occur more frequently during sleep than with exercise, suggesting that for screening purposes a nocturnal SaO_2 profile might be appropriate. Because of this lack of randomized controlled trials, the indication for oxygen therapy is somewhat arbitrary. In the American consensus guideline it is recommended that night-time oxygen therapy is indicated for adults when SaO_2 is below 88% to 90% for 10% or more of the time and oxygen during exercise if SaO_2 falls below 88% to 90% during exercise.[158] There is evidence of modest enhancement of exercise capacity and duration with oxygen supplementation, especially in individuals with more advanced lung disease.[160,163] In a meta-analysis it was concluded by the authors that oxygen therapy should be reserved for those individuals with objective evidence of hypoxemia, either at rest while awake or during either exercise or sleep.[160] Short-term oxygen therapy during sleep and exercise improves oxygenation but is associated with modest and probably clinically inconsequential hypercapnia. Attention to blood gas analysis is warranted in individuals with advanced lung disease and chronic hypercapnia.

The introduction of oxygen therapy suggests a decline in the pulmonary condition of the patient and adds substantially to the daily therapeutic burden. Introduction of oxygen should ideally be done when the patient is motivated and convinced of the potential benefit of such therapy. Clearly, introducing oxygen therapy in the home situation requires quite some organization (Box 62-2). When the initial flow to the patient is below 0.3 L/minute oxygen can be delivered by cylinders. For higher flows an oxygen concentrator is preferred with back-up portable cylinders for breakdowns and for ambulatory use.[164] Many countries have guidelines for home oxygen programs. Flying and holidays at high altitudes expose a CF patient to a reduced inspired oxygen pressure. For a patient with severely impaired lung function this can result in a reduced oxygen saturation and increased work of breathing. From the literature, it is not clear when in-flight oxygen is required or when a holiday at high altitude should be discouraged.[165] Some authors suggest testing the patient with a 20-minute inhalation of a test-mixture of 15% oxygen and nitrogen.[166-168] Others suggest that preflight spirometric tests are a better predictor of desaturation during flight than the preflight hypoxic challenge.[169] If oxygen is required it is important that arrangements with the airline are made well in advance.

BOX 62-2 Requirements for Home Oxygen Therapy in CF

Instruction and support:
- Adequate training and written instructions on safe use of oxygen in home environment
- Round-the-clock technical and medical support in place

Equipment:
- Oxygen cylinders that can be used for flow rates ≤0.3 L/minute
- Oxygen concentrators are usually preferred for flow rates of ≥0.3 L/minute
- Back-up lightweight cylinders for breakdown and ambulatory use
- Humidification system for flows ≥1 L/minute for nasal comfort
- Appropriately-sized soft twin prong nasal cannulas
- In case of use of wheelchair consider cylinder fitting

Based on Balfour-Lynn IM, Primhak RA, Shaw BN: Home oxygen for children: Who, how and when? Thorax 60(1):76-81, 2005.

Physiotherapy of Advanced Lung Disease

Many patients with advanced lung disease have difficulty keeping up with physiotherapy. When the daily production of sputum exceeds the capacity of the patient to expectorate, the patient will deteriorate. It is important to consider that such an imbalance might be developing in a deteriorating patient, and to consider more aggressive support by a physiotherapist or a change in airway clearance technique. If a patient requires intubation and mechanical ventilation for reversible respiratory failure, regular bronchoscopic sessions should be considered to eliminate amounts of sputum comparable to that which the patient was mobilizing before intubation.

Noninvasive Ventilation

For patients with chronic respiratory failure, noninvasive positive pressure ventilation should be considered as supportive therapy. It was shown in patients with daytime hypercapnia ($PaCO_2 > 6$ kPa [45 mm Hg]) and/or symptoms of nocturnal hypoventilation that noninvasive positive pressure ventilation was effective to reduce the work of breathing and in improving gas exchange.[170,171] Because introduction of this therapy requires some time for patient training, it should be considered before the occurrence of acute respiratory failure in patients screened for lung transplantation. For patients who develop acute respiratory failure, invasive mechanical ventilation should be seriously considered because about one half of the patients survive such an intervention.[172] It has been suggested that for CF patients listed for lung transplantation, those requiring short-term mechanical ventilation for respiratory failure have outcomes similar to those who do not require invasive ventilatory support before lung transplantation.[173]

Lung Transplantation

Lung transplantation is a viable option for the treatment of end-stage lung disease in CF.[174] Although models capable of clearly predicting short-term survival in CF are lacking,[175,176] referral criteria have been established and are shown in Box 62-3. Survival of CF patients after transplantation is similar to that of recipients with other pulmonary diseases. Approximately one half of the patients are still alive 4 years after transplantation.[177,178] In most countries there are long waiting lists for a lung transplant owing to the relative shortage of donor lungs. In other countries, about one half of the CF patients listed for transplant actually die waiting for donor organs.[179] In Austria and Belgium with "presumed-consent" donor legislation, rates of heart and lung donation are at least

BOX 62-3 Lung Transplant Referral Criteria

Progressive pulmonary function impairment manifest by $FEV_1 \leq 30\%$ predicted, severe hypoxemia, and hypercarbia

Rapid fall in FEV_1 despite optimal medical management; resting arterial blood gas analysis while breathing room air showing a $PaCO_2$ of >50 mm Hg or a PaO_2 of <55 mm Hg

Increasing functional impairment, evidenced by increasing frequency and duration of hospital treatment for pulmonary exacerbation, and increasing cachexia

Major life-threatening pulmonary complications, such as recurrent massive hemoptysis

Increasing antibiotic resistance of bacteria infecting the lung

Data based on Yankaskas JR, Mallory GB Jr: Lung transplantation in cystic fibrosis: Consensus conference statement. Chest 113(1):217-226, 1998; Glanville AR, Estenne M: Indications, patient selection and timing of referral for lung transplantation. Eur Respir J 22(5):845-852, 2003.

twice as high compared to similar countries with an "explicit consent" legislation. Hence, the waiting times in these countries are lower.[180]

The leading causes of morbidity after lung transplantation for cystic fibrosis are pulmonary bacterial infection and opportunistic infections. Bronchiolitis obliterans develops in more than one half of lung transplant recipients who survive for more than 3 years and is the major cause of death in the late post-transplantation period.[178]

CONCLUSIONS

CF lung inflammation is early, sustained, and severe.[181] The same is true for lung damage. The peripheral airways are involved early in the disease process. Most lung damage is irreversible. The lung condition should be monitored by frequent microbiological sampling, lung function testing, and by lung imaging. Patients should be examined frequently to detect and treat progression of disease at an early stage. Hence, early treatment is focused on prevention. Treatment of more advanced lung disease is focused on maintaining the condition of the lung at the most optimal level and halting disease progression.

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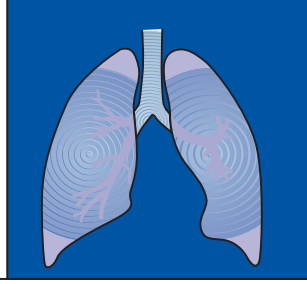

CHAPTER 63 Other Clinical Manifestations

Philip Robinson

TEACHING POINTS

- Cystic fibrosis (CF) is a multisystem condition.
- 90% of persons with CF have pancreatic insufficiency requiring treatment.
- CF may produce clinical symptoms in many body systems including the gastrointestinal tract, hepatobiliary tract, the reproductive system, endocrine system, and cardiac system, as well as the lung.
- Complications from some of these manifestations such as diabetes may have direct influences on patient survival.

PANCREATIC EXOCRINE INSUFFICIENCY

Pathophysiology

Exocrine pancreatic insufficiency occurs to a sufficient degree to produce clinical malabsorption in approximately 90% of patients with cystic fibrosis (CF).[1]

While the exocrine insufficiency results in inefficient digestion and absorption of all three of the major food groups, Fletcher noted over 60 years ago that "of the 3 important ferments normally present in the secretion of the pancreas it would seem that particularly in children the lipase steapsin is the one most liable to show variations in its functional activity as the result of disease of the pancreas."[2]

In patients with pancreatic insufficiency, the pancreas is shrunken and shows marked fibrosis, fatty replacement, and cyst formation.[3,4] Stenosis and atresia of large pancreatic ducts have been reported but, in general, pancreatic lesions are caused by obstruction of small ducts by inspissated secretions. Imrie and others have shown that this obstruction commences in utero, resulting in periductal inflammation, fibrosis, and loss of exocrine function.[3,5,6] Hypoplasia and eventually necrosis of ductal and centroacinar cells, together with inspissated secretions, block pancreatic ductules and can cause atrophy of the lining epithelium.[4,7]

Pancreatic function status is genetically determined by specific CF mutations. Patients carrying one or two mild mutations are almost always pancreatic sufficient. Among patients homozygous for the common ΔF508 mutation, 99% will be pancreatic insufficient. Mutations associated with pancreatic sufficiency are generally class IV or V CF transmembrane conductance regulator (CFTR) defects and include R117H, R334W, R347P, A455E, and P574H.

An International Cystic Fibrosis Genotype-Phenotype Consortium in 1993 examined Δ508 homozygotes and seven of the most common 508 compound heterozygotes (G542X, R552X, N1303K, W1282X, 1717-1G-A, 612 + 1GT, R117H). All 19 patients with the R117H/Δ508 genotype had pancreatic sufficiency, whereas all the matched Δ508 homozygotes had pancreatic insufficiency. Walkowiak and associates[8] correlated exocrine pancreatic function assessed by fecal elastase-1 to 15 different mutations in 394 patients with CF and found again that patients carrying two severe mutations developed pancreatic insufficiency, whereas those who carried at least one mild mutation were generally pancreatic sufficient. The presence of one mild mutation did not, however, exclude pancreatic insufficiency.

Clinical Manifestations

Clinical evidence of exocrine pancreatic insufficiency occurs with loss of over 95% of exocrine output and results in malabsorption of fats and proteins and, to a lesser extent, carbohydrates. Steatorrhea and azotorrhea can be pronounced. Clinically, this malabsorption may manifest as poor or absent weight gain, abdominal distention, deficiency of subcutaneous fat and muscle tissue, frequent loose bulky, foul-smelling, greasy stools, and rectal prolapse.

Pancreatic Function Testing

Exocrine pancreatic function can be assessed by either direct or indirect tests. Direct tests include the gold standard, the secretin-cholecystokinin test, which has high sensitivity and specificity; however, the test has major disadvantages for use in pediatric populations, being expensive, uncomfortable, and poorly standardized in children.[9,10]

Indirect tests are used more widely in clinical practice, as they are generally less invasive, relatively cheap to perform, and less time consuming. Three main categories of indirect tests can be described as follows[11]:

1. Measurement of pancreatic enzymes in the serum (amylase, isoamylase, lipase, trypsinogen, elastase[12-14]) or stool (chymotrypsin, lipase and elastase[15-17])
2. Assessment of the absorption of markers that are hydrolyzed from conjugates by pancreatic enzymes and subsequently appear in urine or serum: pancreolauryl or NBT-PABA test[18-20]

3. Analysis of undigested and unabsorbed food components in feces—fecal fat excretion, fecal fat concentration, steatocrit, acid steatocrit[21-23]—or the analysis of oxidation products of digested and absorbed fat in expired air[24-26]

Assessment of serum enzymes contributes to assessment of exocrine pancreatic function with poor quantitative precision about residual function, while measurement of fecal enzymes provides a more sensitive assessment. Tests from the remaining two categories rely on the biological effect of pancreatic enzymes—digestion and absorption. Tests of fecal fat excretion may be influenced by other factors not related to pancreatic enzyme function such as gastric acid hypersecretion and loss of bile salts, as well as the presence of other conditions such as celiac disease. In CF patients, the correlation between the fecal fat excretion and the secretin-cholecystokinin test is less than that between the fecal elastase-1 concentration and the secretin-cholecystokinin test.[27]

Fecal elastase-1 has been shown to be a more sensitive test of exocrine pancreatic function than fecal chymotrypsin, fecal lipase, or breath test in CF.[27,28]

Although the test has the highest sensitivity of the indirect tests, the practical value of the measurement of fecal elastase-1 concentration in the assessment of mild pancreatic dysfunction is limited; however, it may have a role in assessing declining pancreatic enzyme function, as may occur over the first year in some infants diagnosed on newborn screening.[28]

The fecal elastase-1 test is unable to differentiate between primary exocrine pancreatic dysfunction and exocrine pancreatic dysfunction secondary to intestinal villous atrophy and has been shown to be abnormal in conditions including celiac disease as well as during acute episodes of diarrhea.[29]

While measurement of serum immunoreactive trypsinogen (IRT) is widely used in newborn screening programs for CF, the use of the test in the assessment of pancreatic function is limited. IRT in pancreatic-insufficient infants falls sharply in the first 2 years of life, so that over 95% of patients have subnormal values by the age of 7 years.[13] Under the age of 7 years, IRT has low sensitivity in differentiating between pancreatic-sufficient and pancreatic-insufficient infants.[30]

Several tests of pancreatic function involve the oral administration of a measurable tracer bound to a peptide specifically cleaved by one of the pancreatic enzymes. The synthetic peptide *n*-benzoyl-*l*-tyrosyl-*p*-aminobenzoic acid (bentiromide) is cleaved by chymotrypsin. The liberated *p*-aminobenzoic acid (PABA) is absorbed and excreted in the urine. Accordingly, PABA recovery reflects intraluminal chymotrypsin activity.[18] The sensitivity and specificity of the test can be improved by measuring PABA in plasma 90 minutes after the administration of a large dose of bentiromide or by the administration of a test meal that stimulates enzyme secretion.[31,32]

For practical clinical purposes, the relevance of exocrine pancreatic dysfunction is manifested as steatorrhea, and the measurement of daily fecal fat excretion over a period of 72 hours is the accepted standard procedure. Collected stool can be assayed for fecal fat content by several techniques, including gravimetric analysis, near-infrared analysis, and the generally "standard" but time-consuming technique of chemical analysis.[33,34]

In infants under 6 months of age, including those recently diagnosed by newborn screening programs, the coefficient of fat absorption is approximately 85% and increases with age such that above the age of 4 years the coefficient of fat absorption should exceed 95%.

Several breath tests dependent on the digestion of a substrate have been developed and may offer a useful, albeit expensive, alternative for assessment of fat digestion and absorption. The mixed triglyceride breath test is very sensitive for assessing severe excorine pancreatic deficiency and is a direct assessment of the presence of pancreatic lipase.[35,36]

An alternative breath test uses cholesteryl octanoate, which is hydrolyzed by cholesterol esterase, a process that requires the presence of pancreatic lipase and bile salts. This test has the advantage that cholesteryl octanoate is not hydrolyzed by preduodenal lipase and has been postulated to be an effective assessment for exocrine pancreatic function in young children in whom preduodenal lipase is more active.[11,37,38]

Nutrition

An adequate nutritional status is a key factor for a long-term survival in CF patients.[39] Studies have shown a positive effect of nutrition intervention on anthropometric measurements and pulmonary function.[40,41] Supplemental gastrostomy feedings were shown to be associated with significant improvements in weight and height percentiles for age,[40] increase in percent of body fat and fat-free mass, sustained growth, and stabilization in pulmonary function status.[39-41]

Edema and Hypoproteinemia

As newborn screening for CF is increasingly being introduced in major treatment centers, clinical presentations of CF secondary to prolonged lack of specific treatment are becoming increasingly uncommon. In areas where newborn screening is, however, not established, the presentation of patients with clinical consequences of pancreatic insufficiency may still occur. Secondary to proteolytic enzyme deficiency and malabsorption, infants with underrecognized pancreatic insufficiency may present with edema secondary to hypoproteinemia secondary to protein calorie malnutrition.[42,43]

CF patients may develop severe protein-calorie malnutrition and edema, often as the presenting manifestation of their disease, and particularly in areas without access to newborn screening.[44] Features may include hypoalbuminemia, hepatomegaly, elevation of liver enzyme values, anemia, and a characteristic dermatitis secondary to deficiencies of protein, zinc, and essential fatty acids.[45] A false-negative sweat test result may occur in the presence of edema, probably secondary to a low sweat secretory rate.[37] Infants with this syndrome need intensive nutritional therapy, including adequate calories, essential fatty acids, protein, zinc, and vitamins, along with pancreatic enzyme supplementation. A prolonged course of parenteral nutrition or enteral supplementation often is required.

Vitamins and Trace Metals

FAT-SOLUBLE VITAMINS

Deficiencies of fat-soluble vitamins A, D, E, and K have been repeatedly demonstrated in individuals with CF, particularly

in those with pancreatic insufficiency.[46-48] Fat-soluble vitamin deficiency has been reported to occur in infants as young as 2 months, and thus determination of such vitamin levels and supplementation with such vitamins is often necessary in infants diagnosed by newborn screening programs.[46,47]

Contributing factors that may lead to such a deficiency include suboptimal intake, malabsorption due to inadequate pancreatic enzyme levels either endogenous or as a result of insufficient replacement enzyme therapy, liver disease, bowel resection, and increased consumption.[49-53] Fat-soluble vitamin deficiencies in CF have been shown to be associated with poorer clinical status.[54]

VITAMIN A

Vitamin A is an essential nutrient for epithelial cell maintenance and repair. Dietary vitamin A (retinol or retinol esters) is found in eggs, fish, and dairy products. Both beta- and alpha-carotene can act as precursors for the synthesis of vitamin A and are postulated to function as antioxidants, inhibiting the oxidation of membrane lipids during infection. Deficiency of vitamin A may cause night blindness, conjunctiva and corneal xeroses, dry thickened skin, and abnormalities of bronchial mucosal epithelialization.[55] Vitamin A deficiency in individuals with CF appears to be multifactorial. Low retinol levels have been observed during periods of infection and inflammation.[56]

Assessment should therefore be performed during periods of clinical stability, rather than during acute exacerbation of lung function. Low levels may also be a consequence of low levels of retinol binding protein, which is responsible for transporting vitamin A from the liver to peripheral tissues. In addition, zinc deficiency may result in low vitamin A levels, as zinc is required for the release of vitamin A and retinol binding protein from liver stores.[54]

VITAMIN E

Vitamin E acts as an antioxidant protecting against oxidation of polyunsaturated fatty acids, particularly in lipoproteins and cellular membranes. Vitamin E deficiency is common in individuals with CF, and significant clinical sequelae of vitamin E deficiency have been reported, including hemolytic anemia in infants and ataxia and neuromuscular degeneration or compromised cognitive function in older patients.[57,58]

VITAMIN K

Clinical deficiency of vitamin K is considered to be uncommon in CF; however, Durie[59] has shown that frequent antibiotic treatment can result in a reduction in vitamin K levels by reducing the intestinal microflora capable of producing vitamin K. Subclinical deficiencies have been shown in more than 80% of pancreatic-insufficient children and in all patients with significant liver disease.[60-61]

Water-Soluble Vitamins

In the absence of other mitigating factors, significant deficiencies of water-soluble vitamins have generally been thought to be uncommon in CF.[47] In a study of children with CF who presented with angular stomatitis, over 80% were found to have biochemical evidence of B-group vitamin deficiency.[62] Regular vitamin B_{12} supplementation is required if the terminal ileum has been resected as a result of meconium ileus at birth.[63]

Trace Metals and Salts

Individuals with CF are at risk of increased sweat losses of sodium and chloride, particularly with exercise or exposure to high temperatures. CF infants are particularly at risk of salt depletion due to low levels of sodium in breast milk and substitutes. Sodium chloride deficiency is characterized by hyponatremia, decreased serum osmolarity, decreased appetite, nausea, vomiting, muscle cramps, fatigue, poor concentration, and headaches.[64] Additional sodium supplementation may be needed by infants, as requirements are increased during rapid growth and, due to their relative large body surface area, during periods of illness. During these periods, regular dietary intake decreases and is replaced by oral fluid supplements or enteral tube feeds, which have a low sodium content. This is also applicable in adults before undertaking additional strenuous work or physical activity, and when holidaying or living in hot or humid conditions.

Iron and Zinc

Iron deficiency is common in individuals with CF and may be related to multiple factors including inadequate dietary intake, malabsorption, chronic infection, blood loss, and excessive losses in sputum.[65] Severe zinc deficiency is less common, although there is evidence to suggest that milder zinc deficiency is widespread and associated with fat malabsorption.[66]

Zinc deficiency may have implications on vitamin A status as zinc has been shown to participate in the absorption, mobilization, transport, and metabolism of vitamin A, most likely through its involvement in protein synthesis and cellular enzyme functions.[67] Plasma levels of copper and ceruloplasmin may be elevated, reflecting ceruloplasmin's role as an acute phase reactant.[68]

Symptomatic hypomagnesemia has been reported in patients treated with repeated courses of intravenous aminoglycosides and manifesting as paresthesias, weakness, tremulousness, and muscle cramps.[68,69]

Monitoring

Levels of both iron and zinc should be periodically monitored in individuals with CF, and a trial of supplementation given if necessary, as low levels of either can contribute to suboptimal growth.[48]

Essential Fatty Acids

The essential fatty acid (EFA) status of individuals with CF is variable, ranging from normal to highly disturbed compositions. In general, individuals who are pancreatic sufficient have normal or less-disturbed fatty acid compositions (in plasma phospholipids, cholesteryl esters, triglycerides, nonesterified fatty acids, and erythrocyte lipids) than do individuals who are pancreatic insufficient.[70] Biochemically, EFA deficiency is common in CF; however, unless routinely screened for, it is often not detected as it rarely presents with clinical signs and symptoms.

Pancreatic Enzyme Therapy

Pancreatic enzyme replacement therapy is introduced once clinical evidence of pancreatic insufficiency is confirmed. Due to the progressive nature of CF, individuals who are pancreatic sufficient at diagnosis require periodic assessment of pancreatic function. This can be inferred by knowledge of their genotype and class of their *CFTR* mutation.

Most pancreatic enzyme replacement guidelines[71] recommend using a dietary fat–based dosage to link consumption of grams of fat to units of lipase in the capsules or body weight as a basis and then individualizing the dose based on assessments of efficacy. It is recommended that when commencing pancreatic enzyme replacement therapy (PERT), the minimum dose in the recommended range is used.[71]

Redistribution of pancreatic enzyme capsules over the day, based on the fat content of the foods consumed, has been shown to lead to a significant improvement in the coefficient of fat absorption and hence absorbed energy.[72] Fat-based dosing may assist individuals with CF in achieving the high-energy, high-fat diet recommended by helping to improve patient knowledge of food composition. Patient knowledge, particularly of fat, has been shown to be poor.[73]

Minimum effective doses are recommended in order to decrease the risk of fibrosing colonopathy, which continues to be found in association with "enzyme overdosing."[74] An upper limit of 10,000 IU lipase/kg body weight/day has been recommended to reduce the risk of fibrosing colonopathy. An audit of use of PERT in patients attending CF centers in the United Kingdom (1999-2000) demonstrated that patients on preparations containing 10,000 or 25,000 IU lipase per capsule commonly exceeded recommendation.[75] Further, they reported that use of high-strength PERT increased the risk of overdosing, with two thirds of patients in this group exceeding recommendations compared with one third in the standard-strength preparation group.

Patients with exocrine pancreatic insufficiency require long-term replacement therapy with pancreatic enzyme supplements. Although originally available as powdered pancreatic extracts, most, if not all, pancreatic extracts are prepared today as enteric-coated microsphere or microtablet preparations. The introduction of enteric-coated preparations has increased significantly the efficiency of these enzymes, which work maximally at an alkaline pH and thus, unprotected, would be exposed to significant degradation in their passage through the stomach. In infancy, the capsules containing the microspheres can be opened and administered in a soft non-alkaline food such as applesauce. In infants, enzyme dosing can be based on food intake, starting with 2000 to 4000 lipase units/120 mL formula or per breastfeeding.[76] Beyond infancy, weight-based dosing is more practical. It should begin with 1000 lipase units/kg per meal for children younger than 4 years and 500 lipase units/kg for those older than 4 years.[76] Enzyme dosage expressed as lipase units/kg per meal should be decreased in older patients because they tend to ingest less fat per kilogram of body weight. Usually, half the standard dose is given with snacks. There is great interindividual variation in response to enzymes, so a range of dosages is recommended, based on stool pattern and weight gain. Dosages greater than 2500 lipase units/kg per meal or 10,000 lipase units/kg per day should be used with caution and only if they are documented to be effective by 3-day fecal fat measure. After initiation of enzyme therapy, there should be almost immediate reduction in stool frequency and degree of steatorrhea, improvement in abdominal symptoms, and decrease in appetite. Most patients are able to achieve a coefficient of fat absorption greater than 85%.

Variations in enzyme requirements and patient response may be related to endogenous enzyme output, type of diet, microsphere size, gastric emptying time of microspheres, postprandial duodenal pH, and bile salt concentration.[77] Failure of enzyme release secondary to a low postprandial duodenal pH is probably the major factor leading to inefficient enzyme function.[78] In patients who have persistent steatorrhea (>10% fecal fat loss) despite apparently adequate enzyme dosage, addition of an acid-reducing agent may lead to significant enhancement of fat absorption.[79-82]

Some patients on high-dose enzyme therapy have ongoing abdominal symptoms unrelated to exocrine pancreatic deficiency.[83] In such cases, 72-hour fecal fat measure and evaluation for concurrent gastrointestinal disorders (lactose malabsorption, giardiasis, bacterial overgrowth, celiac disease, Crohn disease) are indicated. The development of constipation in a patient who is taking enzymes may be an indication for increased enzymes. A misguided reduction in enzyme dosage in this situation may precipitate an episode of distal intestinal obstruction syndrome (DIOS).

The most significant complication of pancreatic enzymes is fibrosing colonopathy, a condition associated with the use of high daily doses of enzyme. This diagnosis should be considered in patients who have symptoms of obstruction, bloody diarrhea, chylous ascites, or the combination of abdominal pain with ongoing diarrhea or poor weight gain.[84] Patients at highest risk are those who are younger than 12 years, have taken more than 6000 lipase units/kg per meal for longer than 6 months, or have a history of gastrointestinal surgery or complications.[74,85] Most cases involve the ascending colon, but pancolonic involvement can occur.[84] A barium enema is the most reliable diagnostic measure. Colonic shortening, focal or extensive narrowing, and a lack of distensibility are highly suggestive. Diagnosis is confirmed by biopsy. Bowel wall thickening, which may be a precursor of stricture formation, may be detected by ultrasonography. Most cases of fibrosing colonopathy require hemicolectomy.[86]

NUTRITIONAL MANAGEMENT

The principal aim of nutritional management in CF is the prevention of undernutrition secondary to energy imbalance. This requires both prevention and early interventive treatment, taking into account each individual's energy needs and nutritional status. Intervention is indicated whether nutritional imbalance is a result of either increased resting energy expenditure or decreased nutritional status, and should be instituted sufficiently early enough to prevent inadequate weight gain or a measurable decline in lung function. Comprehensive assessments of body composition, dietary intake, and biochemical markers should be routinely conducted in order to detect deterioration early.

A consensus document on the nutritional assessment and management in CF by Ramsey and associates[87] introduced the concept of anticipatory guidance by specialist CF dieti-

tians. In the review, five response categories for the provision of nutritional support were identified:

1. Routine management of all patients: high energy, high fat, high salt, nutritional education, and dietary counseling; and PERT and vitamin-mineral supplementation for those with pancreatic insufficiency
2. Anticipatory guidance of patients at risk of developing energy imbalance, but who are maintaining adequate nutritional status: energy dense dietary education, close monitoring of dietary intake, and behavioral management counseling
3. Supportive intervention for patients with decreased weight velocity and/or slightly compromised nutritional status: anticipatory guidance plus oral supplements, such as fortified milk drinks and desserts and glucose polymers
4. Rehabilitative care for patients whose nutritional status is compromised: overnight supplementation via an enteral tube
5. Resuscitative and palliative care for patients whose nutritional status is significantly compromised: 24-hour continuous enteral tube feeds and/or total parenteral nutrition, particularly in those awaiting organ transplantation

PANCREATITIS

Approximately 20% of pancreatic-sufficient patients are at risk of developing symptoms of recurrent, acute pancreatitis or chronic pancreatitis.[48] It is postulated that hyperconcentration of pancreatic secretions leads to obstruction of the pancreatic ducts, initiating autodigestion of the pancreas by pancreatic proteolytic enzymes.[88] Patients may present with severe abdominal pain, vomiting, and mid epigastric tenderness. Elevated levels of serum and urinary amylase and serum lipase are present. Increased echogenicity of the pancreas may be seen on ultrasonography.[89] Pancreatic-sufficient patients who develop pancreatitis should be closely monitored for progression to pancreatic insufficiency.

Repeated episodes may occur in patients over several years. Early reports of this occurrence frequently identified individuals as having a mutation on a single copy of the *CFTR* gene but could not rule out the possibility of a second rare mutation. When other hereditary forms of pancreatitis were excluded, however, sequencing analysis of *CFTR* confirmed that increased risk of pancreatitis requires two *CFTR* mutations (or a *5T* allele).[90] Adults who present with pancreatitis and who are found to have two *CFTR* mutations were initially thought to represent a "single-organ" manifestation of CF. Further research, however, has shown that many of these individuals do have extrapancreatic pathology, which may include abnormal sweat test results, congenital bilateral absence of the vas deferens (CBAVD), sinusitis, and chronic bronchial infection.[91]

PANCREATIC ENDOCRINE DEFICIENCY

Islet Cell Pathology

Early pancreatic changes in CF include inspissation of viscid secretions, ductal dilatation, and acinar fibrosis progressing to acinar atrophy, which in combination with fatty cell infiltration characterizes the adult CF pancreas. CF-related diabetes (CFRD) develops in individuals with CF as a consequence of this pancreatic pathology. Islet tissue in ribbon-like strands has been reported in subjects with CFRD. Preservation of islet number is observed in nondiabetic CF subjects; however, a reduction in beta-cell numbers in subjects with CFRD has been reported. Islets from subjects with CFRD show a significant reduction in surface area of insulin-staining cells compared with nondiabetic CF subjects.

Clinical Features

CFRD occurs in about 10% to 15% of all people with CF and increases with age, with a median age of onset of between 18 and 21 years. Lanng and associates[92] found that after 10 years of age, there was an increase in CFRD of 5% per year, with 24% of patients having CFRD by 20 years of age. CFRD generally occurs earlier in females, which is thought to reflect their earlier onset of puberty and the associated increase in insulin resistance that occurs. The incidence of CFRD is also higher in those with CF liver disease.[93]

Diagnosis

Relatively few patients with CFRD are identified by symptoms and diagnostic blood glucose levels. A standardized oral glucose tolerance test (OGTT), interpreted according to accepted international criteria (World Health Organization [WHO], 1999), might be the only means to diagnose diabetes mellitus or impaired glucose tolerance in CF (Table 63-1). Unlike classic type 1 diabetes mellitus, the onset of CFRD is usually insidious, and while many patients may be asymptomatic at diagnosis, a decline in lung function may precede the diagnosis (Table 63-2). Additional difficulty in making the diagnosis may arise as a patient's current clinical status or treatment may alter the glycemic status. A patient who has overt diabetes during an infective exacerbation may develop normal glucose tolerance weeks or months later.[94] Isolated

Table 63-1
Suggested Action on the Results of Routine Oral Glucose Tolerance Test (OGTT)

Possible action on results of screening OGTT	
Normal glucose tolerance (NGT)	Repeat OGTT in 1 year.
Impaired oral glucose tolerance (IGT)	Repeat OGTT in 1 year or sooner if clinical parameters worsen, e.g., lung function, unexplained weight loss.
Diabetic glucose tolerance (cystic fibrosis–related diabetes mellitus [CFRD]) in person who is asymptomatic	Arrange home blood glucose monitoring for 2 weeks with a food/activity diary; if normal, repeat the OGTT within 6 months.

From Management of Cystic Fibrosis Related Diabetes Mellitus: Report of the UK Cystic Fibrosis Trust Diabetes Working Group. Cystic Fibrosis Trust, June 2004.

Table 63-2
Classification of Clinical Categories of Cystic Fibrosis–Related Diabetes Mellitus (CFRD)

Stage of Disease	Premeal Sugar Levels	Postmeal Sugar Levels	Symptoms	Microvascular Complication Risk	Treatment
Reactive hypoglycemia	Normal	Low	Hypoglycemia	Unknown—likely to be very low	
Impaired glucose tolerance	Normal	Intermittently raised	None or weight loss or clinical decline	Unknown—likely to be low	Consider insulin or tablets with meals
CFRD without fasting hyperglycemia	Normal	Mostly raised	None or thirst, polyuria, weight loss, or clinical decline	Unknown—likely to be related to duration, control, and risk factors	Insulin or tablets with meals
CFRD with fasting hyperglycemia	Mostly raised	Mostly raised	Thirst, polyuria, weight loss, or clinical decline	Unknown—likely to be related to duration, control, and risk factors	Insulin or tablets with meals

From Management of Cystic Fibrosis Related Diabetes Mellitus: Report of the UK Cystic Fibrosis Trust Diabetes Working Group. Cystic Fibrosis Trust, June 2004.

random fasting or 2-hour postprandial plasma glucose, glycosylated hemoglobin, and first-phase insulin response to glucagon stimulation, or combinations are not thought to be sufficiently reliable as diagnostic tools in establishing CFRD. Some studies have shown that a normal Hb_{A1c} can be found in up to 70% of patients in whom diabetes is confirmed on an OGTT.

Management

Extensive reviews of CFRD management have been published and are beyond the scope of this chapter. The 2004 guidelines from the UK Cystic Fibrosis Trust Diabetes Working Group summarized its recommendations to include the following (see also Table 63-3):

1. Treatment should be aimed at correcting symptoms of hyperglycemia and maintaining adequate nutrition, growth, and respiratory function and should be initiated in patients with a diabetic OGTT and/or regular hyperglycemia.
2. Treatment should also be considered in the presence of an impaired OGTT when there is associated weight loss or deteriorating clinical condition or with hyperglycemia.
3. Insulin remains the preferred treatment, although oral tablets may be used in some patients initially or where there are practical issues with taking insulin. Regular blood glucose monitoring is an essential part of therapy.
4. A diet advised by a dietitian with CF experience will be high in energy and high in fat and include well-planned use of refined carbohydrates. The insulin dosage should be adjusted to the diet rather than the diet adjusted to the insulin.[95]

Long-term microvascular complications occur in CFRD, including retinopathy, nephropathy, and neuropathy. In a study of 311 patients with CF, microvascular complications were identified in 10% of patients with CFRD with duration of diabetes mellitus of 1 to 7 years.[96] Similar studies have reported incidences of up to 20% to 30%.[97] All patients with CFRD should have annual screening to identify any such complications.[95]

Table 63-3
Management of Cystic Fibrosis–Related Diabetes Mellitus

Energy	Individualized 120% to 150% or normal depending on nutritional state
Fat	40% of total energy
Refined sugars	Allow throughout the day
Carbohydrate	45% to 50% of total energy
Dietary fiber	Encouraged in the well nourished, but in poorly nourished patients may compromise energy intake
Protein	200% of reference nutrient intake (RNI)
Salt	Increased requirement
Snacks	Ad libitum

Adapted from Management of Cystic Fibrosis Related Diabetes Mellitus: Report of the UK Cystic Fibrosis Trust Diabetes Working Group. Cystic Fibrosis Trust, June 2004.

HEPATOBILIARY DISEASE

Liver Pathology

Liver disease, although included in the initial description of CF, accounts for a small percentage of morbidity of the disease. Advances in the management of the pulmonary complications of CF may result in an increasing prevalence of a number of hepatic and biliary abnormalities, which may, therefore, become more important in the long-term management of CF patients. While liver involvement in CF was first described over 50 years ago, the increased survival into adulthood of many CF patients has been associated with an increase in clinically relevant liver dysfunction.[98]

Symptomatic liver disease is still considered uncommon and the cause of death in less than 2% of patients, but typical bilary cirrhosis has been reported in up to 50% of postmortem studies and in approximately 25% of adults.[6,99,100]

The characteristic lesion seen in CF is focal bilary fibrosis with inflammatory cell infiltration, bile duct proliferation, and patchy accumulation of eosinophilic material. The CFTR has been located in the apical membrane of intrahepatic bile duct cells, and the resultant abnormalities in chloride transport are believed to be responsible for the failure to adequately hydrate the canalicular-produced bile, resulting in increased bile viscosity. There is evidence that the increased

bile viscosity is due, in part, also to an increased production of mucus by the intrahepatic biliary epithelial cells.[101]

Prolonged Neonatal Jaundice

Neonates with CF may present with prolonged obstructive jaundice, presumably secondary to obstruction of extrahepatic bile ducts by thick bile along with intrahepatic bile stasis (inspissated bile syndrome).[102] In most cases, liver histology shows features compatible with bile obstruction. The liver is usually enlarged and firm. Approximately 50% of cases occur in association with meconium ileus or delayed passage of meconium. The prognosis for patients with neonatal cholestasis is generally good, although elevated bilirubin values may persist for up to 7 months and early-onset liver failure or cirrhosis may develop.[102] In some patients, the biliary obstruction can be relieved by intraoperative irrigation of the biliary tree with saline and *N*-acetylcysteine.[103]

Cirrhosis and Portal Hypertension

Most patients with CF develop mild liver abnormalities including slightly elevated liver biochemical tests, hepatosteatosis, and focal areas of portal tract disease (biliary plugging with eosinophilic material, bile duct proliferation, and cholangitis). Only a small proportion of CF patients, most of whom have classic CF, develop CF-related liver disease (CFLD) with multilobular cirrhosis leading to portal hypertension and hypersplenism. The median age at diagnosis of CFLD is 9 to 10 years, and most cases of CFLD are diagnosed by mid adolescence. Because the ability of the liver to synthesize proteins, metabolize toxins, and secrete bile tends to remain intact for many years and even decades, most complications of CFLD are attributable to the consequences of portal hypertension. A number of putative modifier genes of CFLD have been reported, but, in a recent study of a larger number of patients with severe CFLD, only two candidate genes (the *Z* allele for α_1-antitrypsin deficiency and polymorphisms of transforming growth factor [TGF]-β1 with increased expression) were shown to be statistically associated with CFLD.

Gallbladder

Approximately 25% of CF patients have a nonfunctioning gallbladder, with anatomic abnormalities present in approximately 33% of patients with CF.[104,105]

A variety of abnormalities may occur including nonvisualization of the gallbladder on oral or intravenous cholecystography, cholecystitis, and radiolucent gallstones, with an increasing incidence with age. In one postmortem study, gallstones were found in 24% of adult patients with CF. A more recent study in children with CF found anomalies of the gallbladder, including absence or microgallbladder or stones, in 24% of 48 patients studied.[106-110]

The high incidence of gallstones, which are almost universally radiolucent, has been related to biliary stasis, increased bile viscosity, and abnormalities of bile salt metabolism.[110] Analysis of gallstones removed from CF patients has shown that they are mainly composed of calcium, bilirubinate, and proteinaceous material.[111] Most CF patients with gallbladder abnormalities are asymptomatic. In a large series, only 24 (3.6%) of 670 patients developed symptomatic disease.[109] All but one of these patients had exocrine pancreatic deficiency and all but one was older than 12 years. In patients with typical biliary colic, cholecystectomy leads to total cessation of symptoms, whereas in patients with atypical symptoms the results of cholecystectomy are often equivocal. Laparoscopic cholecystectomy under continuous epidural anesthesia is preferred, especially in patients with severe pulmonary disease.[112]

GASTROESOPHAGEAL REFLUX

Gastroesophageal reflux (GER) is multifactorial in origin in patients with CF. While significant lung disease may predispose to increased GER due to the generated negative intrathoracic pressures, reflux is not infrequently seen in patients with well-preserved lung function. Other contributing factors that may predispose to GER include the use of pharmacologic agents known to reduce the tone of the lower esophageal sphincter, including salbutamol and aminophylline, and head-down positions during physiotherapy.[113,114]

GER has been documented in approximately 80% of unselected patients with CF younger than 5 years and 75% of symptomatic patients older than 4 years.[115,116] There is evidence that, particularly in young infants, chest physiotherapy can induce episodes of reflux, particularly in the head-down position; however, other investigators have failed to confirm these findings.[117,118] Presenting symptoms include upper abdominal pain, epigastric or substernal burning, vomiting, hematemesis, dysphagia, failure to thrive, or pulmonary disease that does not respond to usual therapy.[116,119] Esophageal strictures secondary to chronic esophagitis have been reported.[120]

Infants with reflux and/or secondary esophagitis may present with irritability, vomiting, regurgitation, poor oral intake, and growth failure. The diagnosis is suspected clinically and then confirmed by prolonged intraesophageal pH monitoring, upper gastrointestinal endoscopy, and esophageal biopsy. An upper gastrointestinal series may be necessary to exclude an anatomic lesion.

Treatment must be tailored to the individual patient, but may include frequent small meals, positioning, antacids, H_2 blockers, or proton pump inhibitors. Most centers would recommend, particularly in young infants, the avoidance of head-down tilting during chest physiotherapy despite the apparent conflicting evidence.[117,118]

The prokinetic agent cisapride, which increases the tone of the lower esophageal sphincter and which had been shown to be effective in young CF patients with GER, is now not generally available because of its potential effect on the cardiac QT interval.[115] When medical management fails, a Nissen fundoplication may be indicated, although published experience with surgical correction of reflux in CF is sparse.

PEPTIC ULCER DISEASE

CF patients have been shown to have acid hypersecretion on pentagastrin testing, and with the additional lack of pancreatic bicarbonate secretion, it is not surprising that there is an increased risk of peptic ulcer disease.[121] This combination will produce a duodenal pH significantly more acidic than

that of non-CF individuals, with second part duodenal pH recordings of between 5.5 and 6.5 compared with pH levels of about 7.0 in non-CF individuals.[78]

In an often-quoted series of 146 CF cases, 8% of patients showed peptic ulcerations involving the stomach and duodenum at postmortem; however, at least part of these lesions are now believed to be terminal events. In addition, many of the symptoms attributed to peptic ulcer disease, such as epigastric pain, nausea, or anorexia, may be attributable to reflux rather than to peptic ulcer disease.

The combination of gastric hypersecretion and diminished pancreatic bicarbonate secretion and the resultant hyperacidic duodenal pH has direct influence on the efficiency of pancreatic enzyme therapy, as a pH above 5.8 is required for dissolution of the enteric coating. In addition, the contained pancreatic enzymes are irreversibly destroyed by exposure to a pH of below 4.0. Manipulation of the duodenal pH by acid-modifying agents has been shown to not only improve GI symptoms but also directly improve pancreatic enzyme efficiency and fat absorption.[78,79]

The causative role of *H. pylori* in gastroduodenal disease in the CF population remains largely unknown. The overall seroprevalence of *H. pylori* in patients with CF has been described in earlier studies as similar to that in non-CF control subjects[122]; however, other investigators have failed to confirm this relationship.[123] Przyklenk and colleagues[122] recently showed cross-reactivity between solid-phase *H. pylori* antigens and anti-*Pseudomonas* antibodies occurring in patients with CF, which means that serologic detection of *H. pylori* infection may be overrepresented in CF populations.

DISTAL INTESTINAL OBSTRUCTION SYNDROME

DIOS, previously called "meconium ileus equivalent," refers to episodes of abdominal pain due to partial or compete intestinal obstruction with abnormally viscid mucofeculent material in the terminal ileum or the ascending colon. It is caused by the impaction of mucofeculent material in the distal ileum, cecum, and proximal colon and increases in frequency with increasing age. It is estimated to occur in some 2% of patients younger than 5 years, increasing to 27% of patients over the age of 30 years. Some 7% to 15% of patients beyond the neonatal period are believed to have experienced episodes of DIOS.[124,125] While much more common in pancreatic-insufficient patients, there have been several reports of its occurring in patients with pancreatic sufficiency.[126,127] Contributing factors include abnormal intestinal mucins, undigested food residues, prolonged intestinal transit time, low dietary fiber content, bowel dilation, and abnormal intestinal electrolyte and water transport. Clinical manifestations include crampy lower abdominal pain, distention, vomiting, anorexia, abdominal tenderness, and palpable masses in the right lower quadrant. Episodes may occur within a normal stooling pattern, even during symptomatic periods. There may be progression to complete obstruction, volvulus, or intussusception. Patients may have isolated episodes with long symptom-free periods or chronic symptoms with intermittent exacerbations. The differential diagnosis includes intussusception, volvulus, appendicitis, esophagitis, peptic ulcer disease, gallbladder disease, pancreatitis, and other non–CF-related conditions. Most cases of DIOS will be suspected on the basis of the history and physical findings. Abdominal radiographs show dilated small bowel loops with a bubbly, granular appearance in the area of the ileum and cecum consistent with retained stool.[128]

When significant impaction is present, without complete obstruction, the treatment of choice is the administration of a balanced intestinal lavage solution (GoLYTELY) orally or by nasogastric tube.[129] Effective therapy may take 4 to 6 hours. The end point of therapy is determined by passage of stool, resolution of symptoms, and disappearance of a previously palpated right lower quadrant mass. If there is complete obstruction or peritoneal irritation, surgical intervention is indicated.[130]

Intussusception

Intussusception is estimated to be up to 10 times more common in those with CF than in the general population, with a risk of around 1%.[131] The true incidence may be unknown because some cases, particularly ileoileal intussusceptions, have been reported to reduce spontaneously.[132] There is a bimodal distribution for intussusception in CF and a male preponderance as reported for non-CF cases. After intussusception of infancy, a second peak occurs in CF at around 10 years of age. Cases occurring in older children and adults have also been reported.[133,134] In older patients, lead points such as polypoid lesions have been identified. In addition, intussusception may complicate DIOS, whereby a tenacious fecal bolus adheres to the mucosa and acts as a lead point[134] (Fig. 63-1). The appendix, often enlarged and distended secondary to inspissated mucofeculent contents, may also act as a lead point in producing intussusception in CF.[135]

Patients usually present with the acute onset of intermittent crampy abdominal pain, often accompanied by vomiting. Other manifestations include a palpable abdominal mass, rectal bleeding, and decreased or absent bowel movements. Atypical or chronic symptoms occur in 25% of patients with intussusception.[131] Most episodes are ileocolic, but ileoileal,

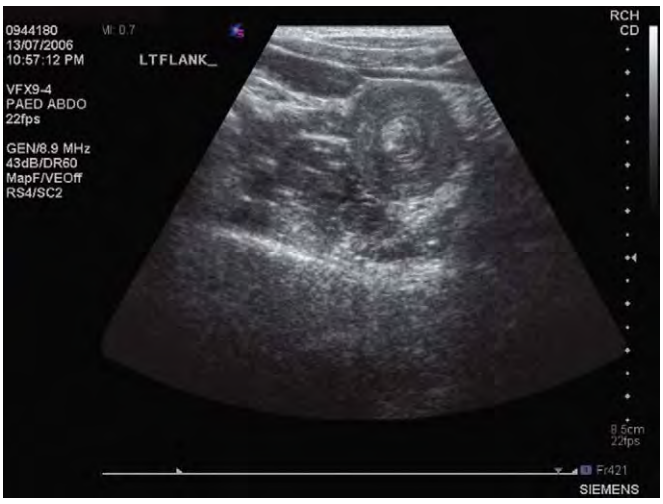

Figure 63-1 Transverse ultrasound image of intussusception in left flank demonstrating typical "target" sign.

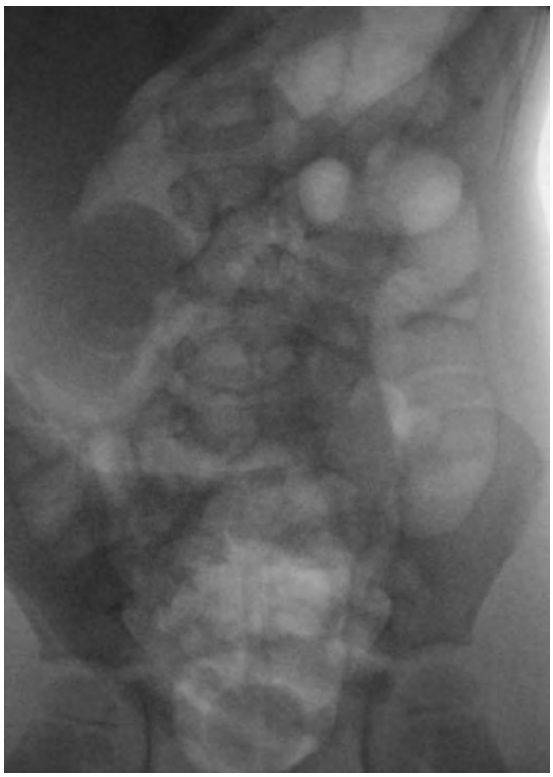

Figure 63-2 Air enema reduction of intussusception. The intussusception is present in the region of the hepatic flexure.

ileocecal, colocolic, and even appendiceal locations have been reported.[136] The diagnosis is usually confirmed by contrast enema, but in some cases is made only at laparotomy. Hydrostatic reduction may be successful, but most cases require surgical correction[131,132] (Fig. 63-2).

APPENDICEAL DISEASE

In patients with CF, there are typical histologic findings in the appendix.[137] The number of goblet cells is increased, and they are often markedly distended with mucus secretions. The crypts are dilated and appear wider, and at times deeper, because of distention of the lumen by accumulated secretions. Eosinophilic casts of the crypts may extrude into the lumen of the appendix. Inspissated secretions may extrude through the orifice of the appendix to form a local cecal mass. There is little or no cellular infiltration, and the muscularis layer is not affected. The diagnosis of CF has been suggested by the histologic appearance of an appendix removed from some patients with acute or recurrent/chronic abdominal pain.[138,139] An asymptomatic right lower quadrant mass secondary to mucoid impaction of the appendix has been described as a presenting manifestation of CF.[140] The reported incidence of acute appendicitis in patients with CF is only 1% to 2%, compared with a rate of 7% in the general population.[141] This may be accounted for by the long-term use of antibiotics in many patients with CF. Patients with CF who have acute appendicitis may present with classic symptoms, but the diagnosis is often delayed because of an atypical or a subacute presentation and confusion with DIOS.[141,142] At laparotomy, a high percentage of patients show appendiceal perforation and periappendiceal abscess formation.[143]

Clinically, CF patients with acute appendicitis have right lower quadrant pain, nausea, and anorexia. Fever and change in stool frequency may or may not be present. The initial diagnosis is usually DIOS. Abdominal ultrasound and gallium scans generally are not helpful in establishing a diagnosis.[141]

A contrast enema may be helpful if it shows extrinsic cecal compression or appendiceal filling. However, failure to visualize (fill) the appendix before or after evacuation of contrast material cannot be used as a sign of appendicitis in patients with CF.[144] Failure of visualization is most often related to mucus plugging of the appendiceal lumen. The possibility of an appendiceal abscess should be considered when a patient with CF presents with pain, a mass, or drainage from the right flank; prolonged fever; a limp; or failure of suspected DIOS to respond to appropriate therapy.[145] In patients with DIOS, abdominal radiographs usually show extensive stool accumulation and the white blood cell count is normal or only mildly elevated. Abdominal computed tomography may be a useful diagnostic tool. Treatment usually involves surgical drainage and intravenous antibiotics followed by an elective appendectomy.

MECONIUM ABNORMALITIES

Meconium Ileus

Meconium ileus, in which intraluminal intestinal obstruction is secondary to inspissation of tenacious meconium in the terminal ileum, occurs in approximately 18% of newborns with CF.[146] With rare exception, almost all full-term infants with meconium ileus eventually have a confirmed diagnosis of CF. There is a strong familial trend for the occurrence of meconium ileus, with a recurrence rate of 29% to 39% in subsequent CF-affected siblings.[147] There is evidence that meconium ileus is, in part, genetically determined. There is a decreased risk in patients who carry R117H, A455E, or other mild mutations that confer pancreatic sufficiency, and an increased risk in patients who carry certain severe mutations or modifier genes that have an impact on the CF alleles.[148]

Affected infants present within the first 48 hours of life with abdominal distention, bilious vomiting, and failure to pass meconium. There may be a maternal history of polyhydramnios. Approximately 50% of cases are complicated by volvulus, atresia, perforation, ischemic necrosis, meconium peritonitis, or pseudocyst formation.[149,150] The diagnosis of meconium ileus is supported by abdominal radiography that shows distended loops of bowel, usually without air-fluid levels, and a granular ground-glass appearance in the area of the terminal ileum, indicating the mixture of air bubbles with meconium (soap-bubble sign). Contrast enema shows an unused microcolon (Fig. 63-3). In the presence of meconium peritonitis, there may be flecks of intraperitoneal calcium throughout the abdomen. The presence of abdominal calcification, is usually associated with non-CF causes of meconium peritonitis; conversely, the absence of calcification favors CF as the cause of meconium peritonitis.[151]

The diagnosis of meconium ileus and meconium peritonitis can be made prenatally by ultrasonography. In several cases, the obstruction has been relieved by intrauterine amniography with urografin.[152] In the absence of complications,

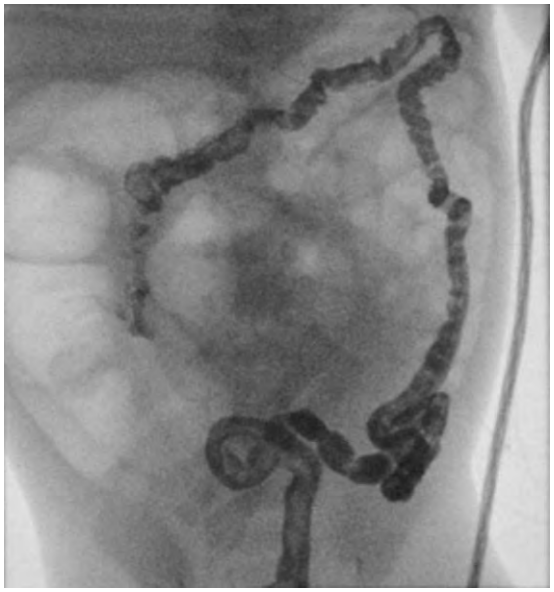

Figure 63-3 Small-caliber colon with filling defects throughout the colon and rectum, largest one in the ascending colon causing obstruction and proximal small bowel dilatation. The contrast could not be passed beyond the distal ascending colon. These features are in favor of meconium ileus.

up to 50% of cases can be treated successfully by the administration of hyperosmolar (Gastrografin) or iso-osmolar contrast enemas under fluoroscopic control.[150] During this therapy, the patient's fluid and electrolyte status must be monitored closely to prevent hypovolemia. Repeated attempts to evacuate meconium may be required. If the patient's condition remains stable without change in abdominal findings, therapeutic enemas can be repeated over several days. The procedure may be complicated by intestinal perforation in up to 15% of cases.[153]

Patients who have complications of meconium ileus or do not respond to nonoperative therapy require surgical intervention. In some instances, the inspissated meconium can be cleared by intraoperative irrigation with acetylcysteine, hyperosmolar contrast, or saline.[154,155] If irrigation is unsuccessful or if there are complications, patients are managed by resection of the involved bowel followed by primary anastomosis or a temporary double-barrel (side-by-side) enterostomy. After surgery, patients will require a period of total parenteral nutrition followed by intensive enteral nutritional support. In patients with a history of meconium ileus, there is earlier acquisition of *P. aeruginosa*. Although previously shown from an unscreened population that at ages 8 and 13 years pulmonary function was similar in patients with and without meconium ileus,[156] a more recent study from a screened population has shown that although there were no differences between those patients born with meconium ileus and those detected by newborn screening with regard to height, weight, incidence of liver function abnormalities, frequency of hospitalization, and airway microbiological colonization, patients born with meconium ileus had a significantly lower FEV_1 and FVC as well as a lower Shwachman chest radiograph score.[156,157] Long-term survival among males and females with meconium ileus is similar to that of females without meconium ileus but significantly shorter than that of males without meconium ileus.[156,157]

Meconium Plug Syndrome

First described in 1956, meconium plug syndrome (MPS) describes a condition occurring in very young infants who present with transient large bowel obstruction relieved by the passage of meconium plugs. Although initially considered a distinct condition in its own right, MPS has since been reported as a presenting feature of Hirschsprung disease or CF.[158] There also appears to be some overlap with small left colon syndrome (SLCS), a condition reported in infants of diabetic mothers (IDDM) in whom contrast enema shows a narrow left colon.[159] In one series, MPS occurred in 12 of 87 newborns (14%) with CF in the absence of meconium ileus, and in another series, 43% of newborns who presented with MPS eventually had a diagnosis of CF made.[158,160] It is likely that MPS and meconium ileus represent gradations of the same underlying abnormality, differing only in degree of severity and site of obstruction. In general, MPS is a benign condition usually relieved following anal stimulation, administration of enemas, or a diagnostic contrast enema. The success of nonoperative treatment is probably a result of the lower site and significantly easier removal of the obstructing meconium in infants with MPS compared with those with meconium ileus.

RECTAL PROLAPSE

Rectal prolapse in CF was much more common in the years immediately following Andersen's original description of CF in 1938 than it is currently, due in a large degree to improved nutrition and more efficient pancreatic enzyme therapy. The introduction of newborn screening programs for CF has also significantly reduced the incidence of rectal prolapse. In unscreened populations, rectal prolapse occurs in approximately 20% of patients with CF, usually between 6 months and 3 years of age, and may precede the diagnosis of CF.[161]

The prolapse may involve only the mucosa (mucosal prolapse) or all layers of the rectum (complete prolapse or procidentia). Predisposing factors in CF include increased intra-abdominal pressure secondary to chronic coughing, diarrhea, malnutrition, and pelvic floor weakness. The treatment of rectal prolapse is mainly conservative and includes optimization of pancreatic enzyme therapy, high-fiber diet, and improved nutrition. Surgical intervention may be required for recurrent rectal prolapse refractory to conservative measures; however, in CF, this is rarely required. A simpler, less invasive, approach for refractory cases may be perirectal injection with a sclerosing agent.[162]

MISCELLANEOUS AND ASSOCIATED INTESTINAL ABNORMALITIES

Cancer

Twenty years ago, Abdul-Karim and associates[163] described a CF patient with cancer, an adult with an extrahepatic biliary tract cancer. Since that initial report and as more CF patients reach adulthood, additional reports have described CF patients with adenocarcinomas of the pancreas,[164-166] ileum,[167,168] and bowel,[169] as well as leukemia[170] and neuroblastoma.[171]

In 1993, Sheldon and colleagues[172] conducted the first cohort study of the association of CF with malignancy and observed a possible association of CF with adenocarcinoma of the pancreas and of the terminal ileum, but only a single case was observed in each organ. In 1995, data from the CF databases of North America and Europe were interrogated for cases of cancer, and an overall increase in the number of digestive tract cancers was observed.[173] Subsequently, cases of colon cancer[174] and embryonal carcinoma of the testis[175] in CF patients have been reported. In a review from the U.S. CF database in 2003 describing over 28,000 CF patients with a total of 202,999 person-years of observation between 1990 and 1999, 75 cancers were observed in nontransplanted CF patients. Of these, 69.7 would have been expected. Twenty-three digestive tract tumors were observed, with some five expected. More cancers than expected were observed of the small bowel, colon, and biliary tract but not of the stomach or rectum.[176]

Celiac Disease

Gluten sensitivity leading to small bowel villous atrophy, as in celiac disease, may be present in CF; however, evidence does not support the previously held belief of an increased risk of celiac disease in patients with CF.[177] Lloyd-Still suggested that the incidence of celiac disease is in fact closer to 10 times less frequent in the CF population than the general population.[178]

Clostridium difficile Infection

Patients with CF have a high rate of C. *difficile* carriage compared with normal children, most likely the result of more widespread use of broad-spectrum antibiotics. Infection may extend from asymptomatic carriage to severe disease such as pseudomembranous colitis with complications including toxic enterocolitis or megacolon. It is unclear whether subclinical infections contribute to malabsorption in patients with CF by causing direct mucosal damage or whether patients with CF develop acquired tolerance to C. *difficile* toxin.[48]

Crohn Disease

In patients with CF, there is evidence of increased small intestinal permeability, probably because of the leakage of large molecules (disaccharides) through paracellular pathways. This increased intestinal permeability is probably related to underlying pancreatic dysfunction. The passive transcellular uptake of small molecules is preserved. Orocecal transit time has been shown to be prolonged in both children and adults with CF.

Crohn disease is another multigenic disease that is said to occur with increased frequency in CF. In a study of over 11,000 CF patients, Lloyd-Still[178] found that there were 28 patients with inflammatory bowel disease including 25 with Crohn disease and 3 with ulcerative colitis. These figures suggest an overall increased prevalence rate of inflammatory bowel disease in CF of 7 times that of controls, with Crohn disease being 17 times more prevalent in CF patients than in controls.

Genetic mapping studies have isolated an important susceptibility gene (*NOD2*) as well as a number of Crohn susceptibility loci on chromosomes 1, 5, 6, 12, 14, 16, and 19.[179] As with celiac disease, it has been postulated that Crohn disease may become manifest in a genetically susceptible individual as a result of one or more second "hits." Aberrant immunologic interactions with gut microflora, pathogenic bacteria, or bacterial antigens are all hypothesized as examples of second hits. It is possible that CF disease increases susceptibility to Crohn disease through an unknown CF-related intestinal mechanism. Possibilities include increased intestinal permeability and inflammation, alterations in the intraluminal environment resulting from maldigestion, the presence of bacteria in the small intestine, or changes in gut microflora.[48]

Intestinal Permeability, Transit Time, and Absorption

In general, small intestine biopsy samples from patients with CF show normal histology; however, there may be a thick mucus cover over the brush border membrane.[180] CFTR expression in the intestinal epithelium is relatively high and is highest in the duodenum. Through the small intestine, CFTR expression decreases steadily and is lowest in the colon. CFTR is uniformly high in the crypts, suggesting that all cell types—goblet cells, Paneth cells, and undifferentiated epithelial cells—express similar levels of CFTR. CFTR expression decreases toward the tips of the villi, and only a weak signal is detected on the top one third of the villi.[180] While absorption of metabolically inert saccharides such as xylose and mannitol have been shown to be absorbed at a normal rate in CF patients, other disaccharides have been shown to be taken up at a faster rate by CF small intestinal mucosa. In addition, Mack and associates[181] were able to show a direct relationship between intestinal lactulose permeability and the degree of exocrine pancreatic dysfunction. Enzyme-depleted small intestinal villi are present in some patients. This may be a result of impaired maturation secondary to nutritional deficiencies or failure of enterocytes to increase their brush border enzymes secondary to impaired absorption of nutrients.[180]

CARDIOVASCULAR COMPLICATIONS

Evaluation of Cardiac Status

Cor pulmonale secondary to chronic hypoxemia is a common complication in CF patients with advanced pulmonary disease and remains a significant cause of morbidity and mortality. In addition, a number of other cardiovascular complications have been documented.

Physical Examination

The early clinical recognition of cor pulmonale may be difficult in patients with CF.[182] Tachypnea, tachycardia, and hepatomegaly are common secondary to underlying pulmonary disease. However, an enlarged tender liver is often an early clue to right ventricular failure.[183] An accentuated second heart sound in the pulmonic area may be a helpful sign but is often blunted by an anterior chest wall deformity

and air trapping. Patients may develop a tricuspid insufficiency murmur, either during or shortly after the onset of cardiac enlargement. Peripheral edema is not a common finding and, when present, appears late in the clinical course. In patients with heart failure, weight loss is as common as weight gain.[183]

Laboratory Findings

The degree of hypoxemia and pulmonary artery pressure are closely correlated. A PaO_2 below 50 mm Hg and PCO_2 above 45 mm Hg are consistently associated with severe cor pulmonale.[184,185] Hypoalbuminemia secondary to expansion of plasma volume may be a helpful early clue to right ventricular failure.[186]

Chest Radiography

Estimation of heart size may be difficult to determine on plain chest radiography because of severe air trapping. In general, there is poor correlation between echocardiographic findings and cardiothoracic ratio.[187] Cardiomegaly may be obvious only in patients with overt right heart failure. There may be enlargement of the main pulmonary arteries, but this is often obscured by significant hilar lymphadenopathy and surrounding parenchymal disease.

Electrocardiogram

Electrocardiographic recording may document right ventricular hypertrophy, right atrial hypertrophy, or right-axis deviation in patients with CF; however, these changes are generally nonspecific and the electrocardiogram (ECG) is usually normal in CF patients with right ventricular enlargement.[188] Significant evidence of right ventricular hypertrophy may be difficult to detect due to chest hyperinflation and abnormal positioning of the heart relative to the chest wall. Several authors do not believe the ECG to be a reliable indicator of right ventricular disease in CF.[182,189]

Echocardiogram

Studies using two-dimensional imaging of the right ventricle in CF have given conflicting results, with some studies showing increased right ventricular dimensions that correlate with a patient's clinical score, whereas others have reported normal right ventricular dimensions in patients with severe lung disease.[187,190,191]

Right ventricular free wall thickness has been used as a marker of right ventricular dysfunction and has been found to be increased in patients with CF, possibly reflecting underlying pulmonary hypertension.[187,192]

Radionuclide Scans

Radionuclide angiography has demonstrated reductions in both right and left ventricular ejection fractions. Reduction in right ventricular ejection fraction has been shown to parallel disease severity with Burghuber and associates[193] demonstrating an inverse linear correlation between right ventricular ejection fraction and afterload, as assessed by mean pulmonary artery pressure and pulmonary vascular resistance.

Cor Pulmonale

The combination of alveolar hypoventilation, chronic hypoxemia, and pulmonary vasoconstriction will result in up to 70% of patients eventually developing pulmonary hypertension and hypertrophy of the right ventricle (cor pulmonale).[194] A clear relationship has been demonstrated between the degree of hypoxemia and pulmonary artery pressure. Echocardiography is the most sensitive noninvasive technique for the early recognition and monitoring of cor pulmonale.[194] For practical purposes, cor pulmonale is assumed to be present when one or more of the following is present: right ventricular hypertrophy on ECG, PaO_2 less than 50 mm Hg, signs of heart failure, radiographic evidence of enlarged pulmonary arteries, and forced vital capacity greater than 60% predicted. After the onset of right-sided failure, most patients are significantly disabled and mean survival is 8 months (range, 1 to 63 months).[183] The presence of pulmonary hypertension has been cited as one of the referral criteria for transplantation in CF patients.[195]

ENDOCRINE AND METABOLIC COMPLICATIONS

Thyroid Gland

The demonstration of expression of CFTR in the thyroid epithelium has raised the possibility of an intrinsic abnormality in thyroid glandular cells and the possibility that changes in the metabolic activation of thyroid follicular cells lead to alterations in colloid secretion. CFTR protein has been described in approximately two thirds of thyroid follicles, but only 16% of follicular cells were positive per follicle, suggesting phase-specific expression of CFTR. Several roles for the function of CFTR in thyroid epithelium have been postulated, including promoting iodide secretion into the thyroid follicles or regulation of electrolyte and fluid transport.[196]

Thyroid function impairment has been sporadically described in CF and ascribed to iodine overload or selenium deficiency.[197] Volta and colleagues[198] evaluated thyroid function in CF in 17 young adult CF patients and 18 age-matched controls and found normal serum levels of TSH, free T_3, and free T_4 in the CF group. Within the CF group thyroid function did not vary in relation to C-reactive protein serum levels, respiratory function, or clinical condition as described by the Shwachman score.

RENAL ABNORMALITIES

Several studies have identified the presence of CFTR in the kidney, and its mRNA has been detected in all nephron segments by reverse transcription–polymerase chain reaction (PCR).[199] CFTR has been demonstrated in the proximal tubule, thin limbs of Henle's loop and luminal membrane of the distal tubule, cortical collecting ducts, and the inner medullary collecting ducts by immunocytochemistry.[200] CFTR has also been detected in the proximal and distal tubules and in cortical and inner medullary collecting ducts.[201] Despite this high expression of CFTR, patients do not show major renal dysfunction, but it is known that the renal excretion of some drugs, particularly antibiotics, and the renal capacity to concentrate and dilute urine are deficient.[199]

Nephrolithiasis has been shown to be increased in CF patients. Chidekel and Dolan[202] found a cumulative incidence of 5.7% in a group of 140 patients. The majority of patients had calcium oxalate stones. An additional 4% of patients showed calcium oxalate crystaluria. All patients had pancreatic insufficiency in keeping with the description of hyperoxaluria in other groups of patients with gastrointestinal diseases and associated fat malabsorption.[202]

Increased renal clearance and subsequent lower serum concentrations of a number of antibiotics, including aminoglycosides, beta-lactam antibiotics, and quinolonones, have been reported. It is believed that the increased clearance is due to impaired tubular reabsorption secondary to alterations in the renal tubular ion-transport mechanism.[203]

ELECTROLYTE ABNORMALITIES

Metabolic Alkalosis

Increased electrolyte loss in the sweat over a prolonged period of time may lead to electrolyte depletion and chronic metabolic alkalosis. Contributory factors include increased gastrointestinal losses, acute intercurrent illness, thermal stress, and limited electrolyte intake. While standard infant feeding recommendations satisfy electrolyte requirements for growth of non-CF infants, they are inadequate to compensate for the increased electrolyte losses present in infants with CF.[204]

Sodium losses of up to 80 mEq and chloride losses of up to 100 mEq have been reported in infants in situations of profuse sweating.[205] Such complications are more frequent in arid climates.[206] Patients often present with anorexia, irritability, vomiting, and failure to thrive, usually in the absence of dehydration or cardiovascular instability. Laboratory abnormalities include elevation of blood pH and P_{CO_2}, bicarbonate and base excess, and low serum concentrations of sodium, chloride, and potassium. Urinary excretion of sodium and chloride is markedly decreased as a result of secondary hyperaldosteronism.[207] Preventive measures include avoidance of thermal stress and provision of adequate salt in the diet. This can be accomplished by adding $^1/_4$ teaspoon table salt (23 mEq sodium) to each liter of infant formula or liberal amounts of salt to solid foods. Treatment consists of the replacement of calculated fluid and electrolyte losses.

FEMALE REPRODUCTIVE TRACT

Genital Abnormalities

Excess cytoplasmic and extracellular cervical mucus is present in patients with CF in the absence of inflammation or other obvious contributory factors. This is a consistent finding in newborns, and although it decreases in frequency, it remains a common finding throughout infancy and childhood.[208] The submucosal glands, uterine cavity, and cervical os may also be filled with mucin-rich material. In one third of adult patients, multicystic ovaries and reduced uterine size are demonstrated on ultrasonography, especially in patients with amenorrhea or irregular menstrual cycles.[209] The histologic appearance of the endometrium, fallopian tubes, and ovaries is otherwise normal.[208]

Analysis of cervical mucus reveals that it is scanty and dehydrated, usually containing less than 80% water.[210] This is below the minimum critical water level of 93% to 95% believed to be essential for sperm migration.[211] Moreover, the typical mid cycle increase in water content and the accompanying thinning of cervical mucus that occur in normal subjects are not seen in patients with CF. This may result in the formation of a tenacious mucus plug in the os that impedes sperm penetration. The electrolyte pattern of the cervical mucus is noncyclic; the average sodium concentration in the dry residue is only one tenth of normal during the critical mid cycle period.[210]

Male Infertility

The majority of men (>95%) with CF have associated congenital bilateral absence of the vas deferens. This abnormality is directly associated with the genetic mutation in the CFTR-regulated gene as the encoded cyclic adenosine monophosphate–regulated chloride channel abnormalities influence the formation of the ejaculatory duct, seminal vesicle, vas deferens and distal two thirds of the epididymis. The anomalies associated with the latter include absent or atrophic seminal vesicles, ejaculatory ducts, and the body and tail of the epididymis in addition to the absence of the vas deferens. Rare case reports of fertile men with CF mutations and mild symptoms of CF have been reported; however, most patients present with azospermia and infertility.[212]

While absence of the vas deferens is not amenable to surgical correction, the advent of assisted reproductive techniques (ARTs) has permitted sperm harvesting from either the epididymis or the testes in combination with oocytes retrieved from the female partner, thus allowing men with CF to be biological parents. The techniques for aspirating sperm include microsurgical epididymal sperm aspiration (MESA), percutaneous epididymal sperm aspiration (PESA), and testicular sperm aspiration (TSA). MESA yields the most sperm and therefore is the preferred method. Aspirated sperm are cultured directly with retrieved oocytes from the female partner in an in vitro fertilization (IVF) system, or an individual sperm is injected directly into the oocyte. This latter technique, referred to as intracytoplasmic sperm injection (ICSI), yields a greater pregnancy rate in the CF setting than does standard IVF.[213]

Hubert and associates[214] reported that of 19 couples undergoing IVF/ICSI because of congenital absences of the vas, 12 (62%) achieved a pregnancy, including 2 ectopic pregnancies, 2 spontaneous abortions, 1 termination of pregnancy for polymalformed twins, and 11 single deliveries in nine couples. Similar results were given in the report by Phillipson and colleagues,[215] in which fresh and cryopreserved sperm were used for ICSI. Of 29 cycles with fresh spermatozoa, a fertilization rate of 76% of oocytes injected and a 17% embryo implantation rate occurred. Twenty-four cycles in which cryopreserved spermatozoa were used resulted in an oocyte fertilization rate of 69% and an embryo implantation rate of 20%. Eighteen clinical pregnancies occurred with 14 live births without congenital anomaly. Multiple pregnancies are a frequent occurrence with this technique.

Female Fertility

CFTR is found in large quantities on the cervix and, although anatomically normal, histologically the columna epithelium is distorted by mucus-filled balloon or signet ring cells. The expression of CFTR is believed to be hormonally mediated; in health, the water content of cervical mucus varies during the menstrual cycle, peaking at ovulation when 93% to 95% hydration allows the passage of sperm through the cervical canal, but these cyclic changes in hydration are not seen in patients with CF and the mucus retains increased tenacity throughout the cycle. Endocervical polyps and mucus plugs have been reported to arise either de novo or triggered by hormonal contraception, and the cervical os and canal may become blocked with mucus plugs, which are thought to be one cause of infertility in patients with CF.[208,210,216,217]

The endometrium and fallopian tubes contain some CFTR but are reportedly normal. The ovaries do not express CFTR, but although they develop normally in children, abnormalities are seen in adolescents and adults with redundant follicular cysts and reduced number of follicles noted from both ultrasound and postmortem studies. Patients with CF who are undernourished may show a delay in pubertal growth spurt by 12 to 14 months. Menarche, which usually occurs around the age of 13 for females without CF, has been reported at between 14.2 and 14.9 years in patients with CF.[218-221]

It has been postulated that menarche is triggered by the achievement of a critical body composition of approximately 17% body fat, which corresponds to approximately the 10th percentile of weight for height.[218] Studies have shown that girls with CF are shorter and lighter than normative data for healthy females but that the height, weight, and percentage fat of menarchal girls with CF are the same as for younger menarchal girls without CF. Menarchal delay is correlated to the severity of malnutrition, and multiple stepwise regression has shown weight to be the most significant determinant of menarchal delay. It has been noted, however, that up to 20% of young women with CF may menstruate without reaching the critical 17% body fat composition, which suggests that when critical body composition is not reached in time, other unspecified factors may become influential.

Pituitary Gonadal Axis

Luteinizing hormone (LH), follicle-stimulating hormone (FSH), testosterone, progesterone, and estrogen have all been measured in large groups of females with CF from the prepubertal to adult age groups. In women, FSH changes follow the same changes with age as in non-CF individuals but at lower levels and result in a delay of approximately 2 years before pubertal levels are reached. Progesterone and estrogen peaks are delayed 2 years. The mechanism of such delay is unknown; however, because infusion of gonadotropin-releasing hormone shows normal or near normal LH and FSH responses, primary pituitary failure appears to be unlikely. CFTR has been identified in the hypothalamus and is postulated to influence the release of GnRH, which may explain the pubertal delay in healthy well-nourished CF individuals.

Menstruation

Once established, the majority of young women with CF develop normal or near normal menstrual cycles,[209] although menstrual problems are frequent. Stead and associates[209] studied 45 female patients with CF aged 15 to 40 years and found that 40 of the 45 patients had commenced menstruation. Of those who had commenced menstruation, 50% were regular, while a further 28% had irregular or missed periods. Only 22% of the group had secondary amenorrhea. Pulmonary function showed considerable overlap between the groups, but all amenorrheic patients had an FVC of less than 55% predicted.

Female Reproduction

Thirty years ago, the first report of fertility in female patients with CF quoted an incidence of less than 20%; however, this is almost certainly an underestimation at this present stage due to the improved overall health of adult females with CF in the 21st century.[210] Because the reproductive tract is normal in most women with CF, those with acceptable weight and lung function would be expected to develop into sexually mature adults who should ovulate and menstruate normally. There appears to be little evidence that fertility is reduced in healthy women with CF except by the mechanical barrier of the cervical mucus plug, a barrier that can be reduced by the administration of contraceptive hormone preparations. Early reports of pregnancies occurring in women with CF occurred in the early 1960s. These early reports, however, were associated with high complication rates and deterioration of maternal health both during and after pregnancy. In a large review of more recent pregnancy outcomes, Kent and Farquharson[211] found a spontaneous abortion rate of 4.6% across 15 separate studies. While 14% of pregnancies were terminated, 82% of pregnancies progressed beyond 20 weeks' gestation, with 24% resulting in premature delivery. Of these, 11.6% of cases were due to maternal complications of CF and 88% were due to spontaneous natural labor.[222]

Pancreatic insufficiency, poor prepregnancy body weight, and poor maternal weight gain were initially considered markers of disease severity associated with a poor outcome during pregnancy. More recently, the number and proportion of mothers with pancreatic insufficiency having a successful pregnancy are increasing, and as nutritional care improves, pancreatic status has become a less significant variable, although recent studies still confirm a better prognosis for patients with pancreatic insufficiency.[222]

The development of diabetes with a diagnosis before pregnancy or during pregnancy confers a worse prognosis to both the mother and the infant.[223,224]

Maternal mortality has been estimated to approach 10% at 6 months after delivery and 14% at 2 years after delivery, and patients with a prepregnancy FVC of less than 60% predicted have an elevated rate of premature delivery and an associated high rate of maternal mortality.

Long-term Outcome for the Mother

Fiel and FitzSimmons[223] used the 1990 North American Cystic Fibrosis Database to examine pregnant women with CF and compared their outcomes to controls matched for

age, lung function, and weight percentile. Two hundred fifty-eight women who had live births were compared with 889 controls, and no differences were found between cases and controls in rates of decline of FEV_1 or in the frequency of complications, including hemoptysis, pneumothorax, and infective exacerbations during pregnancy, or during the subsequent 2 years. Pregnancy was therefore not an independent risk factor for survival but an end point that was equal in both cases and controls while worse for those with poor lung function, low body weight, or diabetes in both groups.

HEMATOLOGIC ABNORMALITIES

Iron deficiency anemia has been reported in 33% to 66% of patients with CF.[225,226] In a study of 71 adult CF patients, Pond[226] found functional iron deficiency (transferrin saturation <16%) in 62% of patients. Hemoglobin concentration and mean cell volume were lower in iron-deficient patients, in whom there was a nonsignificant trend for lower serum ferritin. Ten iron-deficient patients were anemic. There were no significant differences between iron-deficient and normal-iron patients in intake of calories, protein, iron, and vitamin C as determined by dietary records. Dietary iron deficiency was not thought to be an important factor in functional iron deficiency in adult CF patients. Impairment of absorption by exogenous pancreatic enzyme supplements has been postulated as a possible cause of iron deficiency in CF patients; however, Pond's study suggests this is unlikely as enzyme intake was the same in the two groups. Chronic inflammation is likely to be the primary cause of functional iron deficiency in adult CF patients. Thrombocytopenia in patients with CF is almost always related to hypersplenism secondary to cirrhosis and portal hypertension.

OCULAR COMPLICATIONS

Ocular abnormalities in CF include visual field defects, venous engorgement, tortuosity, hyperemia and blurring of the optic nerve head, abnormal pupillary responses, and decreased contrast sensitivity.[227,228] Examination of the ocular surface shows an increase in fluorescein staining and clinical blepharitis, as well as decreased Schirmer testing and tear lysozyme. Conjunctival epithelial cell morphology is normal.[229] Adolescents and young adults with vitamin A deficiency may manifest conjunctival xerosis and night blindness (decreased dark adaptation).[53,230] In patients with hyperglycemia, there is evidence of breakdown of the blood-retina barrier; this is considered to represent a functional abnormality that is a precursor to diabetic microangiopathy.[213] Proliferative diabetic retinopathy with blurred vision, neovascularization, vitreous hemorrhages, and cataract formation has been reported in CF patients with long-standing CFRD.[232]

SALIVARY GLANDS

In patients with CF, there are characteristic histologic abnormalities of the salivary glands. In the submaxillary glands, there are dilated mucus acini and ductules filled with inspissated mucus secretions. In the labial mucus glands, there are dilated ducts with inspissated mucus, atrophy and cyst-like dilation of acini, and metaplasia of the ductile epithelium. While enlargement of the submaxillary glands has been observed in a large proportion of patients, parotid gland enlargement is rare.[233,234]

Studies of flow and constituent composition of the various salivary glands have yielded conflicting data, probably related to differences in methods of salivary gland stimulation and saliva collection. Shori and Asking[235] examined the effects of parasympathetic and sympathetic autonomic nerve stimulation on these glands using a rat model and demonstrated the existence of three separate nerve pathways through which secretion of protein could be evoked from serous and mucous exocrine cells. These pathways allow the secretion of proteins from the intracellular compartments in a constitutive, intermediate, or regulated manner. The primary aspects of the secretory profile, including concentration and the degree of hydration of secreted material, differ greatly between the pathways, are cell type specific, and presumably are a direct consequence of controlled changes in the levels of second messengers induced on stimulation of these cells. Previously published reports suggested that only the β-adrenergic–regulated pathway was affected in CF, and as a result, differences between the pathways in their secretory profiles have been postulated to possibly influence the development of lung disease through disparate disturbances in the secretion of protein and fluid from serous and mucous cells of the submucosal glands lining the bronchiolar tree in humans.

SKIN MANIFESTATIONS

Several reports have described infants displaying generalized erythematous rashes at diagnosis. In these infants, the rash typically begins as erythematous papules in the nappy area, which may then spread, to become generalized and confluent with well-demarcated erythematous, scaly papules covering most of the body. Papules and desquamation occur on palms and soles. This spectrum of symptoms has been attributed to kwashiorkor secondary to pancreatic insufficiency and malabsorption, and is believed to be due possibly to free radical damage to mitochondria and lipid membranes in the skin, due in part to multiple nutritional deficiencies including zinc and essential fatty acids. Zinc replacement and correction of pancreatic insufficiency are associated with clearing of the rash.[236-238]

In patients receiving treatment, the commonest skin manifestations are erythematous or purpuric reactions secondary to medication use, particularly antibiotics. Photosensitivity to quinolone antibiotics is common and has been estimated to develop in up to 50% of adult patients taking ciprofloxacin.[239]

MUSCULOSKELETAL ABNORMALITIES

Over the past two decades, reduced bone mineral density has been recognized in both adult and pediatric CF patients. Gibbens and associates[240] found reduced bone mineral density in 57 patients with CF with a mean age of 12 years. Similar findings were reported by Hendersen and Madsen,[241] who examined 62 patients (mean age, 10.7 years.) and found a mean *Z* score for bone mineral density (BMD) of –1.03 at the lumbar spine and –0.71 at the femoral neck. Additional studies have also shown reduced BMD in adults with CF. Haworth and colleagues[242] found mean BMD *Z* scores of

–1.21 (lumbar spine) and –1.25 (femoral neck) when measured using dual-energy x-ray absorptiometry (DEXA) techniques. Body mass index, percent predicted FEV_1, and physical activity were all positively related to the mean BMD score.

Osteoporosis may manifest as asymptomatic bone loss identified on imaging studies, evidence of asymptomatic bony fractures such as anterior wedge compression of vertebral bodies, or clinically evident fractures, commonly involving ribs.[243] Osteoporosis in CF is generally multifactorial in origin. Identified risk factors for the development of osteoporosis include malabsorption of vitamin D and calcium, low body weight, decreased physical activity, hypogonadism, respiratory acidosis and the osteolytic action of circulating cytokines, amenorrhea, glucocorticoid use, diabetes, chronic infection, and delayed puberty.[244] Osteoporosis may also occur as in association with lung transplantation.[245] In addition to nutritional support, pancreatic enzyme replacement, management of hypogonadism, adequate exercise and avoidance of corticosteroids, and calcium and vitamin D supplements may be useful in preventing bone loss in CF. The use of bisphosphonates, well established in the treatment of osteoporosis in postmenopausal women, is not yet well established in CF. In addition, Haworth and associates[246] reported that in a group of CF adults, the administration of the intravenous bisphosphonate pamidronate was associated with severe bone pain following injection. An increase in circulating cytokines has been postulated as an explanation for this side effect. In a 6-month placebo-controlled study of 31 patients with CF (15 in active treatment), Haworth and associates[246] found that the 3 times monthly administration of pamidronate increased BMD in the lumbar spine and in the hip but decreased BMD in the distal forearm. Bone pain was the most common adverse event, occurring in 11 of 15 participants not receiving corticosteroids. There was no significant difference in survival between the actively treated and placebo groups, although this may have been due in part to short-term follow-up and small sample size.[247]

Digital Clubbing

The well-known clubbing of fingers and toes that occur in CF, as well as other diseases of the chest, has been considered to be a form of hypertrophic pulmonary osteoarthropathy (HPOA).[248] Nakamura found digital clubbing in 75 of 100 (75%) of a group of 100 patients with CF (43 males, 57 females; mean age, 15.7 years). The degree of clubbing was inversely correlated with PaO_2, FEV_1, and FEF_{25-75}. Clubbing was positively correlated with right ventricular hypertrophy and the slope of phase 3 of single-breath nitrogen washout. There was no significant correlation between the degree of clubbing and age, total lung capacity, $PaCO_2$, or a history of liver disease.[249]

HPOA is the most common form of arthropathy in CF. Although its etiology remains obscure, progressive lung suppuration and declining pulmonary function are implicated. The presence of long bone pain and joint swelling that may be aggravated by pulmonary exacerbations in a clubbed patient are the main clinical criteria for diagnosing HPOA. HPOA occurs in 5% to 15% of patients with CF, usually in those over 12 years of age and with advanced suppurative lung disease. By the time radiographic changes such as periostitis appear, HPOA is usually relatively advanced. Bone scintigraphy has been reported as a sensitive method for detecting HPOA, although there is no absolute standard. The features of the delayed phase of the radionuclide bone scan include the appearance of a diffuse, symmetric tracer accumulation in the diaphyses and metaphyses of tubular long bones along their cortical margins, creating a distinctive "parallel track" sign. Radiographs of involved areas may remain normal for several months after positive features are apparent on the delayed bone scan.

HPOA manifests as bilateral painful swelling of the distal third of affected bones, usually the long bones of both upper and lower limbs. Smaller limb bones such as metacarpals and metatarsals are less commonly involved. There may be arthralgia, stiffness, joint swelling, and effusion. In severe cases, involvement of ribs, clavicles, scapulae, pelvis, and malar bones has been reported. Pathologically, there is edematous thickening of the periosteum, inflammatory periostitis, and subperiosteal new bone formation. Synovial biopsy shows cellular infiltration, hyperplasia of synovial cells, and fibrosis. The arthropathy is usually chronic, with intermittent exacerbations at times of pulmonary exacerbations. Management involves optimization of the pulmonary care and treatment of chest exacerbations aggressively. Nonsteroidal anti-inflammatory medication may relieve the discomfort but does not reverse the disease.

Arthritis

Approximately 20% of adult patients with CF have been reported with arthropathy, but the incidence in pediatric populations is less well defined. There is a clear association between age and the presence of musculoskeletal problems, and this probably relates to declining pulmonary function.

Episodic Arthritis

Episodic arthritis (EA) first described by Newman and Ansell in 1979[250] does not appear to be as closely associated with diminished pulmonary function or age as HPOA. While progression to persistent erosive changes has been reported, this appears uncommon.[251] Bone scans show the presence of synovitis, with an appearance distinctly different from that of HPOA. The arthritis may be associated with fever and skin lesions usually located distally on the legs.[252] Neither HPOA nor episodic arthritis has been linked to any particular HLA type.[253]

Back Pain and Spinal Deformity

Mechanical back disorders have received less attention than other musculoskeletal complications of CF. A review from our large pediatric specialist clinic in Melbourne, Australia, found that 25% of adolescents older than 15 years had kyphosis (R. J. Massie, personal communication, 2006) An association with advancing age, female sex, poor lung function, and worse clinical score was evident. None of the kyphoses was considered serious enough to contribute to reductions in pulmonary function. Osteoporosis and crush fractures are a potential cause for serious mechanical back disorders in children and adolescents with CF.

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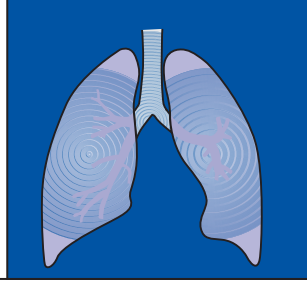


CHAPTER 64 Congenital Malformations of the Lungs and Airways

Jean-Martin Laberge and Pramod Puligandla*

TEACHING POINTS

- The classification of congenital lung lesions is the subject of controversy.
- There are multiple reports of "hybrid" congenital lung lesions, with overlapping features of congenital cystic adenomatoid malformation (CCAM)/congenital pulmonary airway malformation (CPAM), sequestration, and bronchial atresia.
- Echogenic lung lesions may regress or disappear prenatally. Postnatal chest radiograph may appear normal, but computed tomography scan is necessary to confirm true disappearance.
- CCAM/CPAM type 4 may be indistinguishable from type 1 pleuropulmonary blastoma, a malignant tumor.
- Congenital cystic lung lesions should be excised even when asymptomatic.
- Many theories exist to explain lung malformations; recently attention has turned to signaling proteins and growth factors implicated in lung development (Shh, FGF 7 and 10, lgl-1, and retinoic acid, among others).

Congenital anomalies account for one third of infant deaths and are one of the leading causes of death in this age group in most developed countries.[1,2] Congenital malformations of the respiratory system now rank second, behind those of the cardiovascular system, as a cause of infant mortality. With a rate of 0.25 death per 1000 live births, they have surpassed those of the nervous system (0.23 per 1000) in the past decade in the United States.[3] This is mostly due to increased selective termination for the latter.[1] Eighty percent of infant deaths from respiratory system malformations are caused by lung hypoplasia or "dysplasia."[2,3] However, congenital malformations of the lungs and airways include a wide spectrum of developmental anomalies, some of which remain asymptomatic and are discovered incidentally on imaging studies. Their frequency has been reported to range from 7.5% to 18.7% of all congenital malformations,[4,5] but their exact overall incidence is difficult to ascertain. They may be part of more complex syndromes and are often associated with other congenital anomalies, particularly those involving the heart and great vessels. Bohin and Field[6] have divided malformations of the respiratory system into those affecting the upper and the lower airway. Among the former, laryngeal and tracheal defects are the most common, with a reported incidence of 1 in 10,000 to 1 in 50,000 births for laryngeal malformations[7]; however, it is doubtful that this includes all cases of mild laryngomalacia, especially since Callahan estimates the incidence of primary tracheomalacia, which is less common, at 1 in 1445.[8] Furthermore, the incidence jumps if one adds the tracheoesophageal fistulas and tracheomalacia usually accompanying esophageal atresia, which has an incidence around 1 in 4000.[6] Among lower respiratory tract anomalies, one can include (1) anomalies of the chest wall and diaphragm, the most common being congenital diaphragmatic hernia with an incidence around 1 in 3000 live births; (2) pulmonary hypoplasia, which is the most common single abnormality found at autopsy, reported in 15% to 20% of early neonatal deaths, but its exact incidence is difficult to find since it is usually secondary to other conditions; and (3) finally, abnormalities of lung development, which are often described as "rare."[6] Among these, cystic lung lesions are the most common, with an incidence quoted at 4 to 6 per 10,000,[9] but the original article gave an estimate of 4.2 "bronchogenic cysts" per 10,000 hospital admissions.[10] This same 1952 paper quotes an incidence of congenital cystic lung disease discovered on routine chest radiographs in asymptomatic young adults of 5 per 100,000 population. Further difficulties arise with these estimates since many of the cystic lesions in the early series may have been acquired[9]; on the other hand, some lesions may remain asymptomatic and undetected. The incidence just cited can be compared with the incidence reported for congenital cystic adenomatoid malformation (CCAM), reported to occur in 1 in 10,000 to 1 in 25,000 births (see later); this malformation is the most common of the ones involving lung development and comprises about 25% of the congenital parenchymal malformations.[11] Yet, others quote an incidence of pulmonary sequestration at 0.15% to 1.7% in the general population, without providing a reference.[12] Stocker[13] found 13 cases of extralobar sequestrations in a series of 47,000 autopsies performed on stillborn and liveborn infants. Considering that most patients with sequestration do not die, it is unlikely that the incidence could be higher than 1 in 4000 births. Finally, an overall incidence of congenital lung malformations of 2.2%

*The authors with to acknowledge the significant contribution of Dr. Barry S. Clements, who authored this chapter in the previous edition. Some of the text and many figures and references from his chapter were used in the current edition.

is quoted by some authors, but the original article likely refers to the incidence of congenital malformations in relation to acquired lung diseases.[14] In conclusion, congenital parenchymal lung malformations are not so rare, but their exact incidence is elusive.

PATHOGENESIS

Many theories have been proposed to explain the various respiratory tract malformations encountered. Older theories have focused on mechanical and vascular aspects of lung growth; examples are Pryce's vascular traction theory[15] and the accessory bud theory to explain pulmonary sequestration[16,17] and the vascular insufficiency[18] and vascular maldevelopment theories[19] that try to explain all abnormal lung development. Authors have looked at molecular markers of lung development, implicating a dysregulation in branching morphogenesis and/or in cellular proliferation.[20-22] Animal models are providing new information. In the Adriamycin-induced esophageal atresia rat model, various forms of communicating bronchopulmonary foregut malformations can be seen, including tracheal atresia with a right esophageal lung and absent left lung.[23] Signaling proteins associated with lung development and their receptors are also being studied; these include growth factors such as Sonic Hedgehog (Shh), fibroblast growth factors (FGF) 7 and 10, lung growth ligand-1 (lgl-1), and transcription factors such as Hox genes, Gli genes, and thyroid transcription factor-1 (TTF-1).[24] Some of these are responsible for early lung development (FGF-10), lung branching (Shh), and alveolar development (lgl-1). Vitamin A (retinoic acid) and its receptors also play an important role. A multitude of studies using various knock-out models in mice have shed some light on the roles of these factors and their receptors on airway and lung development, and a few reports attempt to establish a correlation in fetuses or neonates with lung malformations.[20,24-33] The reader is referred to an excellent recent review by Groenman and colleagues.[24]

The various theories on normal and abnormal early foregut embryology were recently reviewed by Kluth and Fiegel, who also analyze results from the Adriamycin rat model.[34] Further lung development is described in Chapter 3. Some important principles that help to understand the various malformations encountered are worth repeating here:

1. Bronchial branching to terminal bronchiole is complete 16 weeks after conception.[35] An insult affecting lung development in the 8th week of intrauterine life will result in an entirely different lesion than if the same insult occurred in the 20th week, when bronchial branching is complete.
2. Pulmonary vascular development is similar to the pattern of bronchial branching but occurs slightly later.[36]
3. Alveolar development follows the formation of the respiratory bronchioles, and later the saccules, after the 24th week of gestational age, and continues after birth for some years.[35,37-39]
4. At any stage during pulmonary development, the rate of growth of individual component tissues, namely the airway, alveoli, arteries, veins, and lymphatics, may not be uniform.[35]
5. In the early stages, the tips of the dividing bronchial buds are supplied by primitive bronchial arteries arising from the dorsal aorta near the celiac axis. The extrapulmonary part of these arteries disappears during the 6th week of gestation and the definitive bronchial arteries arising from the aorta develop between the 9th and 12th weeks; their capillary bed is limited to the bronchial wall. Persistence of a primitive bronchial artery explains the infradiaphragmatic origin of the systemic artery supplying some lung sequestrations.[18] Parallel to this, the pulmonary arteries develop and supply lung units starting at the level of respiratory bronchioles. Their proximal part results from angiogenesis (branching from preexisting vessels), while their distal part, in future alveolar regions, forms concurrently by vasculogenesis (blood lakes that form within the mesenchyme and transform into vessels); the two then fuse together, likely in the second trimester of gestation.[40] Of note, all intrapulmonary structures, including bronchi, drain to the pulmonary veins, with connections established as early as 54 days of gestation, much before pulmonary artery supply develops.[40]

The relationship between embryology and pathology is further discussed as we describe individual malformations.

CLASSIFICATION

In the past, many classifications of congenital lung malformations have been proposed, although none has gained universal acceptance. These have been based on anatomic localization, histopathologic type, pathogenesis, or extent of lung involvement. In general, lesions involving the lung unit as a whole, or the trachea and the major bronchi, are simply and easily defined, whereas lesions involving the lung parenchyma tend to be more complex, and it is here where consensus on terminology is lacking. In 1966, the American College of Chest Physicians in their catalogue of congenital lung lesions[41] abandoned any attempt at a formal classification and merely produced an inventory of the different malformations. When Landing produced his review on the subject in 1979,[42] he was forced to use the same format. In 1987, Clements introduced the malinosculation concept, also dubbed the "wheel" theory or classification[43] (Fig. 64-1). Achiron recently suggested a new classification based on Clements' work and two-dimensional and Doppler findings on prenatal ultrasound.[44] Because the term *malinosculation* had not gained wide acceptance, Achiron proposed the term *dysplasia*, meaning "abnormal tissue formation." Although semantically correct, this term would likely lead to more confusion for clinicians, who already use it in the context of bronchopulmonary dysplasia, alveolar capillary dysplasia, and other less common entities.[45] Sebire[45] questions the clinical usefulness of introducing five more categories of "fetal lung dysplasia" to encompass virtually all developmental respiratory tract anomalies. Bush[46] has also proposed a new nomenclature that appears oversimplified and without clinical usefulness, with the term *congenital thoracic malformation* encompassing most of the congenital lung malformations that will be discussed later.

The confusion resulting from attempts to classify complex and overlapping anomalies is best exemplified in the group of parenchymal lesions. CCAM of the lung was classified into three types by Stocker in 1977,[47] who subsequently revised the classification into five types[48] (Table 64-1). He later

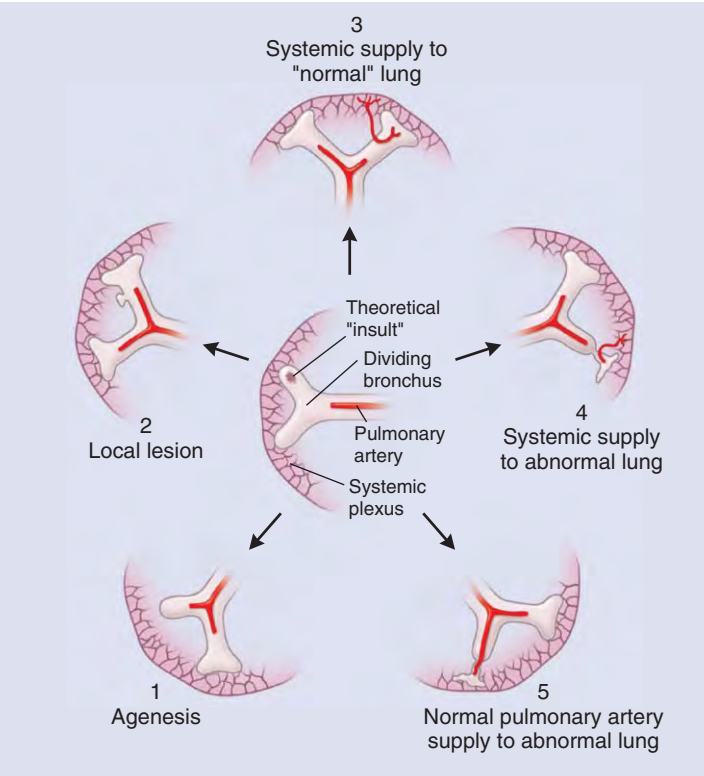


Figure 64-1 Abnormal lung development. The range of possible outcomes following an insult to the developing lung bud *(center)* is simplistically displayed here as the spokes of a wheel.

changed the catchy name "congenital cystic adenomatoid malformation" to "congenital pulmonary airway malformation" (CPAM)[49] because most types are not adenomatoid and only three types are cystic. In recent years, many hybrid lesions have been described, mostly having features of both sequestration and CCAM/CPAM.[50-60] Furthermore, prominent pathologists disagree on the definition and nomenclature, which has changed over time.[47-49] For example, Stocker[49] believes that intrapulmonary bronchogenic cysts and other congenital unilocular lung cysts are type 1 CCAM, whereas others disagree.[51] Other pathologists caution that the new Stocker type 4 has features that overlap with type I pleuropulmonary blastoma (PPB) so much so that they recommend approaching these lesions in infants as malignant until proved otherwise.[61,62] Langston believes that the five types of CPAM represent different malformations with varying etiologies and proposes a new classification.[51]

Back in 1974, Buntain[63] suggested that all congenital lung lesions be considered as one clinical group. Because the purpose of this chapter is to provide clinically useful information for pediatric specialists dealing with patients with respiratory tract malformations, we describe these malformations using the terms generally used, highlighting some of the controversies and overlapping features as we go. Most important, clinicians should use descriptive terms (such as the presence and size of cysts, the presence of a systemic arterial connection) instead of trying to assign a pathologic diagnosis based on imaging alone.

AIRWAY MALFORMATIONS

Larynx

LARYNGOMALACIA

Laryngomalacia is the most common congenital anomaly found in the upper airway. Fortunately, most cases are mild, readily diagnosed clinically, and generally require no more management than parental reassurance. Strictly speaking, it is not a true malformation but represents a delay in the maturation of the supporting structures of the larynx. This causes the larynx to be more collapsible than normal during inspiration, resulting in inspiratory stridor (the most notable symptom associated with this condition), which varies with the inspiratory force at the time. This stridor is usually first noticed in the early neonatal period, with most patients

Table 64-1
Stocker's Classification of CCAM/CPAM

Type/Synonym	0/Acinar Dysplasia or Agenesis	1/Large Cyst or Predominant Cyst	2/Medium Cyst	3/Small Cyst or Solid or Adenomatoid	4/Peripheral Cyst
Approximate frequency (%)	1-3	>65	20-25	8	2-4
Cyst size (maximum, cm)	0.5	10.0	2.5	0.2	7
Microscopic appearance	Ciliated Bronchial-like structures lined by pseudostratified tall columnar epithelium with goblet cells	Multilocular, large cysts Broad fibrous septa Mucogenic cells Ciliated Pseudostratified tall columnar epithelium	Small, uniform cysts Irregular proliferation of ectatic structures resembling bronchioles	Solid, bulky lesion Irregular curving channels and small air spaces lined by cuboidal epithelium	Multilocular, large cysts lined by flattened alveolar lining cells
Muscular wall thickness (μm) of cysts	100-500	100-300	50-100	0-50	25-100
Mucus cells	Present in all cases	Present (33% of cases)	Absent	Absent	Absent
Cartilage	Present in all cases	Present (5%-10% of cases)	Absent	Absent	Rare
Skeletal muscle	Absent	Absent	Present (5% of cases)	Absent	Absent

Modified with permission from Gilbert-Barness E: Respiratory system. In Potter's Pathology of the Fetus and Infant. St. Louis, Mosby, 1997, pp 741-769.

having presented by 6 weeks of age, although some patients appear not to have significant symptoms until a few months of age, when the stridor may be made apparent for the first time following an intercurrent upper respiratory tract infection. In some cases laryngomalacia is due to short arytenoepiglottic folds, to the flaccidity of an omega-shaped epiglottis, or to collapsing arytenoids.[64] Laryngomalacia may also be acquired, as seen in some neonates and infants with Pierre Robin sequence who have upper airway obstruction and must generate high negative pressures during inspiration.[65] The stridor is generally more prominent during crying, feeding, and respiratory tract infections. A sudden, sharp inspiratory effort often results in a loud, high-pitched inspiratory "whoop," which may alarm the parents. Some patients have stridor at rest, and in 10%, a minor expiratory component may occasionally be present as well. Significant airway obstruction in laryngomalacia is unusual, although occasionally patients with severe forms may become quite distressed, particularly during intercurrent respiratory tract infections, requiring in-hospital care and, rarely, ventilatory support. Other potentially serious complications include pulmonary hypertension and cor pulmonale, failure to thrive, and impaired intellectual development secondary to episodes of hypoxia and hypercapnia.[49] Laryngomalacia is associated with multiple congenital anomalies or neurologic compromise in 20% of cases.[66] A familial form has also been described.[67] The diagnosis in most cases should be based on clinical history and physical examination, but flexible laryngoscopy is essential in neonates or infants with associated malformations or conditions such as prematurity, prolonged intubation, or failed extubation. When considering investigating these patients, it should also always be borne in mind that laryngomalacia often coexists with other laryngotracheal malformations (such as tracheomalacia and esophageal atresia) and cardiovascular malformations. In such patients, the flexible endoscopy is often completed by rigid bronchoscopy performed under general anesthesia.

Laryngomalacia in mild cases is a benign, self-limiting condition. Symptoms usually resolve within the first 12 to 18 months and almost always by 2 years of age. However, strong reassurance and ongoing support are often needed to allay parental anxiety. Patients who exhibit significant sleep disturbance, as evidenced on polysomnography, may benefit from administration of positive airway pressure through a closely applied face mask during sleep. However, this form of treatment can be fraught with difficulties and is often not well tolerated, in which case surgical intervention, either epiglottoplasty, epiglottopexy, release of the arytenoepiglottic folds, or rarely tracheostomy, may need to be considered. This is particularly true in cases with severe, potentially life-threatening airway obstruction, or when symptoms are sufficiently severe to interfere with normal growth and development.[64,68] Although it is generally accepted that patients who have had laryngomalacia in infancy show no ill effects clinically once their symptoms have subsided, some follow-up studies of these patients have demonstrated abnormalities of inspiratory flow on pulmonary function testing in late childhood.[69]

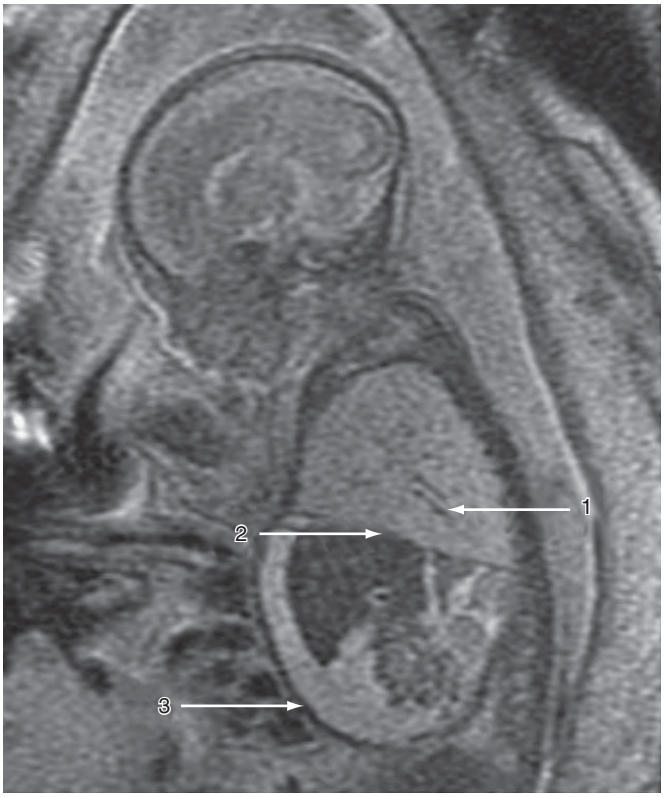
LARYNGEAL ATRESIA, WEBS, AND STENOSIS

Laryngeal atresia is a life-threatening malformation. The lesion results from failure of recanalization of the epithelial septum, which forms around 6 weeks of gestation and separates the developing esophagus from the tracheal bud. At 10 weeks, the epithelial membrane is ready to open again into the now-developing primitive laryngeal aditus. Despite the complete lack of communication with the airway, distal lung development and general fetal growth are usually unaffected, although fetal ascites may develop.[70] In the past, affected babies would often die at birth or have severe neurologic sequelae because of the failure to establish an airway. In recent years, routine prenatal ultrasound examinations have allowed the diagnosis to be made before birth, resulting in a higher survival. On ultrasound, the lungs appear more echogenic and enlarged, causing eversion of the diaphragms; a distended trachea can also be observed. Magnetic resonance imaging confirms the increased fluid content of the lung, with a hyperintense signal on T2-weighed images (Fig. 64-2). Near term, the fetus is delivered using the EXIT procedure (EX-utero Intrapartum Treatment), which is a cesarean section done under deep maternal general anesthesia to provide uterine relaxation.[71,72] The fetal head and neck are exposed and the airway is secured, usually by tracheostomy, while oxygenation is maintained through the placenta. Prognosis has greatly improved with prenatal diagnosis and proper perinatal management, although it may also be affected by the presence of associated defects.[73] Furthermore, subsequent laryngeal function in survivors is usually abnormal, often requiring surgical reconstruction at a later date, particularly to assist with speech.[64] Tracheomalacia and abnormal function of the hyperplastic lungs are also common and often require prolonged ventilator support.

The prognosis is better with *laryngeal webs*, which can present with openings of varying sizes. Of these, 75% are glottic, with the rest supraglottic or subglottic in location. They are usually situated anteriorly, with a posterior concave glottic opening. Complete webs present like atresias, whereas partial webs present with stridor and a hoarse or weak cry and may cause varying degrees of respiratory difficulty depending on the degree of obstruction. Partial webs may also present as a difficult to intubate neonate who is placed under general anesthesia for repair of another malformation such as esophageal atresia. Intubation with a smaller tube may be successful but a stenosis may later develop. The diagnosis of laryngeal webs is confirmed at endoscopy and treatment is excision or laser ablation, although some smaller subglottic webs may respond to dilation.[64,74]

The most common anomalies associated with laryngeal atresia and webs are those of the VACTERL association (*V*ertebral, *A*nal, *C*ardiac, *T*racheo-*E*sophageal, *R*enal, *L*imb).[75] Others include syndromes such as Fraser, Di George, and velocardiofacial (both related to 22q11 deletion) and partial trisomy 9; families with an autosomal dominant inheritance pattern have also been described.[49,70,76,77]

The congenital form of *subglottic stenosis*, similar to laryngeal web and atresia, results from defective recanalization of the larynx, although in subglottic stenosis the defect occurs at the level of, and usually involves, the cricoid cartilage, approximately 2 to 3 mm below the glottis. The most common presenting symptom is stridor, which is worsened by increased respiratory effort and upper respiratory tract infection. In fact, in milder forms the stridor may only be noticed during intercurrent upper respiratory tract infections and be mis-



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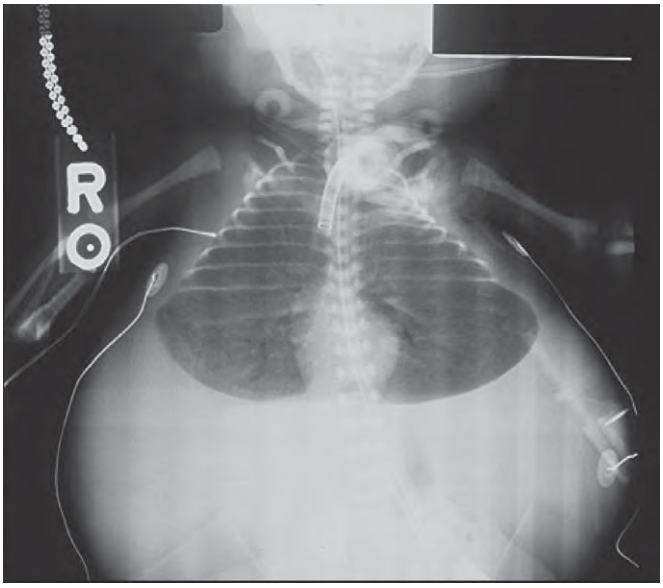

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Figure 64-2 Congenital high airway obstruction syndrome (CHAOS), which can be due to laryngeal or tracheal atresia. **A,** Fetal MRI showing the typical distended airways (1), flattened diaphragms (2), and ascites (3). (Courtesy of Drs. M. R. Harrison and H. Lee, The Fetal Treatment Center, San Francisco, CA.) **B,** Chest radiograph of a neonate with laryngeal atresia delivered by an EXIT procedure showing everted diaphragm and massive ascites. (Courtesy of Dr. N. S. Adzick, The Center for Fetal Diagnosis and Treatment, Philadelphia, PA.)

labeled as croup. Therefore, recurrent "croup" in infancy should always raise the possibility of a fixed upper airway narrowing such as subglottic stenosis, particularly when the course of the illness and response to treatment are atypical. High-voltage radiographs of the upper airway may help with the diagnosis, and both anteroposterior and lateral views should be requested because the narrowing is often maximal in the anteroposterior direction. Flexible endoscopy is useful for initial assessment. Bronchoscopy is the definitive diagnostic tool and is usually necessary to exclude other causes of narrowing in this region, particularly subglottic hemangioma. This lesion may be differentiated clinically from congenital subglottic stenosis in that the history is usually of worsening symptoms with growth of the hemangioma. On plain radiographs, the outline of hemangiomas is generally more ragged and may show a typical unilateral shouldering. Acquired subglottic stenosis is much more common than the congenital form. The diagnosis of the former is supported by a history of laryngeal trauma, the most common of which would be endotracheal intubation. This is particularly true when intubation is prolonged, as in the premature neonate. Treatment is the same for both types. Because the subglottic narrowing generally improves with laryngeal growth, a conservative approach using supportive care, particularly during intermittent episodes of "croup," should be the goal in all patients. Surgery should be reserved for patients who fail to cope with this conservative management, and a cricoid split is often the first line surgical treatment.[78] Treatment options include the cricoid split procedure, laryngotracheoplasty, tracheal resection and anastomosis, and tracheostomy for patients who have lesions that are not amenable to resection or reconstructive procedures. Most tracheostomized patients can be successfully decannulated within 2 to 3 years, although stridor and varying degrees of breathing difficulties may persist for many years.

LARYNGEAL CYSTS

These are usually supraglottic and generally present in the neonatal period (although possibly much later) with hoarse or muffled voice or even aphonia, stridor, and respiratory difficulty.[79,80] A lateral neck radiograph may show a rounded supraglottic swelling, and at laryngoscopy, a bluish fluid-filled cyst is found, usually in the epiglottic folds. Aspiration can relieve acute symptoms, but resection is ultimately necessary to prevent recurrence.[81]

LARYNGOTRACHEOESOPHAGEAL CLEFTS

A cleft larynx occurs in approximately 1 in 10,000 to 20,000 live births and comprises less than 1% of all laryngeal anomalies.[82] Male patients are affected more commonly than are female patients. Familial occurrences have been reported, as well as associations with various syndromes, including G syndrome and Pallister-Hall syndrome.[83,84] Association with other laryngotracheoesophageal anomalies, particularly esophageal atresia and tracheoesophageal fistula, is high. Pulmonary hypoplasia also occurs from the unchecked egress of

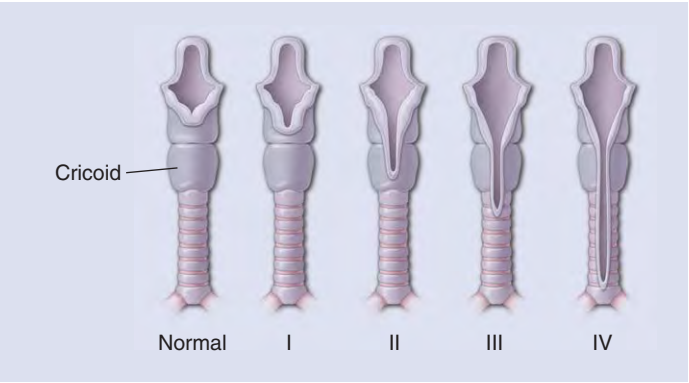


Figure 64-3 Classification of laryngeal and laryngotracheoesophageal clefts. (Redrawn from Dubois JJ, et al: Current management of laryngeal and laryngotracheoesophageal clefts. J Pediatr Surg 25:855-860, 1990.)

pulmonary fluid through a large cleft in fetal life. The clefts are classified into four types according to their severity, from type 1, the most common (50%), which is a simple laryngeal cleft, to type 4, which extends down to the carina and may involve one or both mainstem bronchi[82] (Fig. 64-3). Embryologically, a laryngeal cleft arises from abnormal separation of the trachea from the foregut, which occurs between 25 and 35 days of embryonic life. At the same time, the cricoid cartilage develops as two lateral centers of chondrification from the sixth branchial arch at the origin of the lung bud from the esophagus. Dorsal fusion of the cricoid plate is complete by day 50 to 54 and laryngeal muscular development ensues. The range of abnormalities seen results from defects in cricoid chondrification or fusion (types 1 and 2) or failure of septation of the primitive foregut (types 3 and 4). A multitude of signaling proteins are involved in this process of partition as reviewed by Groenman.[24] Among others, TTF-1 and Shh knock-out mice have demonstrated tracheoesophageal septum defects.[85,86]

These clefts create an abnormal communication between the esophagus and the larynx and trachea, thus increasing the likelihood of repeated aspiration of saliva and milk into the airway. This results in coughing, choking, respiratory distress, and recurrent pneumonia. Type 1 clefts may be asymptomatic, whereas type 2 clefts can cause problems of varying severity, making diagnosis difficult and often delayed. Increased salivation, stridor, and a low soundless cry are said to be characteristic symptoms that would point to the diagnosis of a cleft. However, this triad is rare, and more often stridor is absent and the cry is harsh. Therefore, in any neonate or infant who develops respiratory difficulties associated with feeding, the presence of a laryngotracheoesophageal cleft should be considered. The differential diagnosis also includes choanal atresia, esophageal atresia with or without tracheoesophageal fistula, pure tracheoesophageal fistula, laryngoesophageal dysmotility syndromes (functional or neurologic), esophageal compression (such as with a vascular ring), and gastroesophageal reflux. A contrast swallow and esophagogram (see later under pure tracheoesophageal fistula) is usually done in those neonates who are suspected of aspiration, but it rarely demonstrates the cleft clearly. In neonates who are intubated because of respiratory distress, posterior displacement of the endotracheal tube on radiographs suggests the diagnosis (Fig. 64-4A). The cleft is easily missed on direct laryngoscopy done for intubation.[87] Rigid bronchoscopy is necessary to make the diagnosis and to define the extent of the lesion. Endoscopic surgical correction for minor lesions is possible; however, many type 1 defects may not require correction, particularly if complicating factors such as gastroesophageal reflux are absent or can be controlled. Timing of surgery for type 2, 3, and 4 lesions depends largely on the overall condition of the child at diagnosis. If the child's respiratory and nutritional status are stable, early repair should be considered. If not, staged repair incorporating tracheostomy initially (with or without gastrostomy and fundoplication or gastric division), followed by definitive repair when the child is stable, may be best. Type 4 clefts require special tracheostomy tubes for postoperative stenting. They can be repaired through an anterior transtracheal approach or a lateral approach; cardiopulmonary bypass or extracorporeal membrane oxygenation are often required.[88,89] Overall survival with improved techniques and aggressive treatment is 70% but is significantly less for patients with extensive type 4 defects, significant prematurity, and severe associated anomalies. Complications following surgical repair are common and include wound breakdown and tracheoesophageal fistula formation, continuing aspiration and swallowing difficulties, gastroesophageal reflux, tracheobronchomalacia, and chronic respiratory problems.[88-90]

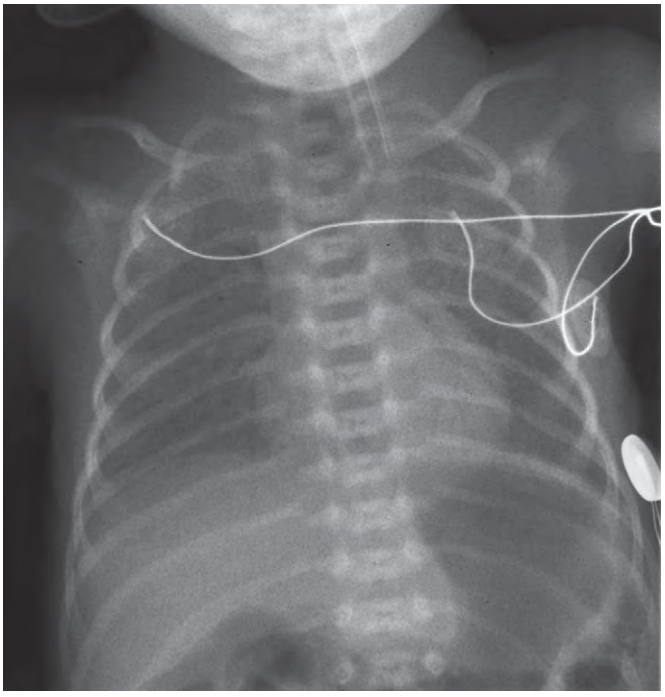
Trachea

TRACHEAL ATRESIA AND AGENESIS

Much like esophageal atresia (see later), various types of tracheal atresia have been described, ranging from complete pulmonary agenesis to segmental atresia with an intervening fibrous cord.[91,92] When no esophageal communication exists, the lungs are distended with fluid as discussed with laryngeal atresia; prenatal imaging, however, will fail to identify a distended trachea. In other cases the lungs appear normal although lobulation defects may occur.[92] Again, this spectrum of anomalies has been described in animal models studying the effects of various growth and transcription factors.[24] Tracheal atresia is commonly observed with anomalies of the VACTERL association, as well as gastrointestinal, genitourinary, and central nervous system anomalies.[93,94] This malformation is usually lethal. Neonates with short-segment atresia of the cervical trachea may be saved by an EXIT procedure with tracheostomy if the diagnosis is established before birth (see Fig. 64-2) or if a cleft or fistula allows temporary ventilation through a tube placed in the esophagus.[73] Even if neonatal survival can be achieved, long-term management is fraught with complications.[91]

ESOPHAGEAL ATRESIA AND RELATED TRACHEOESOPHAGEAL MALFORMATIONS

Laryngotracheoesophageal cleft, tracheal atresia, and esophageal atresia are all malformations related to defective septation of the primitive foregut. The latter is the most common, with an incidence of 1 in 3000 to 5000 live births. In 80% of cases, the esophageal atresia is accompanied by a fistula between the lower trachea or carina and distal esophagus (Fig. 64-5). The diagnosis is easily made, and the well-established management can be found in standard pediatric surgi-



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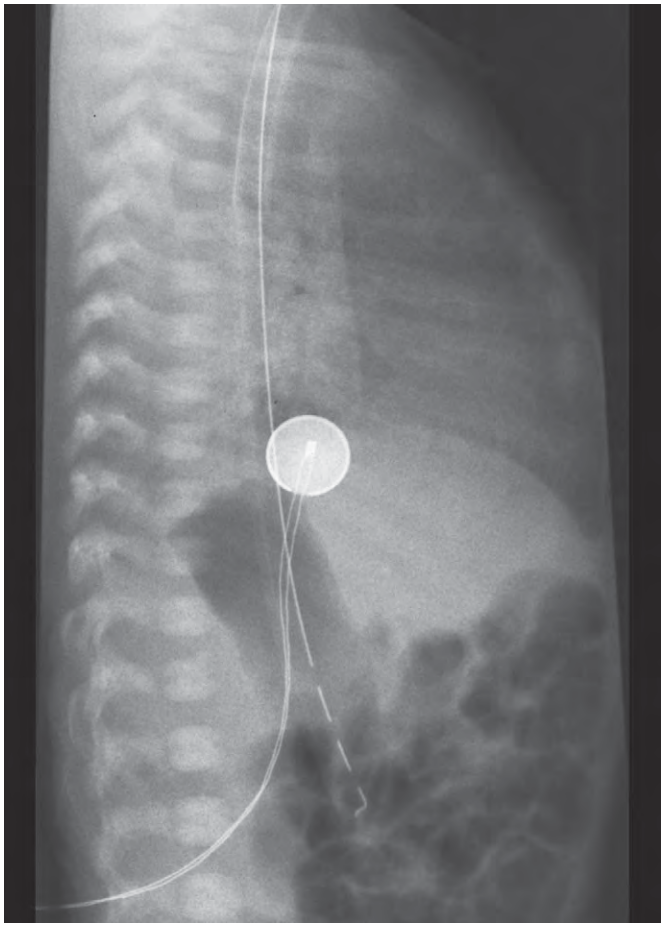

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Figure 64-4 Complete laryngotracheoesophageal cleft in a premature baby with high imperforate anus. The child was breathing spontaneously until surgery for colostomy. Intubation by the anesthesiologist under direct laryngoscopy was uneventful. **A,** Postoperative radiograph, showing a very abnormal position of the endotracheal tube. **B,** Lateral radiograph, showing the posterior displacement of the endotracheal tube overlying the nasogastric tube. A complete cleft was suspected and confirmed by rigid bronchoscopy.

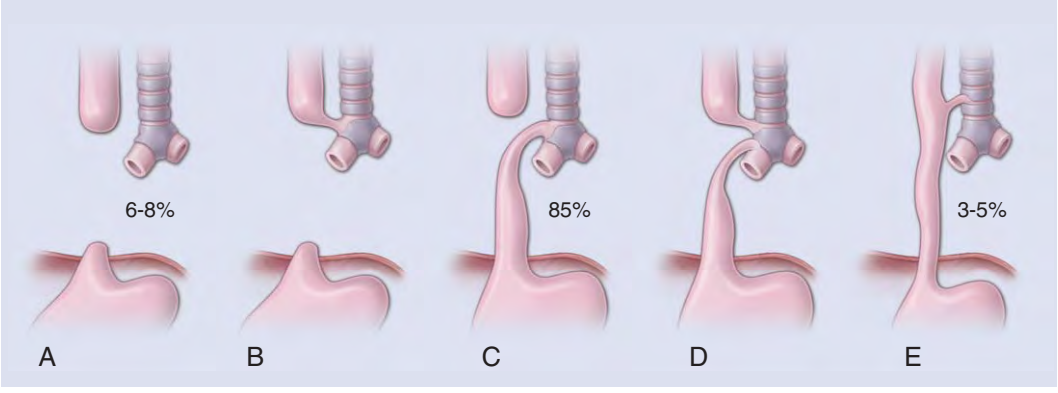


Figure 64-5 Types and incidence of the main esophageal atresia and tracheoesophageal fistulas: **A,** esophageal atresia without fistula, **B,** upper esophageal fistula with distal atresia, **C,** most common type with upper pouch atresia and distal fistula, **D,** proximal and distal esophageal fistulas, and **E,** H-type tracheoesophageal fistula.

cal textbooks.[95-97] The prognosis is excellent unless severe anomalies or extreme prematurity are associated.[98-101] For the purpose of this chapter, we address issues more likely to come to the attention of pediatric respiratory specialists.

Early postoperative complications include esophageal anastomotic stenosis (≈10%), recurrence of the tracheoesophageal fistula (3% to 8%), and gastroesophageal reflux, which is seen in nearly all patients to some degree.[97,102,103] Tracheomalacia is also common and is thought to be related to abnormally shaped tracheal cartilages and a widened pars membranacea,[104,105] especially at the level of the upper esophageal pouch. The differential diagnosis between these four entities can be very difficult to establish when the infant has coughing and choking spells with feedings in the postoperative period. A lateral fluoroscopy of the chest may demonstrate a localized tracheal collapse during expiration when severe tracheomalacia is present. A contrast study is usually done next to assess the swallowing mechanism and the anastomotic patency; some discrepancy is always expected between the dilated upper esophageal pouch and the narrow

distal esophagus. Sometimes this study will start with the injection of contrast medium through a small nasoesophageal tube placed at the level of the anastomosis; a recurrent fistula will be easier to delineate and any contrast in the trachea will not be confused with material aspirated from the pharynx. If a significant stricture is discovered, with delay of passage through the anastomosis, dilation can be performed under fluoroscopy. Even without a significant stricture, the normal distention of the upper pouch during swallowing may compress the trachea because of the associated tracheomalacia, to the point of near-total tracheal occlusion (Fig. 64-6). Tracheal collapse can also occur during forced expiration such as crying. Such infants who present with "blue spells" or "dying spells" are treated with aortopexy; by suturing the aortic arch to the undersurface of the sternum, the anterior wall of the trachea is brought forward, preventing the posterior wall from occluding the lumen during feeding or crying.[106-108] A rigid bronchoscopy is necessary to confirm the severity of the tracheomalacia and exclude the possibility of a recurrent fistula or a missed laryngotracheoesophageal cleft.[87] The tracheomalacia is best appreciated with the patient breathing spontaneously, because positive airway pressure will tend to keep the trachea open. In most cases, the collapse is localized and amenable to treatment by aortopexy (Fig. 64-7); diffuse tracheomalacia is more difficult to treat and requires tracheal, and sometimes bronchial, stenting.[109] Tracheomalacia tends to improve with time, but aortopexy is more effective and less risky than prolonged intubation or tracheostomy for patients with dying spells. In most cases, however, a "barking cough" typical of esophageal atresia patients will be the only symptom of tracheomalacia and this tends to improve over time (see discussion of tracheomalacia later). Despite this, Chetcuti and associates[110] have found that 40% of adults still had the typical barking cough of tracheomalacia. Other late postoperative sequelae after esophageal atresia repair are an increased frequency of respiratory infections, possibly related to impaired mucus clearance from absent or dysfunctional ciliated cells,[111] as well as asthma-like symptoms, whether related to tracheomalacia or reactive airway disease. In the study by Chetcuti and associates, these symptoms were present in 24% of patients.[110] Gastroesophageal reflux often persists and contributes to recurrent respiratory problems. Vaccinations against *Haemophilus influenzae* and respiratory syncytial virus are recommended after esophageal atresia repair. Chest wall deformities may also occur, usually in patients who have required repeated thoracotomies for complications (anastomotic dehiscence, recurrent tracheoesophageal fistula [TEF]) or who have hemivertebrae or other vertebral anomalies, which are commonly seen as part of the VACTERL association.

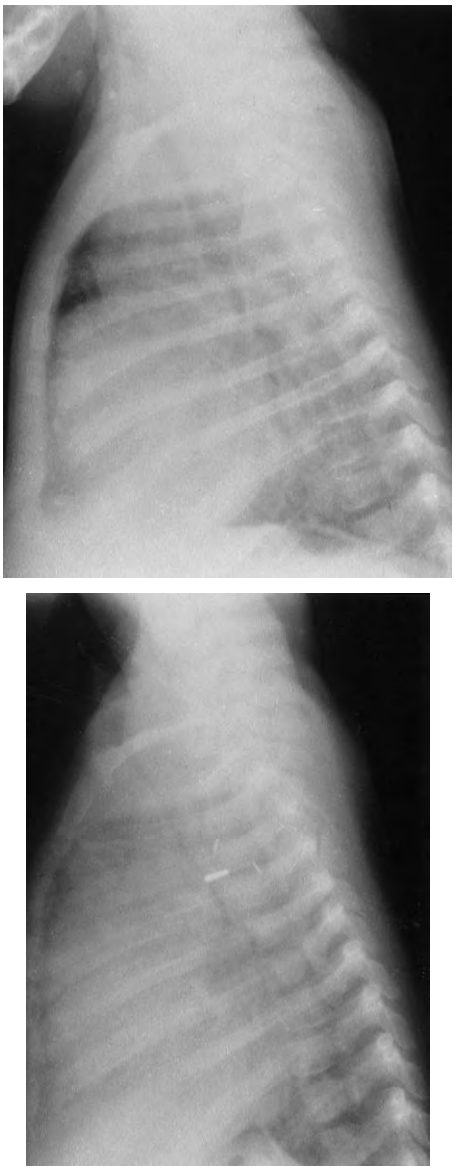
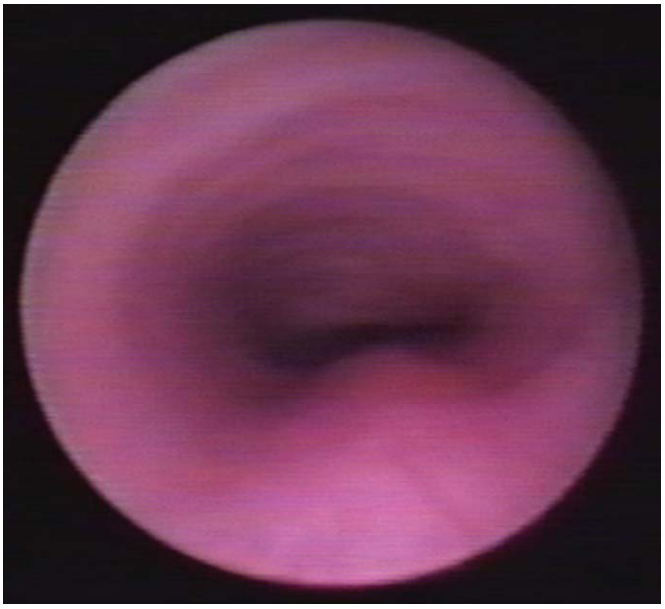


Figure 64-6 Tracheomalacia. Lateral chest radiographs show the abnormally marked collapse of the trachea during expiration *(lower)* compared with normal tracheal diameter during inspiration *(upper)*, which is characteristic of tracheomalacia.

An *isolated tracheoesophageal fistula* is the third most common form of esophageal malformation, seen in about 5%. The symptoms are recurrent coughing and choking, especially during feedings. The diagnosis is often delayed, resulting in recurrent pneumonia.[112,113] A distended abdomen with air-filled loops may also be noted. When the diagnosis is suspected, fluoroscopy is performed in the prone position with contrast injection through a nasoesophageal tube starting in the mid-esophagus and gradually moving up.[114] False-negative studies may occur. Rigid bronchoscopy is essential to confirm the diagnosis and it facilitates the operation. The fistula, usually located in the lower cervical area, is cannulated during bronchoscopy to facilitate intraoperative identification and minimize the amount of dissection, thereby decreasing the risk of recurrent laryngeal nerve injury.[112,113,115] Simple ligation and division of the fistula through a cervical approach give excellent results with few long-term complications.[116] Attempts at endoscopic occlusion of the fistula with glue, laser, or other means is associated with a high recurrence rate and do not appear warranted in H-type fistulas that can be divided through a cervical approach. These techniques may have their place in the management of recurrent TEF.[117] About 10% of H-fistulas are too low to be divided through a cervical approach and require thoracotomy or thoracoscopy.[118]

TRACHEOMALACIA

Tracheomalacia can be primary or secondary and may be localized or generalized. Primary tracheomalacia is usually



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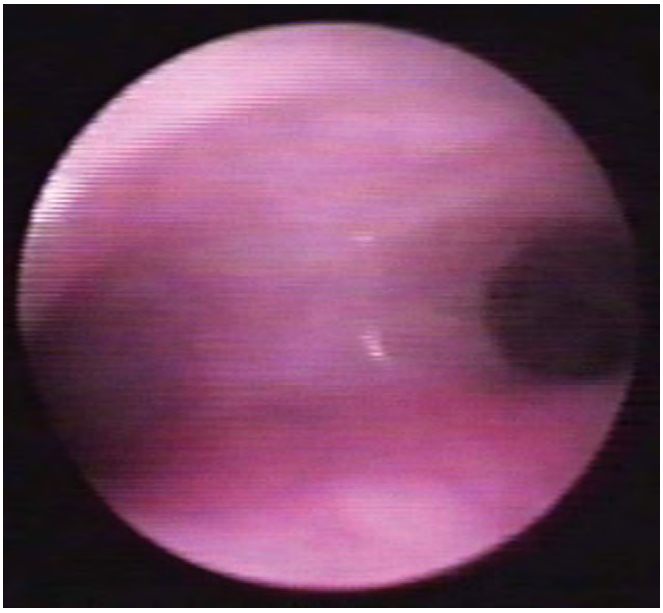

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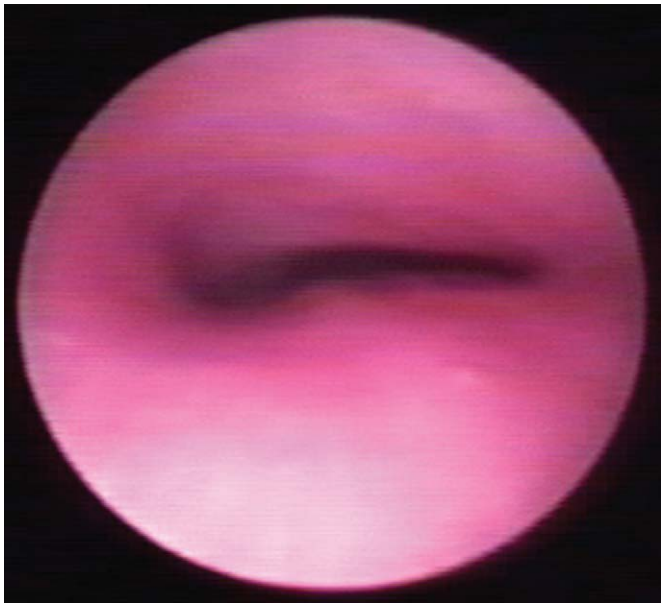

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Figure 64-7 Rigid tracheoscopy on a patient with severe tracheomalacia and desaturations with oral feedings after esophageal atresia repair (type C). **A,** Normal proximal trachea with segmental collapse seen distally. **B,** Severe collapse, corresponding to the level of the aortic arch anteriorly and the esophageal pouch posteriorly. **C,** Distal trachea and mainstem bronchi show minimal collapse. Aortopexy resolved the symptoms.

considered uncommon, but Callahan[8] cites an incidence of 1 in 1445 children based on a small series of patients. When it occurs, it usually takes the form of an abnormal softness of the cartilage, or a shortening of the cartilage rings with a correspondingly large pars membranacea.[64,119] The Williams-Campbell syndrome is a rare and severe familial form of generalized tracheobronchomalacia in which there is marked reduction or absence of cartilage throughout the tracheobronchial airway.[120] However, the deficiency may be more severe in the cartilage distal to the main segmental bronchi.[121] Primary tracheomalacia has been found in association with Down syndrome, trisomy 9, DiGeorge syndrome (22q11 deletion), diastrophic dwarfism, absence of the pectoralis muscle (Poland syndrome), congenital absence of the thumbs, pectus excavatum, Ehlers-Danlos syndrome, Hurler and Hunter syndromes (mucopolysaccharidoses types I and II), and some congenital heart defects.[8] Most commonly, though, tracheomalacia occurs as a localized abnormality secondary to extrinsic compression such as from a vascular ring or mediastinal cyst.[122] It is also found in virtually all patients with esophageal atresia as discussed earlier and can be secondary to prolonged intubation, tracheostomy, and severe tracheobronchitis.

Clinical symptoms usually appear in early infancy and include a harsh loud vibratory cough (the "barking cough" typical of patients after esophageal atresia repair), rattly chest, dyspnea, wheeze, and possibly stridor. The cough and rattly chest are caused by impaired clearance of normal mucous secretions past the abnormal tracheal segment. Collapse of this malacic segment as a result of increased intrathoracic pressure during expiration causes narrowing of the airway lumen, airway obstruction, and expiratory stridor. The stridor may be both inspiratory and expiratory if laryngomalacia coexists.[64] This effect is exaggerated by increased respi-

ratory effort, such as during crying, feeding, and coughing, or during an intercurrent upper or lower respiratory infection, leading rapidly to dyspnea and severe respiratory distress. As the distress increases, inspiratory difficulty may be noted as well. In its severest form, acute severe obstructive episodes with cyanosis ("dying spells," as discussed earlier) may be seen. These require immediate treatment with oxygen and positive-pressure ventilation, although on occasion this can prove surprisingly difficult to achieve until the abnormal segment is bypassed with an endotracheal tube. Because wheezing is a common symptom in these patients, many are mistakenly treated for asthma for long periods. It is now believed that the incidence of asthma is not higher in patients with tracheomalacia than in the rest of the population, so this diagnosis should always be reconsidered in these patients when they show no convincing response to an adequate trial of bronchodilators. Other symptoms include the "bagpipe sign," a sibilant expiratory note persisting after the end of visible expiration.[123] Marked changes in airway caliber of the malacic segment may be detected on lateral inspiratory and expiratory chest radiographs[124] (see Fig. 64-6). This is particularly the case in short-segment malacia, in which the difference between the abnormal segment and the remaining normal trachea is readily discernible. When a large segment or the whole of the trachea is involved, it can be difficult to determine whether the degree of airway caliber change is abnormal, since there is a wide range of "normal" variation. This is particularly true in young infants, where the change in caliber may be as high as 50% during conditions of increased respiratory load such as during respiratory infections.[125] Rigid bronchoscopy affords direct visualization of the malacic area, as discussed earlier. When there is a well-defined, localized area of tracheomalacia in patients without esophageal atresia, an extrinsic lesion compressing the trachea should always be considered. At bronchoscopy, if the abnormal area is seen to pulsate vigorously, a vascular malformation should be suspected. If the pulsation is noted across the anterior wall of the trachea, an "anomalous" innominate artery is the most likely cause. Classically, this diagnosis is confirmed simply by elevating the tip of the bronchoscope, thereby compressing the pulsating mass while palpating the right radial artery for changes in flow and pressure. Most authors now consider that this anterior compression is caused by a normal innominate artery, whose origin is more to the left in infants[64,126]; localized tracheomalacia is the problem rather than an abnormal vessel.[107] Pulsations on the posterior tracheal wall usually suggest the presence of a vascular ring, which may be complete (double aortic arch and right aortic arch variants) or incomplete (retroesophageal right subclavian artery and left pulmonary artery sling).[127] Nonpulsatile lesions compressing the airway include bronchogenic cysts, cystic and solid mediastinal tumors, and enlarged lymph nodes. With all lesions compressing the trachea, computed tomography or magnetic resonance imaging is usually necessary to define the anatomy before surgery.[128,129] In patients with tracheomalacia from an extrinsic compression, the offending lesion usually should be addressed surgically. Occasionally, even after removal of the lesion or division of a vascular ring, the localized malacic segment continues to cause significant symptoms and requires treatment as discussed under the esophageal atresia section. Most patients with isolated tracheomalacia can be managed conservatively, with physiotherapy to improve clearance of trapped secretions, together with antibiotics for recurrent infections. With increasing age, airway function gradually improves as the tracheal diameter increases and the abnormal area stiffens. However, it may be many months or even years before symptoms have resolved. In neonates or young infants with significant ongoing obstructive problems from diffuse tracheomalacia, a period of continuous positive airway pressure can be used to "splint" the airway open until tracheal wall rigidity improves, which takes an average of 22 months. This positive pressure may be administered through a facemask, nasopharyngeal tube, or endotracheal tube. This treatment may be associated with feeding difficulties, delayed speech and language, and potential developmental delay.[130]

Patients with severe obstructive problems refractory to conservative measures have a significant morbidity and mortality risk. Because this may be as high as 80% in some cases, surgical treatment should be offered. Patients with dying spells are part of this group. Other indications for surgery include recurrent pneumonia, inability to extubate, and feeding difficulties with failure to thrive.[108,131] Tracheostomy, with or without continuous positive airway pressure, is one option,[64] although problems may persist when the end of the tracheostomy tube does not extend beyond the malacic segment. Aortopexy is generally effective for localized tracheomalacia.[131-133] Endoscopic stenting has been associated with severe complications such as perforation and arterial fistulization, making it less appealing than aortopexy for localized tracheomalacia. However, it has provided a life-saving option for patients with severe diffuse tracheomalacia.[109,134] The more generalized form of the disorder, Williams-Campbell syndrome, is associated with severe obstruction and recurrent infection progressing to bronchiectasis.[120] Other than physiotherapy and antibiotic treatment, no definitive therapy is available for this disorder; lung transplantation is an option but proximal airway malacia can lead to failure.[135]

TRACHEAL STENOSIS

Fixed narrowing of the trachea may be intrinsic or associated with an external compression. The former can be seen as a less severe form of tracheal atresia in which a narrow patent segment of trachea is present instead of a fibrous cord, while the latter shares common features with localized tracheomalacia. Congenital intrinsic tracheal stenosis is usually associated with complete cartilaginous tracheal rings. A number of forms have been recognized. Wolman described two types.[136] The first is a short narrowed segment with a trachea of normal caliber above and below; the second involves a tracheal lumen that narrows progressively as it descends toward the carina in a carrot-shape or "rat-tail" trachea. Stenosis is often seen in the segment of trachea distal to the origin of a tracheal bronchus (see later), with the narrowing characteristically extending to the carina, whereas the left and right main bronchi are usually normal in diameter (Fig. 64-8). More than 80% of patients with complete tracheal rings have associated anomalies, most frequently cardiovascular (the left pulmonary artery sling syndrome being the most common).[137] Down syndrome, chondrodystrophies such as Ellis–van Creveld syndrome, and congenital stippled epiphyses have also been associated with various forms of tracheal steno-

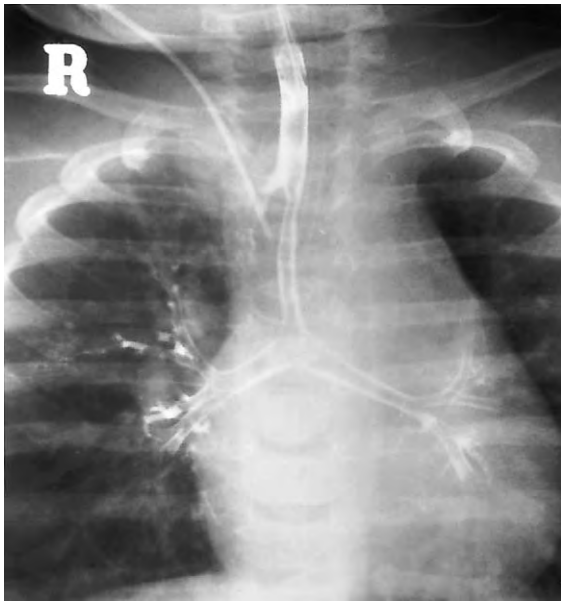


Figure 64-8 Tracheal bronchus with distal tracheal stenosis. A well-recognized configuration of this anomaly is demonstrated in this bronchogram from a 13-month-old girl with a history of bidirectional wheeze and stridor worsening with infection. It shows the tracheal bronchus (invariably right-sided) arising from the intrathoracic trachea, the subsequent portion of trachea stenosed to the carina, normal caliber left and right main bronchi and beyond, and absence of the normal right upper lobe bronchial branch.

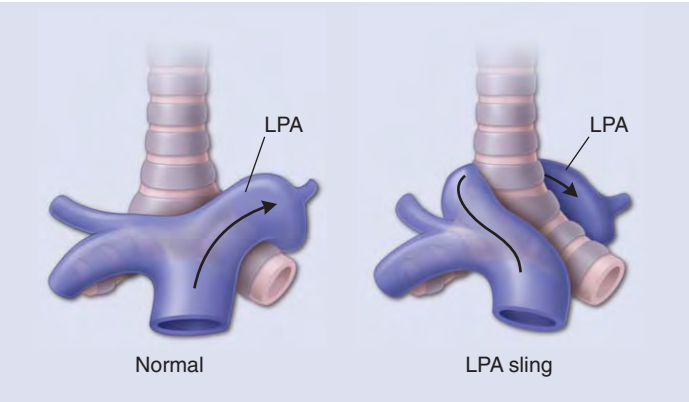


Figure 64-9 Left pulmonary artery (LPA) sling. Diagram showing the normal and abnormal configuration where the left pulmonary artery curls around the right side of the carina before progressing between the trachea and the esophagus to supply the left lung.

sis.[138] Other rare causes of short segment stenosis include tracheal webs (found usually just above the carina), tracheal cysts, and sequestered esophageal tissue in the trachea (which is much less common than the reciprocal, that is, tracheal remnants sequestered in the esophageal wall leading to esophageal stenosis).[139] Characteristically, patients with tracheal stenosis localized to the extrathoracic portion of the trachea present with stridor, which is usually more prominent during inspiration. Patients with intrathoracic stenosis generally present with wheeze or mixed wheeze and stridor, which is predominantly expiratory. In both instances, when the stenosis is severe and fixed, the added noises may be prominent in both inspiration and expiration. A wet-sounding biphasic breathing pattern that transiently clears with coughing is referred to as "washing-machine breathing" by Rutter.[137] Additional factors, such as associated structural weaknesses in the airway adjacent to the stenosis and the increased pressures this airway is subjected to in the presence of narrowing, also influence the sounds produced during respiration. When the narrowing is severe, breath sounds may be accompanied by significant respiratory distress, whereas in mild cases they may be noticeable only when respiratory load is increased, as with exercise or infection. Penetrated radiographs of the airway may identify a narrowed segment, although CT or MRI is necessary to define the extent of the lesion and to search for an extrinsic cause.[140] Bronchoscopy may also be helpful to plan treatment. Respiratory function tests show evidence of fixed obstruction with characteristic flattening of the inspiratory and expiratory portions of the flow-volume loop.

Management is difficult. In some patients the stenosis improves with tracheal growth, and conservative symptomatic treatment and support should be the recommended approach when possible.[141] Results of dilation techniques and laser resection of the intraluminal narrowing have been disappointing, with subsequent recurrence of the stenosis the rule. Endoscopic stenting has been used in some centers.[142,143] This should be avoided when there is an associated vascular ring or sling because of the risk of erosion with arterial fistulization.[137] Surgical options include resection and primary anastomosis for short segment stenosis and the tracheal slide technique for longer narrowings.[144,145] Tissue engineering will undoubtedly provide a useful alternative for tracheal reconstruction in the future.[146,147]

The *left pulmonary artery sling syndrome* is a particularly well-described cause of tracheal stenosis.[127] In this condition, the left pulmonary artery passes initially to the right in front of the carina. It then curls posteriorly over the origin of the right main bronchus before crossing to the left hemithorax between the esophagus and trachea (Fig. 64-9). This looping of the aberrant vessel around the carina usually has a strangling effect, resulting in variable degrees of compression and localized narrowing. The compressed area may be malacic or, in some cases, associated with severe annular constriction of the trachea. This may either be localized to this area or, more commonly, involve the length of the trachea (and possibly major bronchi) in a carrot-shape configuration. When this configuration is present, the tracheal cartilages are characteristically abnormal in that they are increased in number (both in the trachea and major bronchi) and that they take the form of complete annular cartilage, so-called napkin ring cartilages. Although these patients usually present in the first few days of life with severe respiratory distress characterized by inspiratory and expiratory difficulty, some infants surprisingly do not develop significant respiratory difficulties until a few weeks or even several months of age despite an exceedingly narrow trachea. The chest radiograph reveals apparently normal lungs, although the carina and a variable portion of the trachea are not identifiable. Diagnosis is best made on magnetic resonance angiogram, which is complemented by CT scan or bronchoscopy if necessary.[148] Long segment tracheal stenosis is difficult to repair, and often fatal; a localized narrowing may be improved by reimplantation of the left pulmonary artery, but a fixed associated intrinsic stenosis or

localized malacia may persist and should be addressed at the same setting. This may be accomplished with either stenting (for severe malacia) or resection/tracheoplasty as discussed earlier for complete cartilage rings.

TRACHEAL DIVERTICULUM

This is an extremely rare anomaly, usually arising from the right posterolateral surface of the trachea, that may give rise to symptoms only late in adult life when it becomes infected. Because of this, it has been suggested that it may be an acquired rather than a congenital lesion, but a few reports of congenital diverticula exist.[149,150] Some consider this malformation as a blind-ending tracheal bud, i.e., the lesser form of an accessory tracheal bronchus.[151,152]

TRACHEOBRONCHOMEGALY (MOUNIER-KUHN SYNDROME)

This condition is characterized by marked dilation of the trachea and major bronchi, probably as a result of abnormal development of elastic and muscular tissues in the airways.[153] Most patients present in adult life but cases have been reported in children as young as 18 months.[154] It is often associated with other congenital defects of the ribs and lung topography.[155] The finding of this condition coexisting with Ehlers-Danlos syndrome and cutis laxa supports the possibility of an underlying connective tissue abnormality. A familial occurrence suggesting an autosomal recessive inheritance has also been described.[49] Reduced efficiency of airway mucociliary clearance and inefficient cough found in this condition eventually lead to recurrent infection and the development of bronchiectasis, although many of these patients may remain asymptomatic until late adulthood.[156] Marked dilation of the trachea is obvious on the plain radiograph, with the tracheal shadow often being as wide as the vertebral bodies. Physiotherapy and aggressive treatment of infection may retard the development of bronchiectasis.

Mainstem and Lobar Bronchi

TOPOGRAPHIC ANOMALIES

Topographic anomalies of the whole lung such as situs inversus and left mirror image and right mirror image lung (bilateral left or bilateral right lung) have been shown to correlate in almost all instances with topographic anomalies of atrial arrangement (situs inversus, left isomerism, and right isomerism, respectively), and with abdominal aorta and vena caval relationships.[157] Several growth and transcription factors important in early lung development have recently been implicated in right-left asymmetry development in animal models.[24,158-160] Clinically, five types of polysplenia/asplenia syndromes have been described in association with bronchial isomerism (bilateral left or bilateral right lung), some in boys only, some in girls only, some in both sexes equally.[161] Intestinal malrotation and liver isomerism are common in several of the types, including the Ivemark asplenia syndrome.[49,161]

Isolated lobar or segmental topographic bronchial anomalies are now often recognized, although most cause no symptoms and are diagnosed incidentally or at autopsy. Tracheal bronchus, abnormal segmental bronchial branching, supernumerary segmental or lobar bronchi, and bridging bronchi are the most common abnormalities found. Bronchial branching anomalies are also found in the scimitar syndrome, which almost always affects the right side only (see later).

Tracheal Bronchus. Tracheal bronchus always occurs on the right, as do 80% of all bronchial topographic anomalies.[162] It is also known as a pre-eparterial bronchus and often called a "pig-bronchus" because of its normal occurrence in swine.[152,163] The incidence of a tracheal bronchus has been reported from 0.001% to 2%, the latter in a large series of *symptomatic* patients younger than 5 years undergoing bronchoscopy.[152,164] It may be associated with trisomy 21 and other malformations.[152] The abnormal bronchus usually arises from the midthoracic trachea and supplies either:

1. The apical segment of the right upper lobe (with the normal right upper lobe bronchus supplying the rest of the lobe), or
2. An accessory segment within the upper lobe, or
3. An accessory segment completely separate from the upper lobe, or
4. The whole right upper lobe (in which case the normal right upper lobe branch is absent [see Fig. 64-8]).[151]

Structural abnormalities such as stenosis and malacia may be found in these bronchi, although the lung segment supplied by this bronchus is usually normal or at least initially so. Poor drainage of this segment often leads to recurrent infection and bronchiectasis in later life. The bronchus itself is more commonly the site of bronchial adenoma, carcinoma, or bronchogenic cysts. Patients usually present with signs and symptoms of persisting right upper lobe infection or tracheal stenosis. The diagnosis is usually made at bronchoscopy or on imaging studies. Management is directed at improving drainage of the affected segment with physiotherapy and controlling infection with antibiotics. If the segment becomes bronchiectatic and problems persist despite conservative treatment, resection may be necessary. Symptoms caused by any associated tracheal stenosis usually improve with tracheal growth, although if the stenosis is severe, they may prove particularly troublesome and difficult to manage until growth occurs.

Bridging Bronchus. A bridging bronchus is an anomalous bronchial branch arising from the left mainstem bronchus and crossing the mediastinum to enter the right lower lobe. In the first two cases reported, the right lung was bilobed and areas of stenosis in the tracheobronchial tree were present.[165,166] Both children died of recurrent infection in early infancy, but there are recent reports of successful repair.[167] An interesting theory was proposed by Wells and colleagues[168] to explain the anatomy found in patients with a left pulmonary artery sling and a tracheal bronchus supplying the right upper lobe. According to the level of origin of the tracheal bronchus, this would be the normal level of the carina, and the bronchi supplying the right middle and lower lobes would be bridging branches originating from the left main bronchus.

MORPHOLOGIC ABNORMALITIES

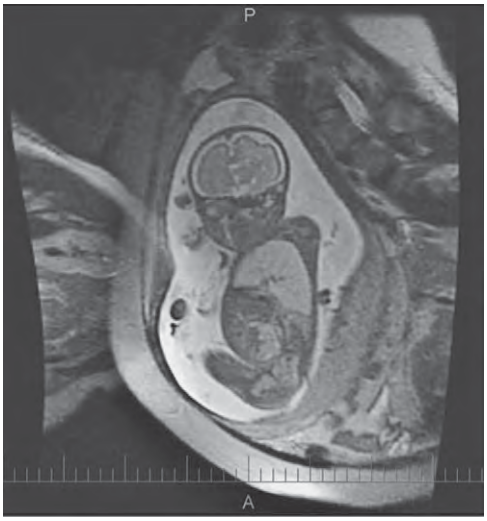
Bronchomalacia. Bronchomalacia is most commonly found in association with tracheomalacia, and the symptoms, diagnosis, and treatment of these combined lesions are discussed in the section on tracheomalacia. It is defined as an abnormal weakness in the airway wall and is found more commonly in premature neonates and patients with Down syndrome,

although it may occur in full-term infants. As with tracheomalacia, spontaneous improvement with age is the rule and only patients with significant respiratory problems require treatment in the meantime. Isolated segments of bronchomalacia are rare and occur most commonly as a result of extrinsic compression. A generalized severe form of bronchomalacia with absence or marked deficiency of airway cartilage, known as Williams-Campbell syndrome, is described in the section on tracheomalacia. Bronchomalacia associated with defective cartilage development has also been implicated in the pathophysiology of congenital lobar emphysema (see later).

Bronchial Stenosis. Congenital isolated stricture of a bronchus occurs predominantly in mainstem or first-generation bronchi and predisposes to recurrent and chronic infection in the area distal to the narrowing as a result of impaired drainage of secretions. Secondary narrowing is far more common and is usually caused by compression by mediastinal cysts, tumors, and vascular anomalies.[42] Apart from infection, these patients may present with a recurrent wheeze that does not respond to bronchodilators. The diagnosis is made on CT scan or MRI or at bronchoscopy. Surgical resection of the stenosed area usually is precluded by inaccessibility and the small size of the lesion. Chronic infection and bronchiectasis distal to the stenosis usually necessitate resection of the affected lung segment or lobe.

Bronchial Atresia. In bronchial atresia, a lobar or segmental bronchus ends blindly, either with an atretic membrane or in a blind pouch, with a short gap to the distal continuation of the airway to that particular lobe or segment. This entity also overlaps with congenital lobar emphysema (CLE) which is discussed later.[169] Older reports of isolated bronchial atresia focus on the predominance of left upper lobe, right middle, and right upper lobe lesions with radiologic and pathologic similarity to CLE.[49,51,170,171] Older patients are often asymptomatic, with the hyperinflated lobe discovered incidentally on chest radiograph. Ventilation of the segment is thought to occur through the pores of Kohn, which favors inspiration rather than expiration, resulting in gas trapping. The only physical finding may be decreased breath sounds over the affected area. When a major bronchus is atretic, the affected distal lobe may be significantly hyperinflated, causing compression of surrounding healthy lung and shift of the mediastinum to the opposite side. In such patients, symptoms of reduced exercise tolerance and possibly wheeze and shortness of breath may be prominent. CT is commonly used to confirm the diagnosis. Surgical excision is indicated when overdistention of the affected lung segment or lobe leads to compromise of surrounding normal lung (as in congenital lobar emphysema) and significant symptoms. Mainstem bronchial atresia is much more serious; a single report describes two fetuses who became hydropic and died, one despite an attempt at fetal intervention.[172]

In recent years, the increasing use of prenatal ultrasound has changed the concept of isolated bronchial atresia.[51] Echogenic lung lesions, with and without cystic changes, are now being discovered in the fetus and resected soon after birth (Fig. 64-10). Many of the lesions previously described as CCAM and intralobar sequestration have been found in association with bronchial atresia, often involving the lower lobes.[51,173,174] These authors now see bronchial atresia as the underlying cause of many congenital lung malformations. This is discussed further in the section on lung malformations.



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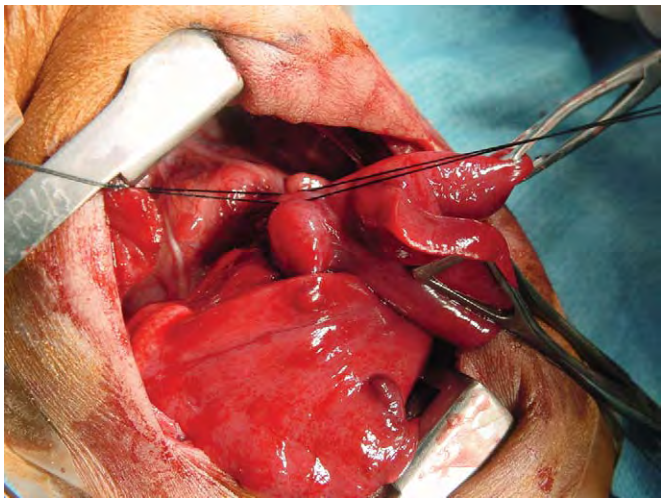


B

Figure 64-10 Prenatal diagnosis of a hybrid lung lesion (bronchial atresia and sequestration). Prenatal ultrasound examination was compatible with a large, mostly echogenic left lung CCAM/CPAM causing severe mediastinal shift and polyhydramnios but no hydrops. **A,** Fetal MRI at 25 weeks' gestation. This coronal (but slightly oblique) T2-weighted view shows the very bright enlarged left upper lobe herniating into the right chest. Only a small rim of normal right lung was seen, and none on the left. Flattening of the left diaphragm was observed on sagittal views (not shown). The fetus was closely monitored with serial ultrasonograns and lung hypoplasia was feared. After 32 weeks of gestation, the mass started regressing and the mediastinal shift improved. At birth, the infant had minimal respiratory symptoms but gradually became more tachypneic, leading to an operation on the second day of life. **B,** At operation, part of the upper lobe was nonaerated. This segment, which was separated from the rest of the upper lobe by a pseudo-fissure, was fed by an aberrant systemic artery (held by silk sutures) from the aorta. There was no bronchus at all to the upper lobe. At pathology a diagnosis of bronchial atresia was made, with dilated distal bronchi filled with mucus, without features of CCAM/CPAM; the systemic artery to the apical segment was confirmed.

Bronchiectasis. Bronchiectasis is not a congenital malformation as such, but develops in several congenital and familial conditions. The most common is cystic fibrosis; others include the immotile cilia syndrome (called Kartagener syndrome

when associated with situs inversus) and several immunodeficiency states (IgG, IgA, alpha$_1$-antitrypsin, neutrophil, complement).[49] In Williams-Campbell syndrome, discussed under tracheomalacia, bronchiectasis may occur early in infancy.

Bronchogenic Cysts. Bronchogenic cysts are part of the spectrum of foregut duplications. They account for approximately 5% of mediastinal masses in infants and children; this percentage is higher in adults. Some are diagnosed incidentally at thoracotomy or at autopsy,[175] which indicates that they may be more common than is normally appreciated. They are solitary, unilocular cystic structures that contain fluid or mucus. They are usually 1 to 3 cm in diameter but may reach up to 10 cm in older patients.[51] Most commonly located in the mediastinum near the tracheal bifurcation, they may be found from the suprasternal area to below the diaphragm, and even within the pleura and subcutaneously.[51,176,177] Some pathologists consider intrapulmonary bronchogenic cysts as instances of type 1 CPAM (see later),[49] but other pathologists disagree.[51] Although it is generally recognized that they do not communicate with the tracheobronchial tree,[51] some series report that such communications are frequent.[178] In at least 20% of the cases the cyst is totally separated from the bronchopulmonary tree, lying subpleurally in the mediastinum or occasionally attached to other structures such as the esophagus or the pericardium.[179] Bronchogenic cysts have been described in association with other congenital lung anomalies such as sequestration.[50] The cyst is thin walled, lined with ciliated respiratory epithelium and mucus glands, and surrounded by smooth muscle and fibrous tissue. The presence of cartilage in the wall is used to differentiate bronchogenic cysts from esophageal duplications, although overlap exists and both can simply be considered as foregut duplications.[179] Foregut duplication cysts may rarely communicate with an abdominal duplication or with the spinal canal; the latter are called neurenteric cysts and are usually associated with hemivertebrae or other vertebral defects[179,180] (Fig. 64-11). The classic embryologic explanation for bronchogenic cysts is that the developing bronchus is disrupted at a particular stage and a fragment of bronchial tissue separates to form the bronchial cyst. The eventual location and histologic features of the cyst depend primarily on the time of the disruption. The recent review of foregut duplications by Azzie and Beasley[179] mentions that altered expression of the *Shh* gene by the notochord could affect the *Shh-Gli* signalling pathway and lead to some of these malformations.

Bronchogenic cysts are found in five major locations within the thorax, according to a classic review[181]:

1. The right paratracheal region (corresponding to the usual site of origin of the tracheal bronchus), 19%
2. The carinal region (where they are most likely to cause symptoms by airway compression), 51.5%
3. The hilar region (where the cyst is located on or near a mainstem or lobar bronchus and is often latent), 8.6%
4. Paraesophageal region (usually low near the cardia and may compress the esophagus), 13.8%
5. Other locations such as pericardial, retrosternal, and paravertebral, 6.9%

A very small number, which would more likely correspond to the histology of esophageal duplications rather than bronchogenic cysts, communicate with the spinal canal or through the diaphragm as mentioned earlier. However, some thoracic foregut duplications may be associated with a separate abdominal duplication.[179] Clinical findings are diverse, depending on the location of the cyst. Proximal tracheal compression can cause stridor and respiratory distress. Compression at the carinal area leads to cough, wheezing, dyspnea, atelectasis, overinflation of one or both lungs, or recurrent infections. Compression of a smaller bronchial branch may cause localized signs with recurrent infections and hyperinflation or atelectasis of the distal lung parenchyma. The cyst itself can become infected (usually by contamination through a tracheobronchial communication), leading to acute distention and exacerbation of compressive symptoms. Hemoptysis can also occur. Dysphagia is a symptom of esophageal compression. Many cysts are asymptomatic and may be diagnosed incidentally on chest radiographs or other imaging modalities performed for other reasons.[182,183] In recent years, bronchogenic cysts have also been diagnosed prenatally by ultrasonography, sometimes resulting in congenital lobar overinflation.[182,184,185] On chest radiography, they appear as rounded space-occupying lesions projecting from the mediastinum, often displacing and compressing the lower trachea and bronchus adjacent to the cyst (Fig. 64-12). A barium swallow may demonstrate esophageal compression or a lesion separating the trachea and esophagus. CT is the most often used modality for identifying, localizing, and defining the cystic mediastinal lesion, although MRI has become more popular in recent years because of the risks of postradiation malignancy.[186] The mucoid content is sometimes so thick

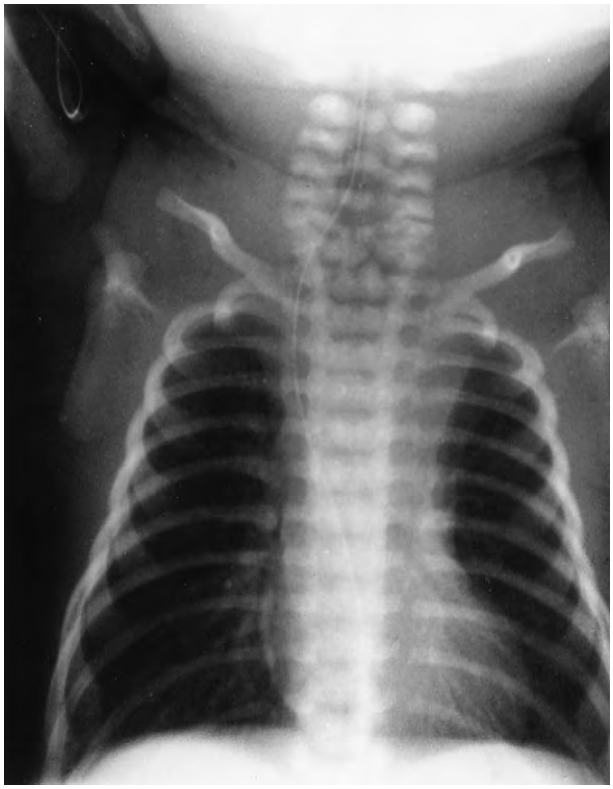


Figure 64-11 Neurenteric cyst. The presence of a cleft vertebral anomaly underlying a rounded mass indenting the upper trachea and deviating to the right, as seen in this chest radiograph, is characteristic of a neurenteric cyst.

that a bronchogenic cyst may be misinterpreted as a solid mass on CT because of its elevated density. On MRI, however, the lesion will appear bright on T2-weighted images as for other fluid-containing structures (Fig. 64-13). For neurenteric cysts, MRI provides the best imaging of all components of the malformation. Drawbacks in its use are that children usually require sedation or even general anesthesia for the procedure, and it is less useful than CT for the evaluation of the bronchial tree. Bronchoscopy is seldom necessary but may demonstrate compression and displacement of the airway. Bronchography has been abandoned in favor of CT and MRI. Surgical excision is indicated in all cases of foregut duplications because of their propensity to produce complications and a higher rate of intraoperative complications. Resection can be accomplished by a thoracoscopic approach in most cases.[182]

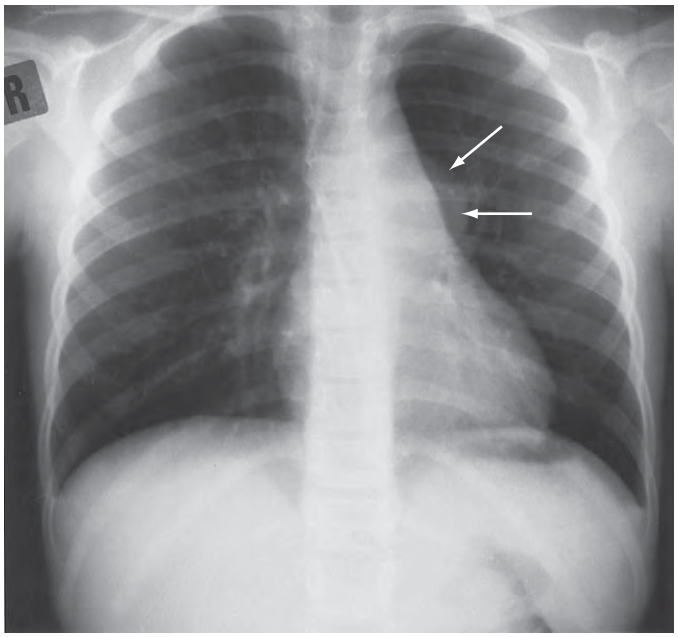


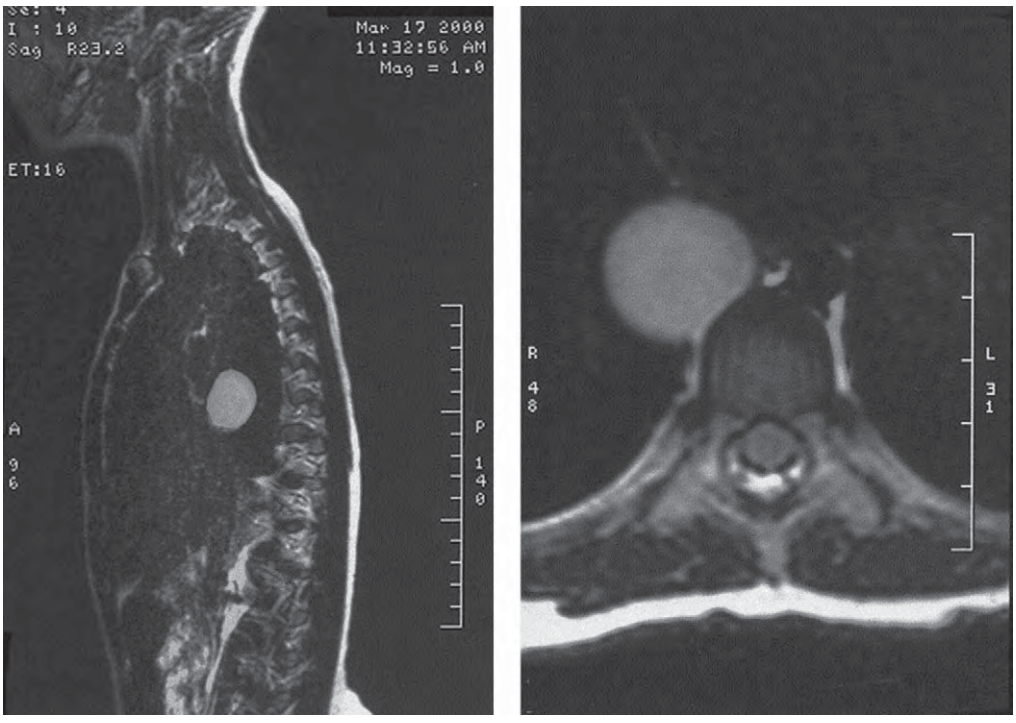
Figure 64-12 Bronchogenic cyst. The typically rounded hilar mass *(arrows)*, seen on this chest radiograph indenting the left main bronchus and lower trachea while deviating the trachea to the right, was confirmed at surgery to be a bronchogenic cyst.

Other Mediastinal Cysts. Enteric duplication cysts have already been discussed; pericardial cysts, benign cystic teratomas, dermoid cysts, thymic cysts, and mediastinal meningoceles should be included in the differential diagnosis of bronchogenic cysts.

Bronchobiliary/Tracheobiliary Fistula. This is a rare anomaly usually presenting early in infancy because of symptoms produced by the intense inflammatory effect of bile secretions in the bronchial tree. Fewer than 30 cases have been described. A tract connects the biliary tree to the lower

PITFALLS IN AIRWAY MALFORMATIONS

- A laryngotracheoesophageal cleft is often missed on direct laryngoscopy and flexible endoscopy; rigid bronchoscopy is required.
- A pure "H-type" tracheoesophageal fistula is easily missed on routine contrast swallow; a tube contrast esophagogram yields better results but rigid tracheoscopy remains the best diagnostic test.
- The extent and severity of tracheomalacia is best appreciated with rigid tracheoscopy under general anesthesia with the patient breathing spontaneously; lateral chest fluoroscopy can be a useful initial investigation.



A B

Figure 64-13 A 6-year-old girl had been operated on and followed since birth for a low lumbar lipomeningocele. An asymptomatic foregut duplication cyst was incidentally detected on these T2-weighted magnetic resonance images done to evaluate for a tethered cord (**A,** sagittal view; **B,** axial view). She underwent an uncomplicated thoracoscopic resection. (From Laberge J-M, Puligandla P, Flageole H: Asymptomatic congenital lung malformations. Semin Pediatr Surg 14:16-33, 2005.)

trachea, carina, or one of the main bronchi, nearly always on the right near the carina.[187,188] Yellow or green bile-stained sputum associated with cough, atelectasis, and infection forms a distinctive clinical picture in infancy. Early surgery is recommended before extensive autolytic damage occurs.[189] The embryologic origin of the lesion remains obscure.[151] Associated anomalies are uncommon but have included esophageal atresia with tracheoesophageal fistula, biliary atresia, and right congenital diaphragmatic hernia.[190-192]

LUNG MALFORMATIONS

Lung Unit as a Whole

PULMONARY AGENESIS

Bilateral agenesis is exceedingly rare and may occur in association with anencephaly.[193] It has been observed in mice deficient in FGF10 or its receptor.[26,194] The role of retinoic acid in lung development was recognized as early as 1949[195] and was recently reviewed[31]; mice deficient in its receptor show a variety of developmental defects such as agenesis of the left lung and pulmonary hypoplasia.

Unilateral agenesis is found in 1 in 10,000 to 20,000 autopsies.[196] The agenesis affects both lungs with equal frequency, with a slight female preponderance of 1.3 : 1.[49] Lobar agenesis is rarer than complete absence of one lung and, when it occurs, usually affects the right upper and middle lobes together. Long-term survival with unilateral lung agenesis is possible in the absence of associated severe anomalies, which include anencephaly and cardiovascular, gastrointestinal, skeletal and urogenital malformations.[178,197-201] Absence of one lung has been described with esophageal atresia and other VACTERL anomalies.[202-204]

Neonatal respiratory distress is common. Chest radiographs show a marked mediastinal shift with herniation of the contralateral lung across the mediastinum. The absence of the carina or, more commonly, a blind-ending bronchus (sometimes termed "aplasia" instead of "agenesis," where there would be no carina or bronchial stump) may be appreciated on a penetrated film or a CT scan with reconstruction (Fig. 64-14). Echocardiography and angiography show absence of the pulmonary artery, and it is always necessary to exclude other associated cardiovascular lesions. There is also agenesis of both sympathetic and parasympathetic plexuses, generally with a lack of parietal pleura.[151] Mortality is said to be higher with right lung agenesis, possibly because of the smaller size of the left lung but also because of a higher incidence of cardiovascular anomalies with right lung absence.[199] A higher risk of vascular compression of the trachea with right lung agenesis has also been implicated.[205] The differential diagnosis includes total atelectasis caused by bronchial obstruction, unilateral emphysema with compression or collapse of the contralateral lung, or severe pulmonary hypoplasia.

With more routine prenatal ultrasound screening, the diagnosis may be made before birth, although the enlarged unilateral lung may be mistaken for an abnormal lung (such as seen with CPAM/CCAM; see later) with mediastinal shift and severe compression of the presumed normal lung (which is in fact absent). Careful repeat imaging, including fetal MRI, should be done to avoid the catastrophic consequences of an EXIT resection of this presumed abnormally enlarged lung, which would in fact be the infant's one and only lung.[206]

Patients presenting late usually have readily detectable flattening and reduced movement of the chest wall on the affected side, with reduced air entry on auscultation, although this often sounds surprisingly better than expected. There may be some breathlessness on exertion and the chest wall deformity may be quite pronounced, with an associated secondary scoliosis. On the chest radiograph, there is considerable mediastinal shift and the involved hemithorax is small, with narrowed intercostal spaces.

Management is initially limited to supportive treatment (including oxygen if necessary), correcting associated malfor-

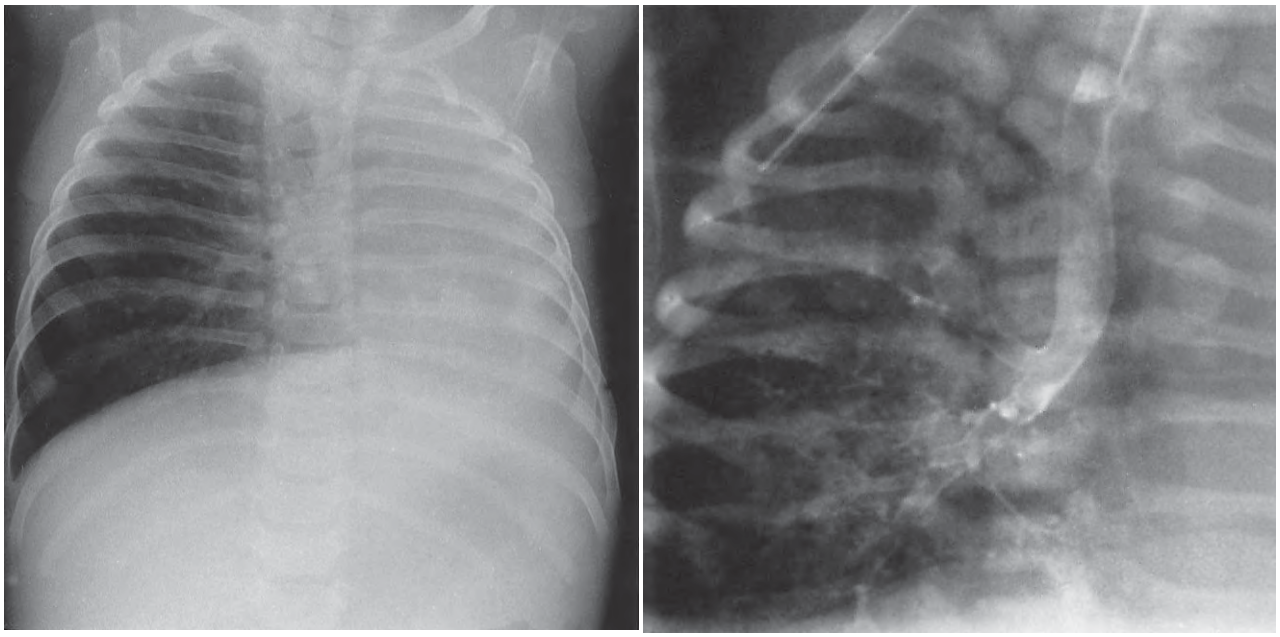


Figure 64-14 Left lung agenesis. Agenesis of the left lung with absence of the carina and left bronchial stump confirmed on tracheobronchogram. Note the associated vertebral anomaly, a common association with major airway abnormalities. Advanced imaging techniques such as CT scan have largely replaced bronchography.

mations, and the prevention and treatment of respiratory infections. In some cases tracheal stenosis or vascular compression may coexist and require treatment.[205,207,208] Imaging techniques combined with rigid bronchoscopy allow a precise diagnosis to be made.[209] Pulmonary hypertension is a complication that requires particular care and attention. It is more common in these patients simply because a normal blood volume must flow through a reduced pulmonary vascular bed. The presence of hypoxia (which is a potent pulmonary vasoconstrictor) or a cardiac left-to-right shunt (which further increases the flow through the already reduced pulmonary vascular bed) will compound this effect and is likely to accelerate the progression of the pulmonary hypertension to irreversible pulmonary vascular disease. Because of the severe mediastinal shift, some patients develop a progressive deterioration similar to the postpneumonectomy syndrome and may improve with the insertion of a tissue expander in the ipsilateral chest.[208]

PULMONARY HYPOPLASIA

Pulmonary hypoplasia is usually defined as a lung weight more than 2 standard deviations below the normal for age (or gestational age), or in terms of lung weight–to–body weight ratio, the normal being 0.222 ± 0.002 for term and near-term infants.[197] Because postnatal events such as pulmonary edema and pneumonia may affect lung weight, the radial alveolar count[210] and the mean terminal bronchiole density[211] are other methods to assess the adequacy of lung development. Alveolar counting and lung volume measurements have also been used.[212,213]

Pulmonary hypoplasia is almost always accompanied by hypoplasia of the corresponding pulmonary vessel. This follows obviously from the second rule of lung embryogenesis, in which the vasculature follows the bronchial development.[214] Hypoplasia as an isolated phenomenon is rare; a familial form has been described.[215] More commonly, pulmonary hypoplasia is associated with conditions that interfere with lung growth; Box 64-1 lists some of these.[49,151,216,217] Severe oligohydramnios (whether from prolonged rupture of membranes or urinary tract malformation) is the most frequent cause of pulmonary hypoplasia. Initially thought by some to be a primary phenomenon as part of the Potter syndrome, its reversibility has been demonstrated experimentally.[218,219] Furthermore, while chest wall compression by the uterus was classically thought to explain the lung hypoplasia, measurements of amniotic fluid pressures in the remaining pockets have shown pressures to be lower than normal.[220,221] In experimental studies, it was also found that severe oligohydramnios increased spinal flexion, causing compression of abdominal contents, elevation of the diaphragm and lung compression.[222] Lower amniotic fluid pressures combined with elevation of the diaphragm causes more lung fluid to egress through the larynx; a decrease of alveolar distention by lung fluid results in pulmonary hypoplasia, as demonstrated experimentally by Moessinger and colleagues.[223] The same mechanism explains the pulmonary hypoplasia that can be seen with large tracheoesophageal fistulas and complete laryngotracheoesophageal clefts; in these cases the pulmonary fluid escapes through the defect, resulting in the loss of the 1 to 2 cm H_2O gradient normally maintained by the larynx.[224]

BOX 64-1 Most Common Causes of Pulmonary Hypoplasia

Conditions Leading to an Egress of Lung Fluid

Severe oligohydramnios (from premature rupture of membranes, bilateral renal agenesis, or urinary tract obstruction). Compression of the thoracic cage and abdominal contents by the uterus and limitation of breathing movements may also play a role.
Laryngotracheoesophageal cleft
Large tracheoesophageal fistula

Space-Occupying Lesions

Congenital diaphragmatic hernia, eventration
Lung malformations (CCAM, sequestration, others)
Thoracic tumors
Pleural effusion, chylothorax
Abdominal conditions pressing on the diaphragm (massive ascites, cysts, and tumors)

Thoracic Cage Anomalies

Jeune syndrome (asphyxiating thoracic dystrophy)
Achondroplasia, others
Scoliosis

Conditions Preventing Normal Fetal Breathing Movements

Anencephaly
Phrenic nerve agenesis
Other syndromes and conditions affecting the central nervous system

Miscellaneous Conditions, Where the Mechanism of Lung Hypoplasia Is Unclear or Multifactorial

Giant omphalocele
Chromosomal anomalies, including trisomy 13, 18, and 21.

With space-occupying lesions such as congenital diaphragmatic hernia (discussed in more detail later), the hypoplasia is more severe on the ipsilateral side, although the contralateral side is also affected, to a lesser degree, because of the fetus' mobile mediastinum. Sometimes the hypoplasia is part of an intrinsic developmental problem, such as seen with the abnormally formed right lung in the scimitar syndrome (see later).

Clinically, patients with pulmonary hypoplasia may present in early infancy with respiratory distress ranging from mild to severe, depending on the degree of hypoplasia. Commonly, it is the associated anomalies that draw the attention. In severe bilateral hypoplasia the thoracic cage is obviously reduced in size and characteristically bell shaped, with the base of the chest widening at diaphragmatic level to a normal-sized abdomen. The patient is tachypneic, with restricted chest wall movement, and in respiratory distress. Less severe degrees of hypoplasia—unilateral or bilateral—may present later with persistent tachypnea or disproportionate shortness of breath with exercise. Occasionally, the abnormality is coin-

cidentally noticed on examination or chest radiograph when the patient presents with an intercurrent infection. In unilateral hypoplasia, the chest cage appears asymmetric, with diminished air entry and chest expansion on the side of the lesion together with mediastinal shift to that side. The chest radiograph confirms mediastinal deviation and a lung that often appears hyperlucent. Isotope scanning usually reveals a greater impairment of perfusion than ventilation on the side of the lesion. In right-sided hypoplasia, it may be important to establish the pattern of vasculature because of the common association with scimitar syndrome (see later). In the absence of associated lesions, unilateral pulmonary hypoplasia is compatible with normal growth, development, and survival. Long-term complications include reduced exercise tolerance, recurrent infections and sometimes a worsening chest deformity with scoliosis.

PULMONARY HYPERPLASIA

Pulmonary hyperplasia is the growth of lung parenchyma beyond its normal control. It is always a secondary phenomenon, usually in response to airway obstruction in utero.[51] Diffusely enlarged lungs are seen with laryngeal and tracheal atresia as discussed earlier, and can be reproduced experimentally with fetal tracheal occlusion.[223-225] More localized areas of lung hyperplasia will be discussed in the next section.

Parenchymal Malformations

This is where most of the controversies lie regarding pathogenesis and classification of congenital lung lesions. For the purpose of this chapter we will use the terms currently employed in clinical practice, recognizing that they are changing and that overlap exists between some of these malformations. Box 64-2 shows a pathologic classification recently proposed by Langston. This can be contrasted with the more "old-fashioned" or clinically oriented approach used here.

CONGENITAL LOBAR EMPHYSEMA

Congenital lobar emphysema (CLE) is used to describe a distended, hyperlucent lobe on plain radiographs, most often the left upper lobe, followed by the right middle and the right upper lobes.[151,226] The term *emphysema* is often considered a misnomer because it implies parenchymal destruction to pathologists, but it is consistent with the meaning of its Greek root "inflation." Pathologically, a distinction is made between a *polyalveolar lobe*, in which the number of alveoli is greatly increased, and *congenital lobar overinflation* (CLO), in which the alveoli are markedly distended but normal in number. CLO is thought to be caused by a partial bronchial obstruction creating a ball-valve effect. This obstruction may be intrinsic (bronchomalacia) or less commonly extrinsic (vascular, bronchogenic cyst), but in many instances an exact cause cannot be determined.[49,227,228] The pathogenesis of a polyalveolar lobe remains uncertain but transient bronchial obstruction in utero has been suggested.[229]

CLE is rarely detected prenatally.[229,230] It appears as an echogenic homogeneous lung mass that may regress before birth.[229,231] The typical postnatal presentation is progressive tachypnea with lobar hyperinflation, mediastinal shift, and sometimes contralateral atelectasis. Occasionally, it is difficult to determine whether the contralateral collapse is the primary phenomenon or if it is secondary to the CLE; identifying a collapsed ipsilateral lobe is helpful. Initial postnatal films may show fluid retention, as seen in Figure 64-15, although the pathologic diagnosis was different in that case; as the fluid clears the lobe gradually becomes hyperinflated. When this leads to respiratory distress, lobectomy is indicated. Positive pressure ventilation will only worsen the hyperinflation. High-frequency oscillating ventilation may be useful as a temporary preoperative measure. The diagnosis is based on the clinical course and plain radiographs. Because extrinsic lesions are uncommon, the limited benefits of CT scan should be weighed against the potential risks of respira-

BOX 64-2 Langston's Classification of Congenital Lung Malformations

Bronchopulmonary Malformation

- Bronchogenic cyst (noncommunicating bronchopulmonary foregut malformation)
- Bronchial atresia
  - Isolated
  - With systemic arterial/venous connection (intralobar sequestration)
  - With connection to gastrointestinal tract (intralobar sequestration/complex or communicating bronchopulmonary foregut malformation)
  - Systemic arterial connection to normal lung
- Cystic adenomatoid malformation, large cyst type (Stocker type 1)
  - Isolated
  - With systemic arterial/venous connection (hybrid lesion/intralobar sequestration)
- Cystic adenomatoid malformation, small cyst type (Stocker type 2)
  - Isolated
  - With systemic arterial/venous connection (hybrid lesion/intralobar sequestration)
- Extralobar sequestration
  - Without connection to gastrointestinal tract (with/without CAM, small cyst type)
  - With connection to gastrointestinal tract (complex/communicating bronchopulmonary foregut malformation)

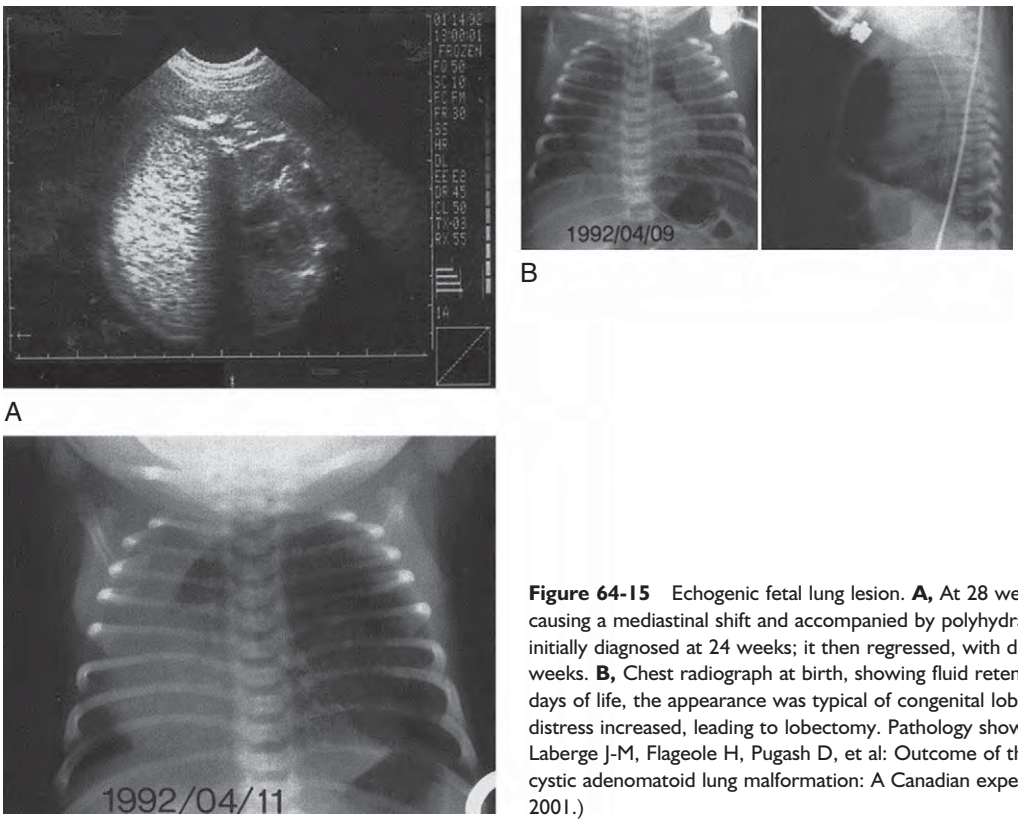
Pulmonary Hyperplasia and Related Lesions

- Laryngeal atresia
- Solid or adenomatoid form of cystic adenomatoid malformation (Stocker type 3)
- Polyalveolar lobe

Congenital Lobar Overinflation

Other Cystic Lesions

- Lymphatic/lymphangiomatous cysts
- Enteric cysts
- Mesothelial cysts
- Simple parenchymal cysts
- Low-grade cystic pleuropulmonary blastoma



A B C

Figure 64-15 Echogenic fetal lung lesion. **A,** At 28 weeks' gestation, hyperechogenic mass causing a mediastinal shift and accompanied by polyhydramnios and mild ascites. The lesion was initially diagnosed at 24 weeks; it then regressed, with disappearance of the ascites at 31 weeks. **B,** Chest radiograph at birth, showing fluid retention in the left upper lobe. **C,** At 2 days of life, the appearance was typical of congenital lobar emphysema and the respiratory distress increased, leading to lobectomy. Pathology showed a CCAM/CPAM type 2. (From Laberge J-M, Flageole H, Pugash D, et al: Outcome of the prenatally diagnosed congenital cystic adenomatoid lung malformation: A Canadian experience. Fetal Diagn Ther 16:178-186, 2001.)

tory deterioration. The same holds true about rigid bronchoscopy. Lobectomy is performed via a thoracotomy because the involved lobe does not collapse, making a thoracoscopic approach difficult. When CLE is discovered in an asymptomatic patient, treatment is usually conservative because the lesion may regress.

In neonates, the lesion should be distinguished from pulmonary interstitial emphysema, which is secondary to barotrauma in small premature infants. Most cases of lobar emphysema discovered beyond the neonatal period are acquired, often after bronchiolitis, and tend to resolve spontaneously.[232]

CONGENITAL CYSTIC ADENOMATOID MALFORMATION (CONGENITAL PULMONARY AIRWAY MALFORMATION)

CCAM is considered a hamartomatous lesion of the bronchial tree by some, whereas others favor a localized arrest in the development of the fetal bronchial tree as the etiology.[49,183,227,228] Recent evidence points toward an arrest in lung development.[233] Ch'in and Tang[234] first distinguished this entity from other types of congenital cystic lung disease in 1949. These lesions were initially classified into three types by Stocker,[47] who later added two more variants, types 0 and 4 (Fig. 64-16; see also Table 64-1).[48] Because some types are not cystic and only one type has the adenomatoid appearance, the term *congenital pulmonary airway malformation* (CPAM) was recently proposed.[49] The malformation is usually limited to a lobe, with 10% involving a whole lung or being bilateral. There is no clear predilection between upper and lower lobes, or between right and left involvement. Once considered a rare defect, an increase in the rate of detection and reporting of this lesion appeared with the introduction of routine prenatal ultrasound examination. The incidence of CCAM/CPAM has been estimated at 1 per 25,000 to 35,000 pregnancies in one study,[235] while another reports a population prevalence of 9 per 100,000 total births.[236] The International Pleuropulmonary Blastoma Registry based in St. Paul, Minnesota, has obtained incidences of congenital lung cysts varying from 1 per 8300 to 1 per 18,500 from Australian, Canadian, and New York State congenital malformations registries (J. R. Priest, personal communication). For the purposes of prenatal diagnosis and management, the lesions are better classified as macrocystic or microcystic because Stocker's classification was not meant for mid-gestation fetuses and cannot be based on cyst size alone.[235,237,238]

Type 1 CCAM/CPAM is generally considered the most frequent, comprising more than half of cases.[49] Traditionally, it presented in early infancy with respiratory distress, or later in life, and even in adulthood, with recurrent infection[239,240] (Fig. 64-17). Less common forms of presentation include pneumothorax, hemoptysis, and bronchioloalveolar carcinoma, which is thought to arise from the mucigenic epithelium.[183,240-243] In recent years, it has been diagnosed prenatally in many instances.[235] Although the prognosis is generally favorable, some cysts may become so large in the fetus as to cause fetal hydrops or pulmonary hypoplasia and lead to fetal or neonatal death; thus fetal treatment, usually in the form of a thoracoamniotic shunt, is indicated in selected cases[55,235,244] (Fig. 64-18). Many large fetal thoracic masses are also accompanied by polyhydramnios, presumably secondary to the mediastinal shift impairing the swallowing of amniotic fluid; this may result in premature labor and delivery, leading to further morbidity or mortality. Therefore, amnioreduction is

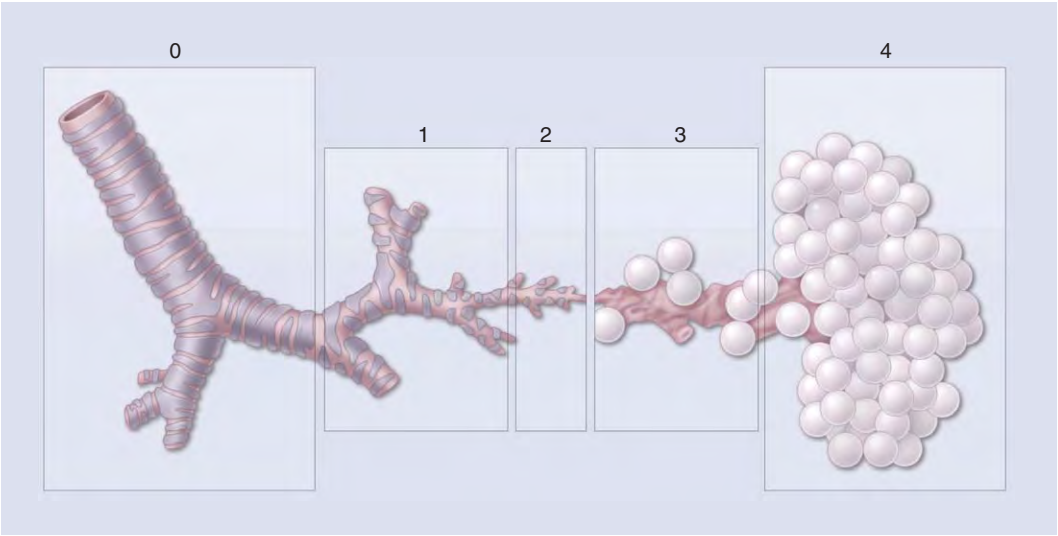


Figure 64-16 Stocker's classification of congenital cystic adenomatoid malformation, now called congenital pulmonary airway malformation. (From Gilbert-Barness E: Respiratory system. In Potter's Pathology of the Fetus and Infant. St. Louis, Mosby, 1997, pp 741-769.)

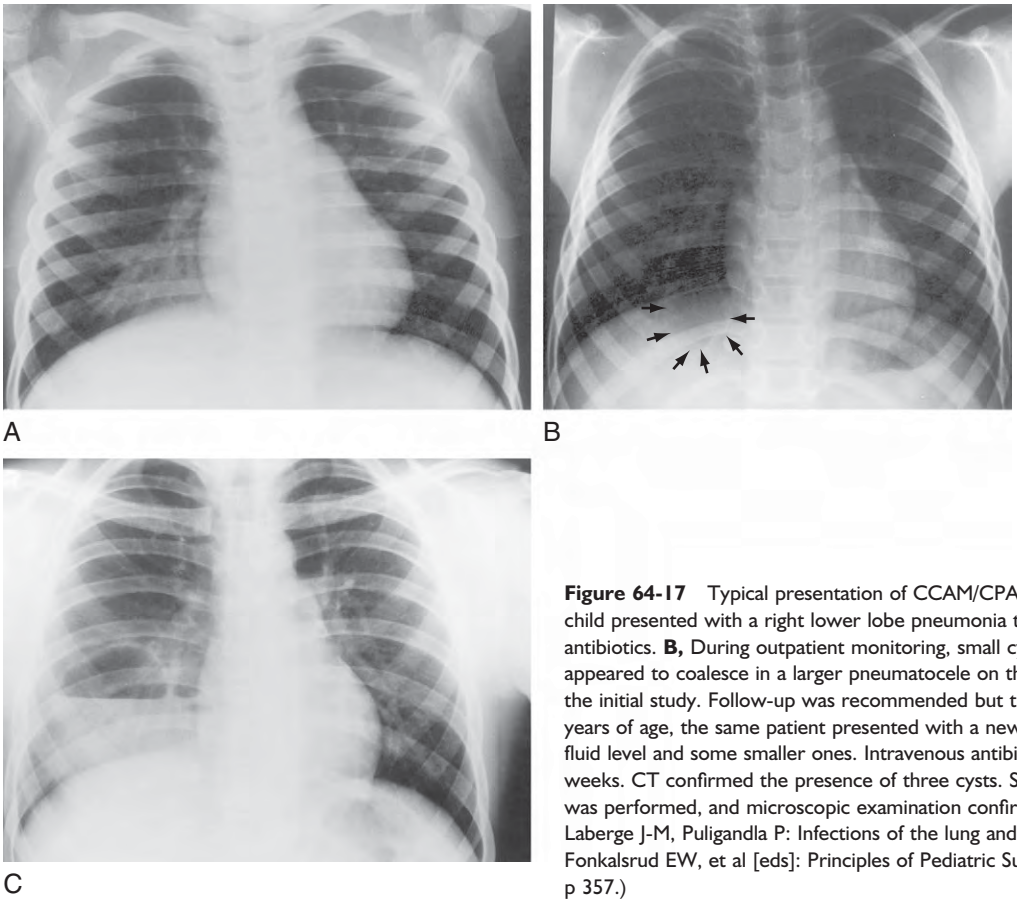
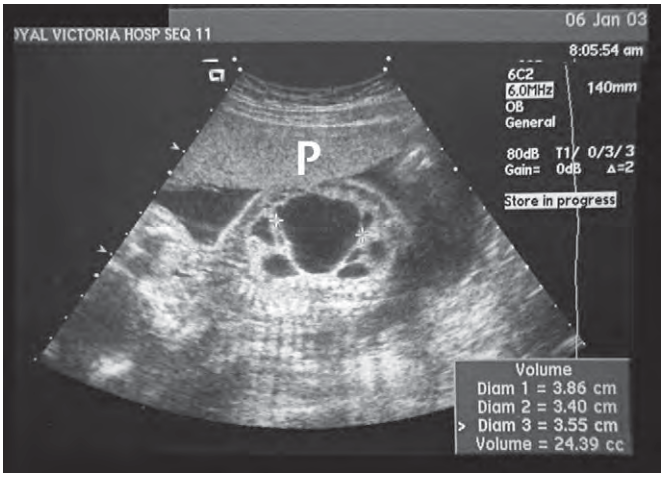


Figure 64-17 Typical presentation of CCAM/CPAM in the older child. **A,** A 5-year-old child presented with a right lower lobe pneumonia that responded to intravenous antibiotics. **B,** During outpatient monitoring, small cysts were noted 6 weeks later and appeared to coalesce in a larger pneumatocele on this radiograph, taken 11 weeks after the initial study. Follow-up was recommended but the family did not comply. **C,** At 14 years of age, the same patient presented with a new episode of infection with a large air-fluid level and some smaller ones. Intravenous antibiotics were required for more than 2 weeks. CT confirmed the presence of three cysts. Six weeks later, a right lower lobectomy was performed, and microscopic examination confirmed a type 1 CCAM/CPAM. (From Laberge J-M, Puligandla P: Infections of the lung and airway. In O'Neill JA, Grosfeld JL, Fonkalsrud EW, et al [eds]: Principles of Pediatric Surgery, 2nd ed. St. Louis, Mosby, 2004, p 357.)

another form of prenatal intervention that is beneficial in certain cases.

Postnatally, the diagnosis is suspected on plain radiographs, which demonstrate one or more air-filled cystic areas. In a neonate with respiratory distress, a "babygram" is useful to exclude a congenital diaphragmatic hernia; no other investigation is necessary before surgery. In less symptomatic patients, the diagnosis is confirmed with CT scan. The differential diagnosis includes pneumatoceles following pneumonia, pulmonary interstitial emphysema, simple lung cysts, bronchogenic cysts that may have eroded into and communicate with a bronchus, and cystic pleuropulmonary blastoma.[51,61,183] This tumor will be discussed further later. Unless there has been a prior chest radiograph showing lung cysts, the differ-



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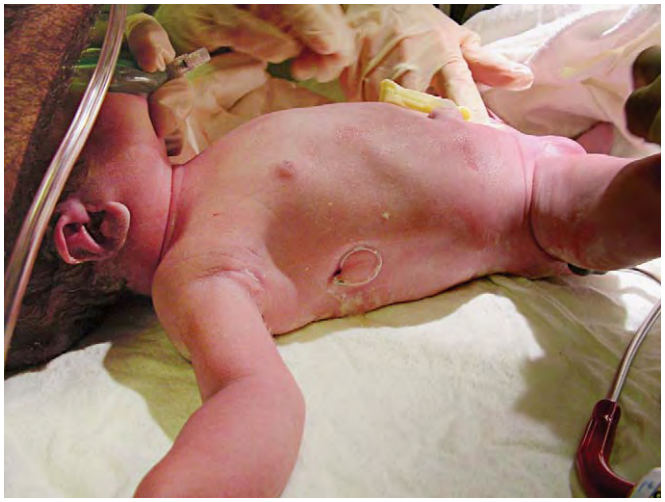

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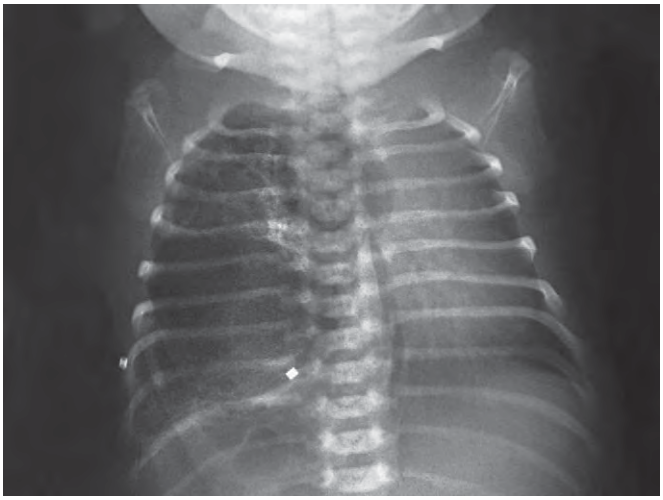

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Figure 64-18 Fetal shunt for CCAM. A macrocystic CCAM was diagnosed at 18 weeks' gestation. It was initially observed but at 21 weeks signs of hydrops appeared, necessitating cyst decompression. **A,** Longitudinal section showing the large cyst surrounded by several smaller ones. The head is on the left; notice the anterior placenta (P), which prevented initial placement of a thoracoamniotic shunt. After 8 weeks of twice-a-week needle thoracentesis, polyhydramnios helped to stretch the uterus and move the placenta away, allowing placement of the shunt. **B,** The baby was born after induced vaginal delivery at term with the shunt in place, with minimal respiratory distress. **C,** The chest radiograph shows the cystic disease on the right with marked mediastinal shift. A right lower lobectomy was performed the same night; microscopic examination showed a type I CCAM/CPAM. The postoperative course and long-term follow-up were uneventful.

entiation between a suprainfected CCAM/CPAM and post-pneumonia pneumatoceles (typically staphylococcal) requires a period of observation; the latter should regress within a period of months (see Fig. 64-17).

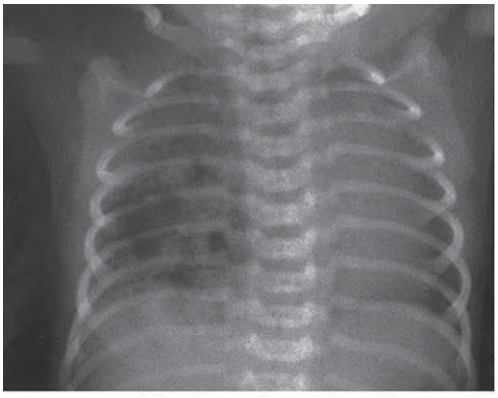
Type 2 CCAM/CPAM was initially described mostly in autopsy series, often in association with other malformations, and was considered to have a poor prognosis.[47,49] However, many cases of cystic lung lesions now diagnosed prenatally turn out to be type 2 malformations without associated anomalies and an excellent prognosis[183,235] (Fig. 64-19). Langston[51] believes that this pattern of maldevelopment is secondary to airway obstruction during development and, as such, should be considered as part of a malformation sequence rather than a separate entity. Indeed, bronchial atresia has been identified in many instances, and may have been overlooked in others.[51,173,174] Furthermore, the type 2 histology is identified in 40% to 50% of extralobar sequestration, a malformation where there is no bronchial connection[227,245]; if the "bronchial atresia sequence" theory was correct, it is unclear why we do not see the same maldevelopment in *all* cases of extralobar sequestration.

Type 3 CCAM/CPAM is the adenomatoid variant. It is less common, more often involves a whole lung, and has a poorer prognosis compared with types 1 and 2. Some pathologists consider this as simple lung hyperplasia, as seen with airway obstruction such as laryngeal atresia; they imply that the immature-appearing tissue is due to the fact that these lesions were most often found in preterm fetuses and stillborns.[51] However, airway obstruction is not identified in most cases, and the lesion has been described in surviving term neonates and infants.[235,238,239]

Type 4 CCAM/CPAM is a recent addition to Stocker's classification. Because of its large cysts, most cases were previously considered as type 1. Immunohistochemistry studies have demonstrated an acinar-alveolar type of epithelium, in contrast with the bronchiolar type found in types 1 to 3.[233] Other than the usual presentation with respiratory distress or pneumonia, perhaps the type 4 is more notable for the frequent occurrence of spontaneous pneumothorax. A major difficulty with this type is its differentiation from cystic pleuropulmonary blastoma, both from the clinical presentation and the histologic appearance.[61,62,246] This tumor is discussed in more detail further.[247,248]

Type 0 CCAM/CPAM is rare and of interest mostly to pathologists. It is generally lethal and is associated with cardiovascular anomalies and dermal hypoplasia.[49]

The pathogenesis of CCAM has been the subject of controversy. Langston[51] believes that the five types may repre-



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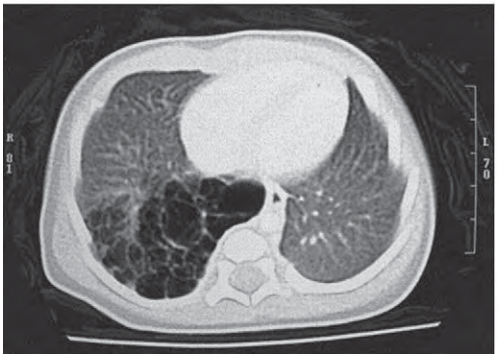

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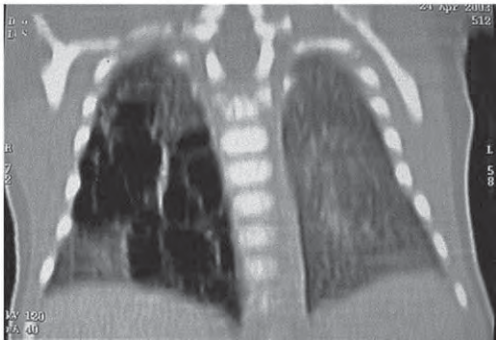

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Figure 64-19 A fetus was diagnosed with a large mixed solid/cystic lung lesion filling 80% of the thoracic cavity at 19 weeks' gestation. Despite severe mediastinal shift and inversion of the diaphragm, hydrops did not develop and the lesion gradually regressed after 24 weeks' gestation. The baby was asymptomatic at birth. **A,** Chest radiograph at birth showed multiple lucencies in the right lung with mediastinal shift. **B,** Given the initial size of the lesion, CT scan was performed earlier than usual, at 3 weeks of age. Multiple cysts are seen in the right lower lobe. **C,** This reconstructed CT image demonstrates the cysts involving most of the lower lobe, reaching up to the apex of the thorax. Although the baby remained asymptomatic, the fear of sudden enlargement with respiratory distress led to an early elective lobectomy at 5 weeks of age. She was discharged 4 days after surgery. Microscopic examination was consistent with a type 2 CCAM/CPAM. (From Laberge J-M, Puligandla P, Flageole H: Asymptomatic congenital lung malformations. Semin Pediatr Surg 14:16-33, 2005.)

sent different malformations with varying etiologies. Other studies support the notion that dysregulation in the branching morphogenesis of the lung is associated with the development of abnormal lung tissue, in both CCAM and sequestration.[20] A dysregulation of lung maturation is also suggested by the increased cell proliferation seen in CCAM.[21,22]

Several areas of controversy exist in the management of CCAM/CPAM. Patients who are *symptomatic* require surgery, but the surgical approach and extent of surgery are debated. Some authors have advocated segmental resection, but this often results in incomplete resection, persistent pneumothorax, and the need for completion lobectomy.[9,249-254] Many surgeons and pathologists agree that lobectomy is safer, in part because the limit between CCAM and normal parenchyma is impossible to determine grossly.[48,50,55,60,255-258] The impossibility to distinguish type 4 CCAM from type I PPB and the development of malignancy years after a segmentectomy lends further support to this recommendation.[61,246,259] Several studies have demonstrated compensatory lung growth after a pulmonary lobectomy in infancy, with normal pulmonary function tests in follow-up.[260-264] Interestingly, dell'Agnola and colleagues[265] performed intraoperative measurement of pulmonary function in infants with asymptomatic CCAM and demonstrated significant improvement after resection of the affected lobe. Hence, segmentectomy should be reserved for patients with bilobar or bilateral disease. Lobectomy by thoracoscopy has been advocated in some centers. Albanese[266] has reported a series of 14 consecutive thoracoscopic lobectomies in patients with asymptomatic congenital lung lesions without any complication and a mean postoperative stay of 38 hours. These excellent results may not be generalizable and the technique may not apply to neonates with respiratory compromise or older children who have had recurrent infections. A limited lateral thoracotomy is safe, well tolerated in children, and compatible with lengths of stay of 3 to 5 days in most cases.

The management of *asymptomatic* patients is more controversial.[183] While a few authors recommend simple observation, the majority favor surgical resection, mostly because of the risk of infection, which increases the surgical complication rate and can be lethal.[60,228,265,267-269] Other risks include pneumothorax, hemoptysis, and malignancy.[183,270] Some of these complications occur in adulthood, making long-term follow-up nearly impossible. Of note, the risk of malignancy in congenital lung cysts appears to be greater when there is associated childhood neoplasia or dysplasia in the patient or family.[271] The presence of cystic renal lesions in children with lung cysts particularly heralds the risk of pulmonary malignancy.[272,273]

PULMONARY SEQUESTRATION

Pulmonary sequestration is generally thought to result from an abnormal accessory tracheobronchial bud arising from the foregut.[49,228] Intralobar sequestration (ILS) and extralobar sequestration (ELS) types are recognized, based on whether the visceral pleura is shared with the adjacent normal lobe or not. ELS is sometimes referred to as a "Rokitansky lobe" in old texts.[11,151] Typically, the lung tissue in sequestrations does not have a connection to the normal tracheobronchial tree and is supplied by an anomalous systemic artery, but many variants exist.[49,50,228] Most ILSs are located in the lower lobes; most ELSs are found posteromedially in the left lower chest but can occur within the diaphragm, below it, or rarely in other locations.[52,274,275]

Extralobar sequestrations situated in the lower chest receive their blood supply through one or several branches of

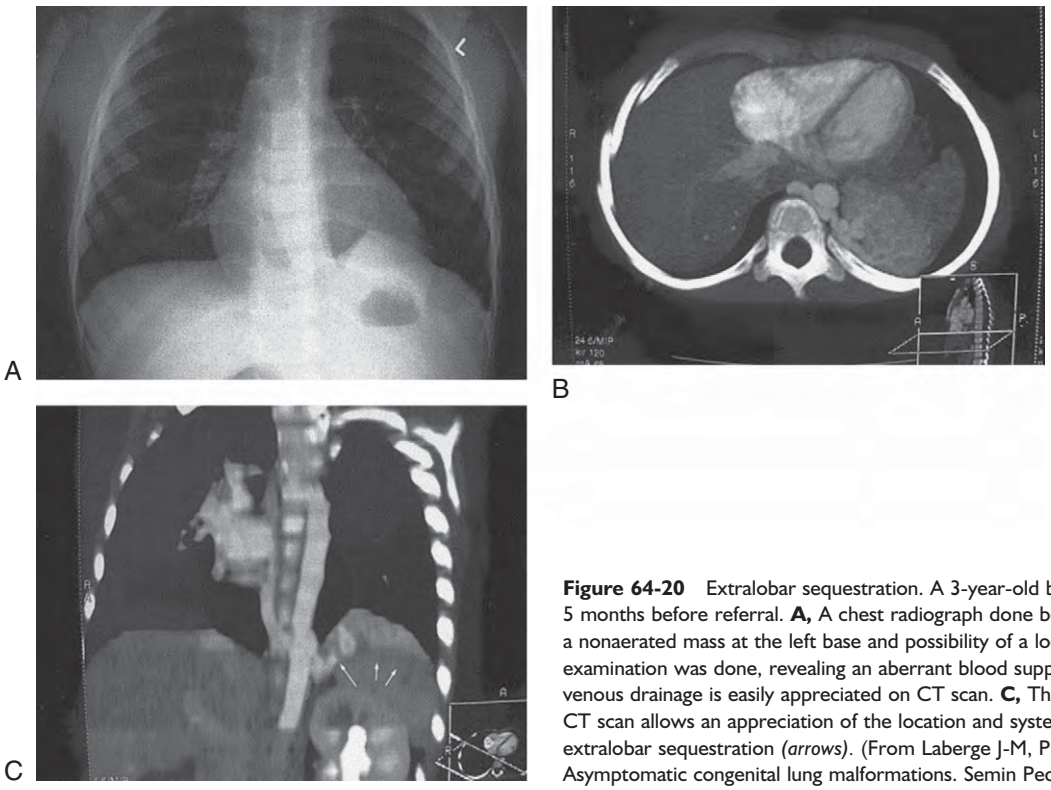


Figure 64-20 Extralobar sequestration. A 3-year-old boy was diagnosed with pneumonia 5 months before referral. **A,** A chest radiograph done because of persistent cough showed a nonaerated mass at the left base and possibility of a localized eventration. An ultrasound examination was done, revealing an aberrant blood supply to the mass. **B,** The aberrant venous drainage is easily appreciated on CT scan. **C,** This reconstructed image from the CT scan allows an appreciation of the location and systemic arterial supply of this extralobar sequestration *(arrows)*. (From Laberge J-M, Puligandla P, Flageole H: Asymptomatic congenital lung malformations. Semin Pediatr Surg 14:16-33, 2005.)

the thoracic or abdominal aorta (Fig. 64-20) and, rarely, from a branch of the pulmonary artery. The venous drainage is usually through the systemic circulation, although 20% are drained partially or completely by the pulmonary veins.[49,276] Other systemic arterial origins may be encountered, especially with ELS in unusual locations.[51,275] There is a 3 : 1 male predominance.[13,277]

Although some authors state that only 10% of patients with ELS are asymptomatic,[49] these malformations are often discovered because of an associated congenital diaphragmatic defect, which was present in over 40% of cases in a large review.[276] Many recognize that ELS may remain asymptomatic through life.[183,228,277] Uncommon complications from isolated ELS include respiratory distress, symptomatic shunting with right heart failure, and infection, which is rare unless the sequestration is connected to the esophagus through a patent bronchus (see in discussion on communicating bronchopulmonary foregut malformation later). There are rare reports of hemothorax, torsion, and malignancy.[183] Antenatal complications will be discussed later.

Extralobar sequestrations usually present as a solid nonaerated, pyramid-shaped, or ovoid mass found on chest radiography, with nearly 80% occurring above the left diaphragm. Less frequently, the lesion may be cystic; the presence of air usually signifies an esophageal connection. Ultrasound with Doppler, CT scan with intravenous contrast infusion, and MRI can all be useful in demonstrating the systemic arterial supply (see Fig. 64-20), making diagnostic arteriography obsolete.[52]

Microscopically, the lesion may consist of nonaerated pulmonary parenchyma with dilated bronchioles, alveolar ducts, and alveoli. It is now recognized that in about half of the cases the histology is similar to type 2 CCAM, while 15 years ago this finding was the subject of case reports.[11,49,51,227,278] Prominent subpleural lymphatic channels reminiscent of congenital pulmonary lymphangiectasis may be seen in up to one third of cases.[13] The coexistence of type 2 CCAM features within ELS lends further support to the theory that the former would be a pattern of maldevelopment secondary to obstruction rather than a separate entity. However, it does not answer all questions, as mentioned previously in the CCAM section.

Some sequestrations have been shown to completely and spontaneously involute[279-282]; therefore, small asymptomatic lesions without significant shunting may be observed.[183] Others have proposed embolization,[283] simple ligation of the aberrant artery,[284] and thoracoscopic resection.[266,285] Neuroblastoma has to be considered in the differential diagnosis of ELS, whether intrathoracic or subdiaphragmatic. However, because these tumors may also regress spontaneously when discovered in neonates and young infants,[286,287] close observation may be preferable to biopsy or excision even if a precise diagnosis cannot be confirmed.

Intralobar sequestrations are usually situated in the lower lobes. They also have a systemic blood supply, with more than one branch in 15% of cases, as in ELSs.[276] In contrast, however, the venous drainage is usually through the inferior pulmonary vein and rarely systemic. Only 15% are associated with other anomalies compared to 50% or more of ELSs.[276] Although some authors think that most ILSs are acquired lesions formed through repeated episodes of pneumonia,[49] the majority of those dealing with children recognize their congenital nature in this age group.[50,51,59] Even though sequestrations should not have a normal bronchial connection, the lesions are usually aerated, presumably from the adjacent normal segments through the pores of Kohn. Ventilation is inefficient, resulting in the trapping of air, mucus, and bacteria and leading to recurrent infection, which is the usual

mode of presentation. The development of cysts is common, and pneumothorax, congestive heart failure, and hemoptysis have also been described.[183,288]

Recurrent infection and/or persistent consolidation or cystic changes of basal segments on chest radiograph should raise the suspicion of ILS. CT scan is most often used to confirm the diagnosis, but ultrasound with Doppler and MRI can also play a role. Resection is indicated in all cases,[11] although embolization alone or prior to surgery has been proposed.[43] Particular attention is required to avoid bleeding complications from the systemic arterial supply.

PRENATAL DIAGNOSIS AND MANAGEMENT OF CONGENITAL LUNG LESIONS

As discussed earlier, the precise differentiation between the various congenital lung lesions may be difficult even after microscopic analysis by experienced pathologists. It is therefore not surprising that an exact diagnosis is difficult to achieve in a second trimester fetus. Too often, obstetricians or radiologists try to make a diagnosis of a precise type of CCAM/CPAM based on the ultrasound size of lung cysts and make prognostic implications based on this.[183] The emerging consensus is that imaging findings should simply be described, without attempting to make a pathologic diagnosis. Adzick, in 1985,[238] first made the distinction between macrocystic and microcystic (hyperechoic) lung lesions on prenatal sonograms. This is frequently interpreted as CCAM but can be found in sequestration and other lung malformations or may represent a transient finding in normal babies.[58,60,235,236,289,290]

With the increasing number of obstetrical ultrasounds performed and the improving quality of these examinations, congenital lung malformations are diagnosed more frequently before birth. They appear as hyperechoic or cystic or mixed lesions within the chest (or abdomen for some sequestrations) that may displace the heart and mediastinum and occupy most of the thoracic cavity. Doppler interrogation may reveal a systemic arterial supply from the thoracic or abdominal aorta. This generally confirms a diagnosis of sequestration, although mixed lesions can occur, as discussed earlier. While some congenital lung malformations may give rise to serious complications in utero, such as polyhydramnios with premature labor or hydrops with fetal demise, most remain stable or show evidence of regression.[55,58,235,236,249,291]

In a small percentage of cases, fetal intervention may be warranted. The mere presence of a large mass causing mediastinal shift, even diaphragmatic eversion, is not an indication for treatment (see Fig. 64-10). However, the size of the mass and its rate of growth may help to predict which fetus is at risk for developing signs of hydrops, which is an indication for intervention. The CCAM volume ratio (CVR) was developed as a means to tailor the frequency of repeat sonograms to the risk of developing hydrops.[292] Maternal betamethasone administration may decrease the rate of growth of the lesion and prevent complications.[293,294] Figure 64-21 illustrates the algorithm followed in several centers for monitoring such fetuses. This mentions CCAM (or CPAM) as the main diagnosis because it is the most frequent, but a final diagnosis cannot be established until postnatal imaging, followed by surgical resection if the lesion persists. Extralobar sequestrations may occasionally produce massive pleural effusions (possibly from obstructed lymphatic or venous return), which also can lead to hydrops and pulmonary hypoplasia.[13] This is amenable to fetal intervention through thoracentesis, pleuroamniotic shunting or laser ablation of the feeding artery.[295] Fortunately, prenatal intervention is not required in the majority of cases, but having detected a lesion before birth ensures proper postnatal follow-up. For asymptomatic neonates who have a normal or near-normal chest radiograph, a CT scan is necessary to evaluate the presence or absence of a lesion. Sometimes an echogenic lung "lesion" in utero regresses in the third trimester and the CT scan (usually done after a few weeks of age to allow any retained lung fluid to be evacuated) is completely normal. Such instances are presumed to be secondary to a transient bronchial obstruction or plugging in utero. Most often, however, the lesion will be visible on postnatal CT scan. Any congenital cystic lung lesion should be removed electively at 3 to 6 months of age, mainly because of the risks of infection and the impossibility of differentiating these from type I pleuropulmonary blastoma.[183]

PLEUROPULMONARY BLASTOMA

Pleuropulmonary blastoma (PPB) is a rare intrathoracic neoplasm of early childhood with an unfavorable outcome. It is discussed here because of its overlapping features with congenital cystic lung lesions and its recent description in fetuses and neonates. The term was defined in 1988[296] and regroups tumors previously described as pulmonary rhabdomyosarcomas, cystic mesenchymal hamartomas, blastomas, and other types of undifferentiated sarcomas.[247] PPB has been classified into three groups based upon the gross characteristics of the tumor: type I, purely cystic; type II, intermediate cystic/solid; and type III, predominantly solid. Evidence, based on patient age at diagnosis, as well as recurrence with more advanced type, would suggest that type I tumors may evolve into the more malignant type II and III if undiagnosed or inadequately treated.[62,247,297] PPB, a mesenchymal childhood neoplasm, is very different from adult-type pulmonary blastoma which has malignant mesenchymal and epithelial tissue. Adult pulmonary blastoma has not been associated with congenital lung cysts. PPB commonly presents with symptoms that are mistaken for a lower respiratory tract infection. The cystic types can also present with pneumothorax. The tumor is usually located at the periphery of the lung, but it may also be located in extrapulmonary locations, such as the mediastinum, diaphragm, and/or pleura. Common metastatic sites for PPB include the brain, bone, and liver. Lymph nodes, pancreas, kidneys, and adrenal glands are rarely involved.[62,298] The diagnosis is made by histopathology. Despite aggressive treatment protocols, the prognosis for patients with PPB is not good, with 5-year survival rates of 83% for type 1 and 42% for types 2 and 3.[62,247,297] Furthermore, it appears that type II and III lesions have a tendency to recur, even at remote or contralateral sites, despite presumed complete primary resection.

PPB has frequently been described in association with cystic lung disease including bronchogenic cysts, CCAM/CPAM, and air-filled cysts.[183,299-301] It is not known whether the tumor can develop in preexisting benign cystic lung disease or whether the cysts in these cases are type I PPB from the outset.[61,62] The latter opinion has been favored recently, espe-

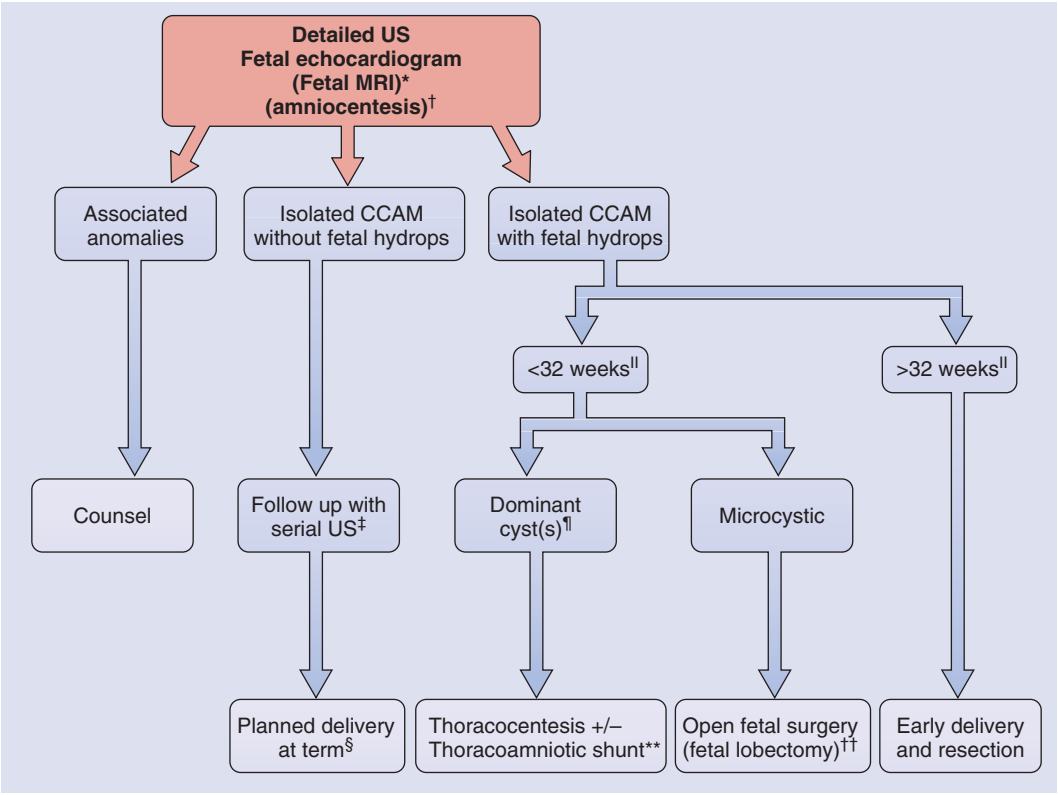


Figure 64-21 Prenatal management of congenital lung lesions.

*Magnetic resonance imaging (MRI) is not done routinely but can be useful to eliminate other diagnoses if repeat ultrasonography (US) performed by an experienced sonographer leaves any doubt.

†Chromosomal anomalies are rare in isolated CCAM.

‡Serial US should be weekly initially, since rapid growth can be observed between 18 and 24 weeks. This is increased to twice weekly if CCAM volume ratio (CVR) is greater than 1.6.[292] If the lesion is stable after 2 to 3 weeks, surveillance can decrease to every two weeks, and every month after 26 to 28 weeks if the lesion has regressed and mediastinal shift is absent. CVR is a useful parameter to follow in assessment of CCAM and for prognostic purposes. CVRs greater than 1.6 on presenation in microcystic CCAM are predictive of evolution of hydrops. CVR tends to increase until 25 to 26 weeks, after which regression is observed.

§In cases in which the lesion has regressed and lung hypoplasia and respiratory distress are not of concern, we allow spontaneous vaginal delivery.

‖Maternal betamethasone administration may be considered in an effort to arrest CCAM growth and reverse hydrops.[293,294] Some advocate early delivery of a hydropic fetus after 28 weeks and postnatal (or intrapartum, i.e., EXIT) resection, but the mortality in such cases is very high. Discussion with a fetal treatment center is warranted.

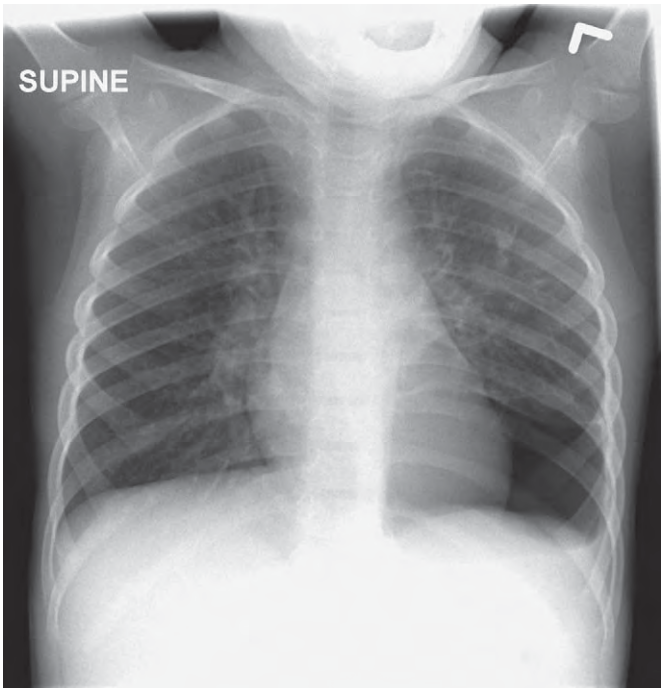
¶In cases of macrocystic CCAM, multiple cysts often communicate, allowing thoracentesis or thoracoamniotic shunt to provide adequate decompression.

**In cases of macrocystic CCAM, at the first sign of hydrops (skin edema, mild ascites, or pleural effusion), aspiration of the cyst can be done to relieve the pressure. An associated significant pleural effusion can also be drained. Because of rapid reaccumulation, cyst aspirations should be done twice weekly and, preferably, a thoracoamniotic shunt can be placed (Rocket KCH catheter, Rocket Medical, Herts, England; introducer from De Ellis or Storz [Bausch and Lomb, San Dimas, Calif]). Repeat thoracentesis may be useful when an anterior placenta or difficult fetal positioning makes shunting more hazardous.

††A 50% long-term survival rate (11 of 22 patients) has been reported for fetal lobectomy for microcystic CCAM with hydrops.

(Modified from Adzick NS, Kitano Y: Fetal surgery for lung lesions, congenital diaphragmatic hernia and sacrococcygeal teratoma. Semin Pediatr Surg 12:154–167, 2003.)

cially because it has been identified in fetuses and neonates.[248,302] Being an uncommon tumor, PPB is rarely considered in the differential diagnosis of cystic lung disease in children. Subtle findings in support of a preoperative diagnosis of PPB include the presence of peripherally based lung cysts (Fig. 64-22) and multifocal and/or bilateral cystic disease. A history of neoplasia, hyperplasia, or dysplasia, and particularly of cystic renal lesions, in the patient, sibling, or close relative should also raise suspicion of PPB since such an association is found in approximately 25% of patients as reported in the International Registry[271,272] (www.ppbregistry.org). The difficulty in making a diagnosis of PPB based on imaging alone has led many authors to propose prophylactic removal of all congenital cystic lung lesions, even if asymptomatic.[183,302,303] The surgical procedure of choice for PPB is lobectomy because the limit between the lesion and normal parenchyma may be difficult to determine grossly. Furthermore, the subsequent development of cystic lung



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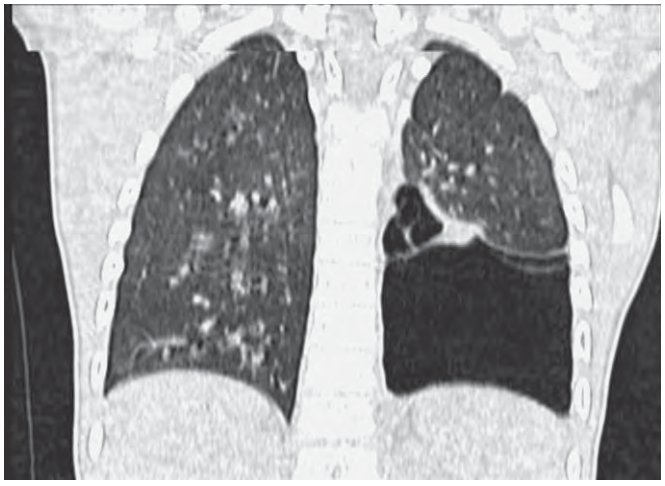

B

Figure 64-22 Pleuropulmonary blastoma. A 3-year-old child presented with a 2-month history of low-grade fever and cough. The examination was normal except for decreased breath sounds in the left lower chest. **A,** Posteroanterior chest radiograph demonstrating a large hyperlucency in the lower left hemithorax with some subsegmental collapse in the upper lobe. **B,** Computed tomography scan of the chest confirmed the presence of a multicystic air-filled lesion in the left hemithorax. One large and several smaller cysts were identified on coronal reconstruction films that appeared to compress the left upper lobe. The left lower lobe was superimposed upon these cystic lesions. Neither calcification nor air-fluid levels were observed within the cysts. At thoracoscopy, the large cystic lesion was attached to the left lower lobe by only a small band of tissue. A margin of normal lung tissue was removed en bloc with the specimen, which was placed in an endo-bag. A diagnosis of type I pleuropulmonary blastoma was made on microscopic examination, and the case was submitted to the registry (www.ppbregistry.org). (From Al-Backer N, Puligandla PS, Su W, Anselmo M, Laberge J-M: Type I pleuropulmonary blastoma in a 3-year-old male with a cystic lung mass. J Pediatr Surg 41:E13-E15, 2006.)

lesions after histologic confirmation of PPB should be treated by resection whenever feasible, because these lesions invariably demonstrate malignant features. Even with a resected lesion, the diagnosis of type I PPB is not always easy to make, and this tumor may be confused with a type 4 CCAM/CPAM.[61,62] Adjuvant chemotherapy is indicated for PPB.

HYBRID AND RARE LESIONS

As previously mentioned, there are multiple reports describing single lesions that fulfill the criteria for CCAM and ILS or ELS, coexisting lesions in different lobes, and lesions typical of one entity on imaging but corresponding to another pathologically[50-60,174,183] (see Fig. 64-15).

Any time a congenital lung lesion is approached surgically, the surgeon should be aware of the possibility of an aberrant arterial supply, even if this is not demonstrated by advanced imaging techniques. The possibility of separate coexisting lesions should also be considered[50] (see Fig. 64-10). These unusual combinations are being recognized more frequently and they may help to uncover the pathogenesis of congenital lung malformations.[56] For example, the coexistence of bronchogenic cysts in close proximity to ELSs allows speculation as to a common etiology, hence the regroupment under the term "bronchopulmonary foregut malformations."[13,304]

Communicating Bronchopulmonary Foregut Malformations. Gerle introduced the term *congenital* bronchopulmonary foregut malformation to describe cases of sequestrations that communicate with the upper digestive tract, usually the esophagus.[305] Other authors have since used this to include a variety of malformations such as sequestrations and bronchogenic cysts.[304] For the sake of clarity, we agree with Srikanth and colleagues to use the term *communicating bronchopulmonary foregut malformation* to describe a segment, lobe, or whole lung that communicates with the digestive tract.[16] One could recognize a *forme fruste,* where there is only a nonpatent fibrous attachment, but most often the malformation presents as either an accessory lobe or lung attached to the esophagus (Fig. 64-23), or a normal lobe or lung with an esophageal instead of a bronchial connection. Interestingly, in the Adriamycin-induced rat model of esophageal atresia, 30% of the fetuses with esophageal atresia and tracheoesophageal fistula exhibit a communicating bronchopulmonary foregut malformation that consists of either an accessory lung attached to the lower esophagus via a patent bronchus, an anomalous bronchus originating from the lower esophagus and communicating with the lower left lung, or tracheal atresia with a right esophageal lung and absent left lung. This suggests that communicating bronchopulmonary foregut malformation, and esophageal atresia and tracheoesophageal fistula, may be part of a common spectrum of abnormalities caused by defective budding, differentiation, and separation of the primitive foregut.[23,306] This fits well with the proposed classification and embryogenesis suggested more than a decade ago.[16]

Scimitar Syndrome. This syndrome takes its name from the presence of an anomalous pulmonary venous drainage, typically of the right lung, which gives a scimitar-shaped shadow on chest radiographs (Fig. 64-24). Many other anomalies are associated with this syndrome, including right lung hypoplasia, hypoplastic right pulmonary arteries, systemic arterial supply to the right lung (partial or total), and congenital heart disease.[307] Two forms of the scimitar syndrome exist: a severe infantile form that presents with tachypnea, heart failure, and failure to thrive and a milder pediatric/adult form where symptoms may be totally absent. Cardiac catheterization is necessary to establish a diagnosis and identify the scimitar vein, which usually traverses anterior to the hilum of the lung and connects to the inferior vena cava below the diaphragm. This vein provides drainage of the whole lung in two thirds of cases; in the other patients there is a normally connected superior pulmonary vein.[307] Coil embolization of the systemic arterial supply of the lung for infantile forms, if possible, allows time for growth and reversal of cardiac insufficiency.[308] Corrective surgery, through either rerouting of the anomalous pulmonary venous drainage to the left atrium or resection of the lung drained by the scimitar vein, may then be delayed until 1 year of age.[307] In the latter case, total pneumonectomy may be required due to the abnormal lobulation of the lung often observed with this syndrome. Surgical intervention for pediatric or adult patients is debated, especially if asymptomatic.[309]

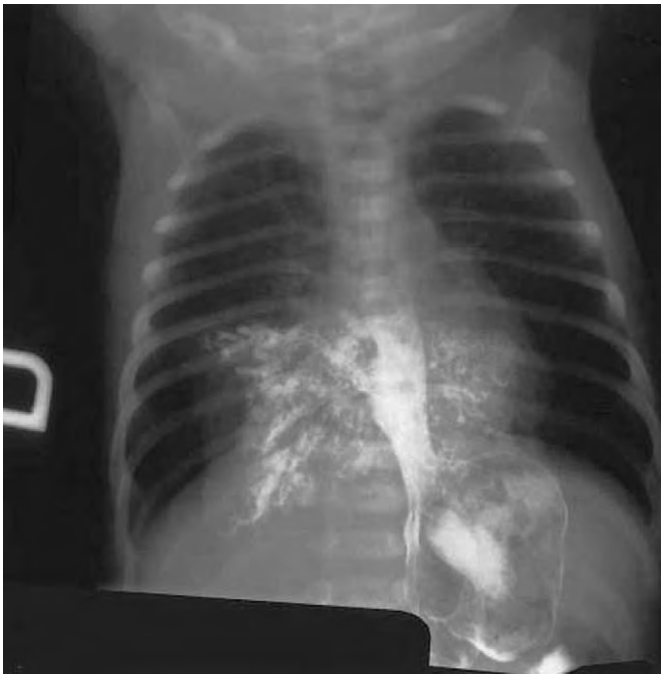

Figure 64-23 Communicating bronchopulmonary foregut malformation. This neonate presented with cyanosis and respiratory distress with feeding. A barium swallow showed an accessory "trachea" originating from the distal third of the esophagus which divided into right and left "main bronchi," each then subdividing to supply an extralobar and an intralobar sequestration on each side. (From Bratu I, Di Lorenzo M, Chen MF, et al, The multiple facets of pulmonary sequestration. J Pediatr Surg 36:784-790, 2001.)

OTHER PARENCHYMAL MALFORMATIONS

Simple lung cysts are included in the differential diagnosis of cystic lung lesions. Some of these may actually be intrapulmonary bronchogenic cysts or unilocular variants of CCAM/CPAM. From the clinical point of view, simple lung cysts have to be distinguished from postinfectious pneumatoceles as discussed earlier. Any localized cystic lung lesion that appears congenital and is confirmed on CT scan or MRI should be excised because of the potential risks of infection, erosion into an adjacent bronchus, pneumothorax and the inability to distinguish it from the type I pleuropulmonary blastoma.

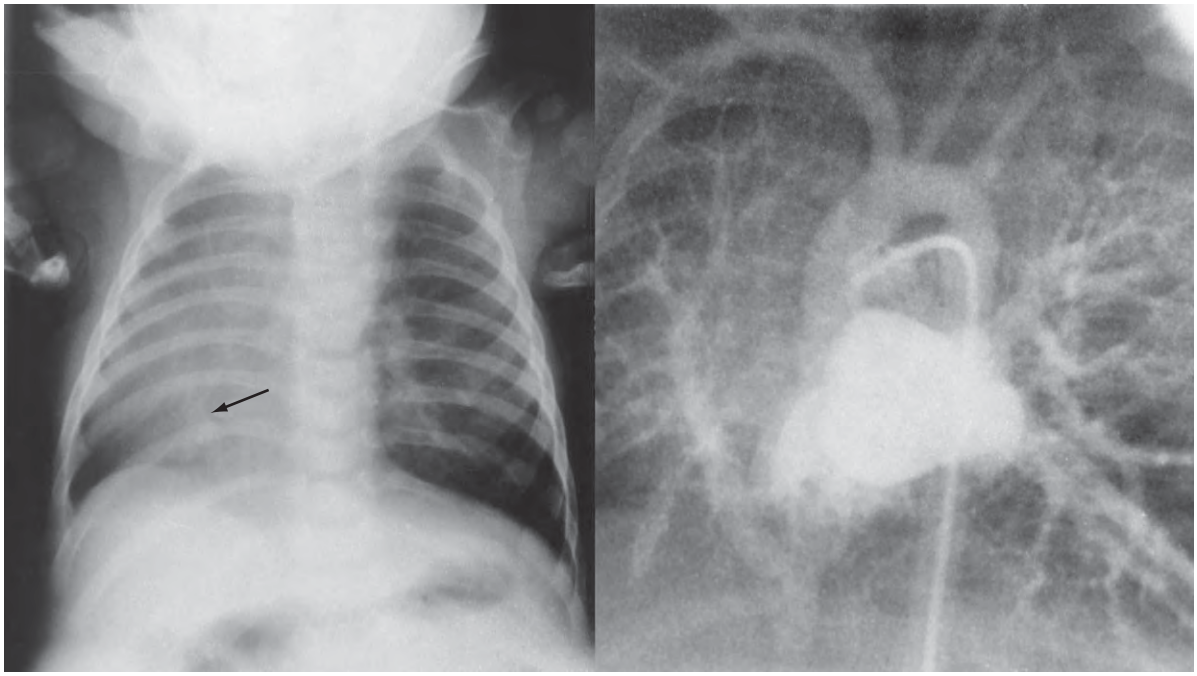

Figure 64-24 Scimitar syndrome. Chest radiograph *(left)* demonstrating the scimitar-shaped shadow *(arrow)* that represents the anomalous vein and gives the syndrome its name. Angiography *(right)* subsequently confirmed this shadow to be the scimitar vein draining the right lung anomalously to the inferior vena cava.

Once the lesion is excised, the pathologist can usually determine its exact nature.

Multiple peripheral "cysts" may occur in patients with Down syndrome or congenital heart disease or as a result of pulmonary infarction.[49,227,310] These are subpleural air collections, lined with alveolar cells, which communicate with alveolar ducts and bronchioles. Resection is not indicated. Pulmonary interstitial emphysema, usually a result of barotrauma, may also result in large air-filled spaces that may be confused with lung cysts.

Apical blebs are often considered in the same category as peripheral lung cysts. They are typically seen in tall thin adolescents and young adults who present with spontaneous pneumothorax. The cysts are most often located at the apex of the lung, but can sometimes be found in the superior segment of the lower lobes.[311] According to Stocker,[49] these cysts resemble those seen in patients with Down syndrome. Whether these are congenital, appear during postnatal lung growth, or during the adolescent growth spurt remains unclear.[310]

ABNORMAL PARENCHYMAL SHAPE OR LOCATION

Variations in lung fissures and septation may occur without alteration of the underlying bronchial pattern.[151] Fissures may be incomplete or completely absent, and extra fissures are found in about 20% of the population, most commonly those defining the "dorsal lobe" (superior segment of either lower lobe) or the "cardiac lobe" (medial basal segment of the right lower lobe).[151] The *azygous lobe* results from a septum impressed on the lung by an aberrant azygos vein in the apical portion of the right upper lobe. It is not a true accessory segment or lobe. It can be detected radiologically in 0.1% to 0.4% of the population.[151]

A *horseshoe lung* has been described, analogous to a horseshoe kidney; the lungs are fused in the midline behind the heart.[312] This connection, which may be separated by visceral pleura, usually occurs behind the esophagus but anterior to the descending aorta. The bronchial and vascular connections to the isthmus usually arise from the right mainstem bronchus and right pulmonary artery, respectively. The diagnosis is best made through computed tomography but bronchography may be more useful in delineating the tracheobronchial anatomy.[312] This anomaly has a strong association with the scimitar syndrome, which has been shown to occur in 80% of cases,[313] as well as the VACTERL association.[309,314] Complications of this anomaly include pulmonary hypertension, and the development of recurrent pulmonary infection that may require resection.

Cervical Herniation. Lung herniation is congenital in 15% to 20% of cases.[315] One third occurs in the cervical region. Some consider cervical herniation of the lung in neonates a normal variant, but it has been reported in association with iniencephalus and syndromes such as Klippel-Feil and cri du chat (trisomy 13); an autosomal dominant familial occurrence has been described.[49,316] It is thought to result from congenital absence of the endothoracic fascia in the cervical thoracic outlet region. This unusual abnormality presents in the neonatal period as bilateral supraclavicular masses that increase in size with crying. Most patients are asymptomatic but chronic cough, dysphagia, and neck pain have been described.[317] Nerve compression has been described in acquired hernias in adults.[315] Surgery, involving the closure of the defect and the reinforcement of the surrounding structures, is only indicated in symptomatic patients. Diaphragmatic and intercostal herniation also occur, but the majority are acquired after trauma or surgery.[318]

Pulmonary Vascular Malformations

Abnormalities of the pulmonary arteries or veins associated with congenital heart disease are not considered to be primary anomalies of lung development and are not discussed here; nor do we discuss the hypoplastic vascular bed associated with pulmonary hypoplasia (see discussion on congenital diaphragmatic hernia).

ARTERIOVENOUS MALFORMATIONS

Pulmonary arteriovenous malformations are most commonly found at the capillary or arteriolar level but may occur more proximally (Figs. 64-25 and 64-26). Some of these may occur

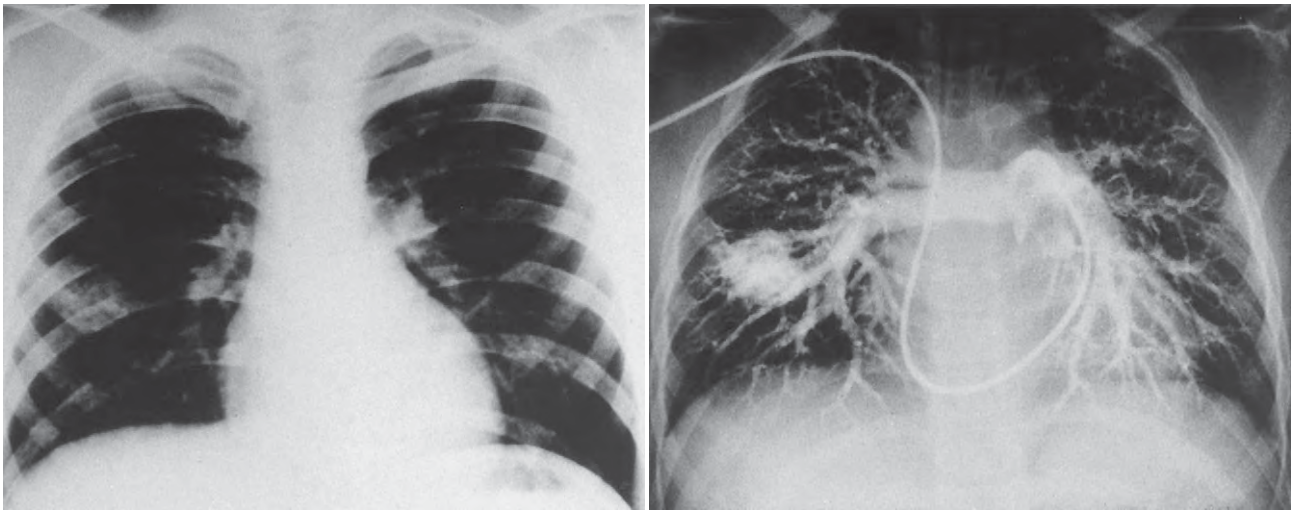

Figure 64-25 Pulmonary arteriovenous malformation. The chest radiograph *(left)* in a patient with cyanosis, finger clubbing, and a bruit heard in the right chest revealed a rounded parenchymal shadow in the right lung, which was confirmed on pulmonary arteriography *(right)* to represent a large pulmonary arteriovenous malformation.

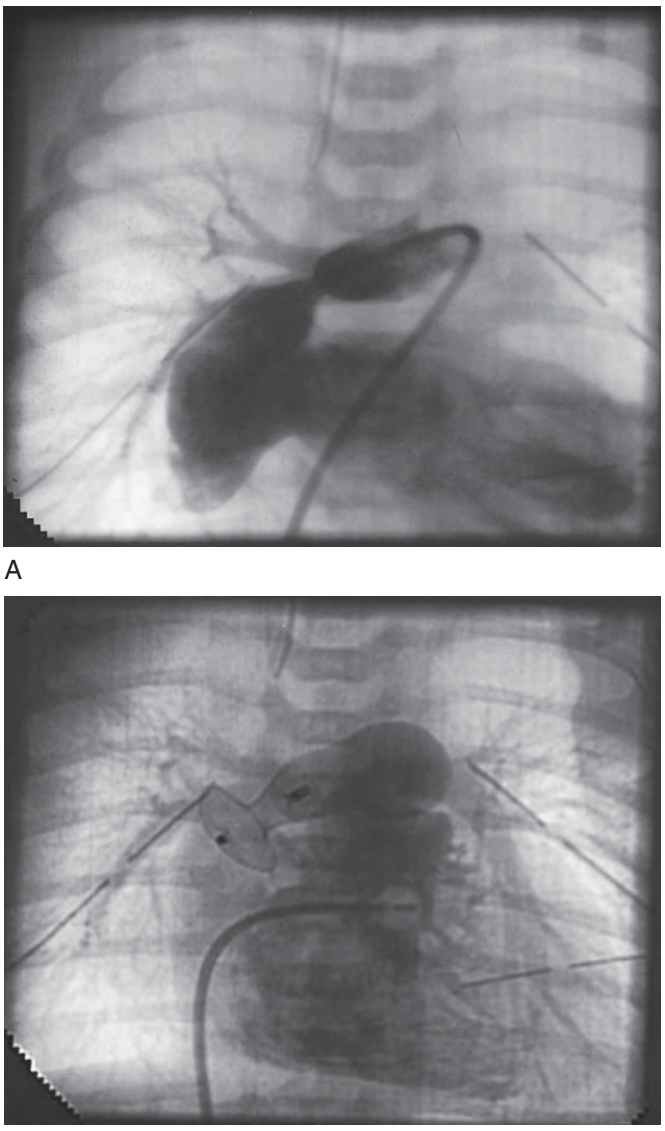

Figure 64-26 Large proximal arteriovenous fistula **(A)** in a newborn baby referred to our center at 5 days of life with cyanosis and severe desaturation unresponsive to medical treatment. During the angiogram, a ductus-occluding device (Amplatzer Duct Occluder, AGA Medical Corporation, Golden Valley, MN) was successfully deployed **(B).**

within a parenchymal malformation such as sequestration or the scimitar syndrome. These malformations function as a right-to-left shunt delivering unoxygenated blood directly into the systemic circulation. Multiple pulmonary arteriovenous malformations are found in 14% of patients with hereditary telangiectasia (Osler-Weber-Rendu disease), an autosomal dominant condition in which telangiectases may occur in any organ in the body.[319] These patients account for approximately half of the cases of pulmonary arteriovenous fistula. Primary pulmonary arteriovenous malformations form the majority of the remaining cases. They may be single but are usually multiple. The differential diagnosis includes pulmonary hemangioma, a rare lesion in this location, which may lead to shunting or hemothorax.[227,320]

Symptoms develop in up to 50% of patients with pulmonary arteriovenous malformations but sometimes only in the second or third decade.[42] When symptoms develop in the neonatal period, these usually consist of cyanosis and cardiac failure. Symptoms of a delayed presentation include bleeding with hemoptysis, or cyanosis when a large pulmonary-to-systemic vascular shunt occurs through the malformation. Finger clubbing and polycythemia may be present and a systolic or continuous murmur may be heard over the lesion. Rarely, seeding of emboli from infected lesions can cause cerebral ischemia or abscess formation. Spontaneous rupture of the lesion has been reported.[321] Evidence of telangiectasia in other organs (such as the skin), epistaxis, or gastrointestinal bleeding suggests the diagnosis of hereditary telangiectasia, and relatives should be examined for evidence of similar lesions. Single or multiple nonspecific, poorly defined parenchymal radiodensities may be seen on the chest radiograph, although pulmonary angiography or magnetic resonance angiography is necessary for definitive diagnosis (see Fig. 64-25). In the past, treatment consisted of surgical resection of the arteriovenous malformation or segment of lung involved. Currently, embolization techniques during cardiac catheterization have proved equally successful and less invasive (see Fig. 64-26). Both forms of treatment result in increased blood flow to the remaining lung, and this increase in flow may reveal additional arteriovenous malformations hitherto unnoticed, or impart additional stress on other inherently weak areas, thus leading to the development of new lesions. In these patients, vascular occlusion of the new lesions can be repeated if clinically indicated. The number of repeats, however, is limited by the accumulative reduction in the size of the pulmonary vascular bed with each attempt. Although the prognosis in patients with multiple pulmonary arteriovenous malformations remains poor, there has been some improvement with the development of embolization techniques that give superior results to lung transplant.[322] Patients with hereditary hemorrhagic telangiectasia should be screened for pulmonary arteriovenous malformations with contrast echocardiography.[323]

ALVEOLAR CAPILLARY DYSPLASIA

Alveolar capillary dysplasia is a rare malformation characterized by failure of formation and ingrowth of alveolar capillaries. It is usually accompanied by *misalignment of the pulmonary veins,* which can be seen coursing with the bronchoarterial bundle instead of the intersegmental septae on microscopic examination.[324,325] It presents in newborns with progressive hypoxia and pulmonary hypertension refractory to all forms of treatment, including high-frequency ventilation, inhaled nitric oxide and extracorporeal life support (ECLS, better known as ECMO).[326] The diagnosis may be suspected when a patient on ECLS fails to improve; it is confirmed with a lung biopsy. Although there were less than 40 cases reported before 2000, this entity is recognized with increased frequency with a protocol of early lung biopsy.[327,328] The condition is fatal and can only be cured with lung transplantation. This treatment has been used with success but is not yet widely applicable to neonates.[329] We have seen this malformation associated with congenital diaphragmatic hernia; others have seen it with Down syndrome, congenital heart disease, duodenal atresia, Hirschsprung's disease, asplenia, phocomelia, and urinary tract anomalies.[49,327,328,330-332] A familial occurrence has also been noted.[333]

LYMPHATIC MALFORMATIONS

Lymphatic development is first seen in the lung from about the 8th week of intrauterine life. By the 14th week, the lymphatic plexuses are well established, and from the 20th week, growth of other mesenchymal connective tissue elements predominates, with the pulmonary lymphatics becoming less conspicuous.[334,335]

Congenital pulmonary lymphangiectasia may result from continued proliferation of the lymphatic network beyond the 20th week of intrauterine life or from a failure of peripheral lymphatics to establish communication.[335,336] Noonan identified three groups[337]:

1. Pulmonary lymphangiectasia associated with cardiovascular malformations, particularly total anomalous pulmonary venous return and in the context of the asplenia/polysplenia syndromes. This group is often termed secondary lymphangiectasia, but the cardiovascular lesion is not always obstructive. More than half of the cases fall in this category, and their prognosis is poor.
2. Generalized lymphangiectasia, involving intestines, bone, and soft tissue, often with lymphedema
3. Isolated pulmonary lymphangiectasia, the least common, which may involve the whole lung, or rarely, a single lobe

Associated noncardiac anomalies are common, especially Noonan, Turner, and Down syndromes; familial cases have been reported.[338] A male predominance of 2 : 1 is generally recognized.[49,339] The disease may present in utero with pleural effusion and nonimmune hydrops, with fetal death or stillbirth.[336,339,340] Usually the lymphangiectatic changes are generalized over the lung surface, causing a visible network of dilated lymphatics and a pronounced lobular appearance. There are multiple small cysts less than 5 mm in diameter giving a "foam rubber" appearance on cross-section. Microscopy shows increased numbers of dilated lymphatic channels in the subpleural and interlobar septae.[49] The absence of muscular hypertrophy in the walls of the dilated lymphatic channels is used by some to distinguish primary intrapulmonary lymphangiectasia from dilation secondary to extrapulmonary anomalies of the lymphatic system such as thoracic duct obstruction. Generalized lymphangiectasia almost invariably presents soon after birth with tachypnea, intercostal recession, and usually cyanosis. On auscultation, the lungs may sound surprisingly normal. The chest radiograph classically shows a diffuse reticulonodular shadowing throughout the lung fields that fails to clear with time or diuretic treatment. In other patients hyperinflation/hyperlucency of the pulmonary parenchyma is prominent and may lead to confusion with congenital lobar emphysema if the disease is unilobar.[341] Pulmonary lymphangiectasia may be confused with pulmonary interstitial emphysema, both radiologically and pathologically.[49]

Only symptomatic treatment can be offered to these patients, and more than half die prenatally or within 24 hours of birth. Others die in the ensuing days from prematurity or their associated anomalies, especially cardiac. In recent years, some long-term survivors have been reported.[339,342] These patients often had severe respiratory compromise initially, followed by recurrent infections, but tended to improve with time. Rarely, patients with localized disease may present later in childhood, usually with infection. These lesions are amenable to surgical resection, although preoperative assessment must include investigations of associated anomalies of pulmonary vasculature.

Congenital chylothorax or hydrothorax is the leading cause of pleural effusions in neonates. It may be a manifestation of pulmonary lymphangiectasia in some cases but a specific cause is not identified in many instances. Various mechanisms implicated include rupture of the thoracic duct, a congenital defect affecting the thoracic duct or other mediastinal or pleural lymphatics. It is associated with the same syndromes as pulmonary lymphangiectasia.[232] Congenital chylothorax was formerly thought to occur from thoracic duct rupture at the time of vaginal delivery, but it has now been recognized prenatally for more than two decades, with an estimated incidence of 1 in 15,000 pregnancies.[343] For prenatally diagnosed patients, the mortality exceeds 50%, in contrast with a mortality of 15% for patients diagnosed postnatally. In the absence of severe associated anomalies (chromosomal, cardiac, or other), fetal thoracentesis is indicated for large primary pleural effusions; the diagnosis of chylothorax is confirmed when there are more than 80% lymphocytes in the pleural fluid. When a fetal pleural effusion is large and causes significant mediastinal shift and early signs of right heart failure, there is an indication for prenatal intervention such as repeated thoracentesis, or preferably thoracoamniotic shunting, to prevent mortality from nonimmune hydrops and pulmonary hypoplasia.[343,344] For unknown reasons, the effusion may regress prenatally. Chylothorax in neonates often causes respiratory distress and requires thoracentesis or the placement of a chest tube. Of note, the fluid will not have the typical milky appearance unless the child has been fed; the diagnosis can safely be made based on the relative lymphocyte count as discussed earlier. The child is kept on total parenteral nutrition until drainage stops, then fed with a medium-chain triglyceride diet initially, and switched to a regular diet if the effusion does not reaccumulate. Surprisingly, drainage often stops spontaneously within a few days after birth. Octreotide has been used successfully to decrease lymphatic flow in some cases; surgical intervention to ligate the thoracic duct or remove a localized area of pulmonary lymphangiectasia is rarely indicated, and pleuroperitoneal shunts have been used for refractory cases.[232]

Congenital Diaphragmatic Hernia

DEMOGRAPHICS

Congenital diaphragmatic hernia (CDH) is a developmental abnormality of the diaphragm that allows the abdominal viscera to enter the thoracic cavity. It occurs with an overall incidence ranging from 1 in 2000 to 4000 live births.[345,346] There is a slight male preponderance with a ratio of 1.5 : 1. The risk of recurrent CDH in future siblings is approximately 2%. Most CDHs occur through a posterolateral defect (Bochdalek hernia), with 90% of these on the left side, 10% on the right and less than 1% bilateral. Less than 5% of CDHs are located anteriorly (Morgagni hernia).[346]

THE DEFECT: EMBRYOLOGY AND PATHOGENESIS

Several theories have been proposed regarding the pathogenesis of diaphragmatic hernia. These include (1) premature

migration of the gut into the abdominal cavity after the period of extracoelomic growth, thus interfering with the development of the diaphragm ("compression theory"), (2) abnormal lung development/hypoplasia which permits the herniation of the gut into the chest, (3) problems with phrenic nerve development leading to incomplete formation of the diaphragm, and (4) delayed closure of the pleuroperitoneal fold. Recent animal studies have shed more light onto the pathogenesis of the diaphragmatic defect and contradict previously held theories. In separate studies, Greer[347] and Babiuk[348] independently demonstrated that abnormal development of the pleuroperitoneal canal leads to a posterolateral diaphragmatic defect, the most common location for CDH. Additional studies using the nitrofen model of CDH in rats have revealed that the lung hypoplasia precedes the development of the diaphragm and is thus independent of the formation of the defect in this animal model.[349]

PRENATAL DIAGNOSIS

The prenatal diagnosis of CDH has been greatly facilitated by the improved technology and interpretation of prenatal imaging studies. Indeed, CDH is readily identified on routine prenatal ultrasonography as early as 18 weeks of gestational age by the presence of the stomach in the left chest adjacent to the heart. The impact of prenatal diagnosis, however, is more difficult to evaluate. Several studies have attempted to identify factors that may be used to assess the severity of fetal pulmonary hypoplasia and pulmonary hypertension, which are leading determinants of postnatal morbidity and mortality in these patients.[350-355] Furthermore, all patients with a suspected diagnosis of CDH on prenatal imaging studies should have a thorough examination for other anomalies, particularly cardiovascular, chromosomal, and neurologic defects, because the survival of these patients has been reported to be as low as 15%.[356,357] It is also vitally important that patients with a prenatal diagnosis of CDH be referred to tertiary-care centers so that the families of these patients can be appropriately counseled regarding the prognosis, outcome and options available.

The two most commonly used prenatal predictors of postnatal morbidity in infants with CDH are liver position and lung-to-head ratio (LHR). An intrathoracic location of the liver and a low LHR (<1.0) predicts a poor prognosis.[350,352,358] The LHR is measured between 26 and 28 weeks of gestational age when the surface of the contralateral lung at the level of the standard four-chamber view of the heart is compared to the biparietal diameter of the fetal head on prenatal ultrasonography.[350,358] Fetal surgical interventions have been evaluated using these two factors in an attempt to improve the postnatal outcome of patients with these poor prognostic indicators (see later). Lung volume on magnetic resonance imaging has also been used as a prognostic indicator.[351,359]

CLINICAL PRESENTATION AND INITIAL MANAGEMENT

The clinical presentation of infants with CDH varies according to the severity of pulmonary hypoplasia and pulmonary hypertension in the immediate postnatal period. With the advantage of prenatal diagnosis, and the evaluation of liver position and/or measurement of the LHR, treatment teams can be prepared to institute a variety of interventions and therapies. In the absence of prenatal diagnosis, the newborn typically presents with respiratory distress, a scaphoid abdomen, apparent dextrocardia (since 90% of CDH are on the left) and decreased breath sounds over the involved chest. With these symptoms and signs, bag-and-mask ventilation should be avoided to minimize gaseous distention of the stomach and intestines, which would further compromise lung function. Prompt endotracheal intubation and limitation of ventilation pressures are essential. A nasogastric tube is passed and placed on suction and a chest radiograph is done (Fig. 64-27). Occasionally, the child may become symptomatic only after a few hours, sometimes days and rarely after several months or years of life. Obviously these patients do not have any significant pulmonary hypoplasia; they have a congenital defect but may not have herniation of abdominal viscera until later in life. Those presenting late often have gastrointestinal symptoms (such as bowel obstruction or gastric volvulus) rather than respiratory symptoms.[360,361]

The basic tenets of management for the infant with CDH are based on the support of the cardiorespiratory system. The clinical status of the patient is the key determinant for which therapies, if any, will be initiated. In many institutions, a protocolized management scheme is in place for all infants born with CDH. First, the patient is placed on monitoring equipment, intravenous access established (umbilical artery and vein), and pre- and postductal oxygen saturations recorded with pulse oximetry. Postductal saturations provide caregivers with an indication of the severity of pulmonary hypertension and right-to-left shunting. However, we pre-

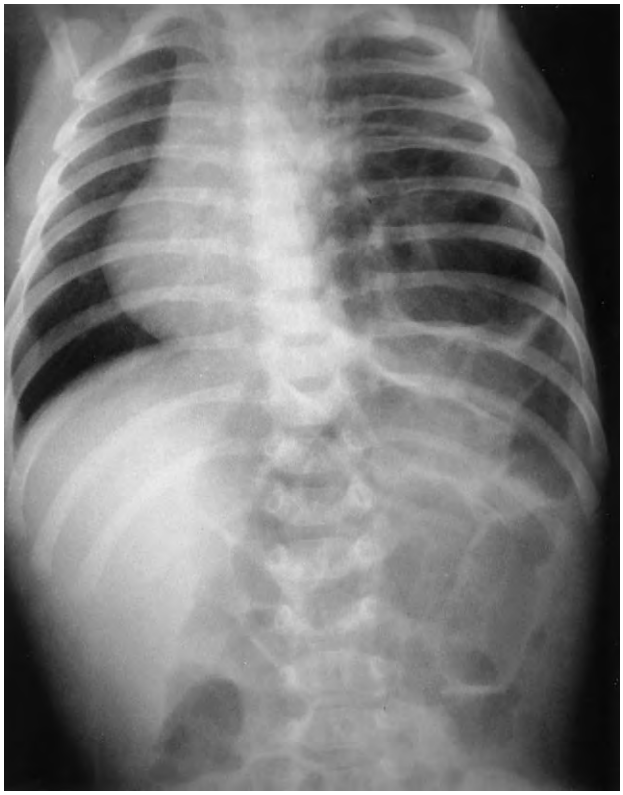

Figure 64-27 Diaphragmatic hernia. Chest radiograph of a newborn infant showing the characteristic picture seen with a posterolateral diaphragmatic hernia (Bochdalek hernia) with absence of the left diaphragmatic shadow, the left chest filled with gas-filled loops of bowel, and the heart and mediastinum shifted to the right.

dominantly use preductal oxygen saturation to assess the overall clinical status of the infant since this is what is being delivered to the cerebral and coronary circulations. If the neonate experiences respiratory distress, then the infant should be intubated and mechanically ventilated by conventional means, initially keeping peak inspiratory pressures below 25 cm H_2O. Respiratory rates should also be kept below 100 per minute if possible. A philosophy of permissive hypercapnia and gentle ventilation should be followed to prevent barotrauma and volutrauma to the lungs.[362] Partial pressures of carbon dioxide between 55 and 65 mmHg should be accepted. Positive end-expiratory pressures of approximately 5 cm H_2O may also help recruit atelectatic areas in both lungs. Sedation is necessary in most instances to allow coordination of the patient with the ventilator and to prevent pulmonary hypertensive crises secondary to agitation or discomfort. It is also important to realize that oxygen saturation targets for infants with CDH change with time. For instance, preductal oxygen saturations above 70% within the first 2 hours of life may be acceptable. However, these should rise to above 85% over the ensuing 4 to 6 hours after birth. In addition to the use of oxygen saturation measurements to assess the status of the respiratory system in these patients, we also calculate the oxygenation index [(FIO_2 × mean airway pressure × 100)/$PaO_{2(postductal)}$]. An increasing oxygenation index over time (especially if >40) on serial arterial blood gas measurements indicates deterioration of the respiratory status of the patient and the need for more advanced therapy and physiologic support. Postnatal echocardiographic evaluations are also needed in the immediate postnatal period to assess the degree of pulmonary hypertension, rule out cardiac anomalies, as well as guide management.[363] Inotropic support to improve the circulatory status of the patient may also be considered for patients with low mean arterial pressure and derangements in systemic perfusion. Excessive amounts of intravenous fluid should also be avoided because pulmonary edema with worsening pulmonary hypertension and gas exchange may ensue.

ADVANCED THERAPIES AND PHYSIOLOGIC SUPPORT

Controversies exist as to the optimal management scheme for infants with CDH, especially those that are in marked distress and for whom conventional treatment is inadequate. Several forms of advanced physiologic support are currently available for these difficult situations, but the evidence of their benefit is often lacking or anecdotal. For instance, despite observations of the relative surfactant deficiency and lung immaturity in animals and infants with CDH, for which steroid administration may be useful, the use of antenatal steroids has not been shown to be effective for infants with CDH.[364] Other therapies such as nitric oxide[365,366] and surfactant replacement[367] are also not uniformly effective for infants with CDH, despite a physiologic rationale for their use.[368,369]

The biggest changes in the management of infants with CDH in the last two decades have involved ventilatory strategies. Previous ventilator management of infants with CDH was based on observations that normal partial pressures of carbon dioxide and pH reduced pulmonary hypertension as well as shunting through the patent ductus arteriosus.[370,371] Thus, patients were hyperventilated, often with high ventilatory pressures, to achieve this goal. This strategy persisted for many years until Wung and associates[372] demonstrated that this philosophy of ventilator management led to the development of ventilator-induced lung injury which negatively impacted the outcome of these patients. Since then, strict avoidance of barotrauma through the use of lower ventilator pressures and acceptance of permissive hypercapnia have improved the outcome of infants with CDH, as well as reducing the need for ECLS in some centers.[362] Advanced ventilatory support through the use of high frequency oscillation ventilation has been proposed, as an initial therapy, to be more useful in protecting the lung from barotrauma and ventilator-induced lung injury than ventilation by conventional means in infants with CDH.[373-375] However, the evidence is not clear if its beneficial effect is solely due to the effects of oscillation or other concurrent therapies.[376]

The use of ECLS in infants with CDH has increased dramatically since its introduction for use in neonatal respiratory failure.[377] This therapy has traditionally been offered to patients with greater than 80% risk of dying postnatally as a consequence of severe pulmonary hypertension. ECLS may "rest" the lung so that local vasoactive cascades, which increase pulmonary vascular reactivity of the lung in the immediate perinatal period, may be allowed to stabilize.[378] The criteria for determining the risk of death attempt to indirectly assess the severity of pulmonary hypertension. Even with prenatal diagnosis, there are no criteria that allow for an absolute determination of outcome in this patient population. Classically, circulatory collapse/refractory hypotension, alveolar-arterial oxygen gradients greater than 600 mm Hg for more than 24 hours, oxygenation index greater than 40 on three consecutive arterial blood gases, partial pressures of oxygen less than 40 mm Hg and pH < 7.15 have been used as criteria for the institution of ECLS.[379] The main modes of ECLS for neonatal respiratory failure are venoarterial (cannulation of the internal jugular vein and carotid artery) and venovenous (double-lumen catheter inserted into the internal jugular vein). Based on the most recent extracorporeal life support database, the vast majority of centers are still using venoarterial ECLS despite the technical ease of and equivalent outcomes with venovenous ECLS.[380]

The institution of ECLS is not without risks. These risks most often relate to hemorrhagic complications resulting from systemic anticoagulation, which is still necessary during an ECLS run, despite the promise of heparin-bonded circuits. Contraindications to its use are based upon pre-ECLS states that may exacerbate these complications or upon technical limitations (i.e., cannula size). Thus, the relative contraindications for ECLS include weight less than 2 kg, gestational age less than 34 weeks, the presence of lethal systemic or cardiac disease, and the presence of intracranial hemorrhage (grade II or more). In the end, ECLS has contributed to the survival of infants with CDH who would have likely died without it. Indeed, the overall survival rate for CDH infants placed on ECLS is 53%.[381] In comparison, infants who met ECLS criteria but did not receive support had survival rates of 38.5%.[379]

SURGICAL CORRECTION

The principles for the repair of diaphragmatic hernia have not changed greatly over the past 20 years. The philosophy

regarding the timing of surgical repair has generally shifted from emergent repair to a delayed approach after stabilization of the infant.[382] However, this has come under recent debate.[376] A recent Cochrane review was unable to find a difference in outcome for those infants repaired early (within 48 hours) compared to those infants repaired in a delayed fashion (greater than 48 hours).[383] At our institution, infants undergo repair within 24 to 48 hours if the postnatal status of the infant is stable. This also allows time for a thorough evaluation of associated anomalies, especially cardiac defects, which may influence perioperative care and outcome. For patients who require ECLS or other advanced physiologic support, we wait for clinical stabilization, and in the case of ECLS, decannulation and reversal of anticoagulation, prior to definitive surgical repair. However, centers have performed diaphragmatic hernia repair while on ECLS without much increased morbidity or bleeding complications in recent years.[384]

The optimal type of closure is still the primary repair where the patient's own diaphragmatic muscle is used to close the defect. When this is not possible, a patch is often used. The overall recurrence rate with CDH repair is generally reported to range between 5% and 25%.[385,386] Although uncommon in patients receiving a primary repair, hernia recurrence is a particular problem for those patients undergoing a patch repair. Indeed, Moss and colleagues[387] described evidence of hernia recurrence, within 3 years of repair, with nonabsorbable, prosthetic patches in almost half of the 109 patients included in their review. The lack of durability of prosthetic patches (i.e., Gore-Tex) has led to the trial of bioactive materials (i.e., Surgisis, Alloderm) as a possible solution to reduce recurrence rates and improve long-term outcome. However, no difference in the recurrence rate has been observed between standard, nonabsorbable materials and newer, bioactive products.[388] Autologous muscle such as latissimus dorsi[389] or transversus abdominis[390] muscle flaps have been used with good results, although the former is more applicable to the repair of recurrent CDH. Minimally invasive techniques have also been described in the neonatal period with encouraging preliminary results.[391-393] During repair, a hernia sac, if present, should be resected; this occurs in only 10% of cases and is associated with a better prognosis.

CURRENT OUTCOME, MORBIDITY, AND LONG-TERM FOLLOW-UP

Several recent reviews have documented an improved overall outcome for infants with CDH compared to 20 years ago with survival rates as high as 90%.[362,394-397] Interestingly, infants receiving an antenatal diagnosis of CDH may have survival rates as low as 20%.[346] This has been termed the "hidden mortality" of CDH.[398] Despite advances in care, intervention, and technology, CDH still carries a high mortality rate due to associated anomalies, particularly cardiac, chromosomal, and neurologic, with prematurity and low birth weight also affecting prognosis.[346]

Until relatively recently, the long-term sequelae for infants with CDH have been underappreciated. With increasing survival of the sickest infants and the advent of multidisciplinary teams who coordinate the overall care and follow-up of these patients, it has become quite clear that the morbidity experienced by infants with CDH is not limited to respiratory consequences secondary to pulmonary hypoplasia and pulmonary hypertension.[399,400] Indeed, derangements in neurocognitive,[401-403] cardiac[395,404] and musculoskeletal function,[405] as well as problems with sensorineural hearing,[401] feeding,[406] gastroesophageal reflux,[394,395] and growth,[395,407] have been identified (Box 64-3). The use of ECLS has been found to be a significant independent predictor for the development of these problems.[408,409]

BOX 64-3 Long-term Complications of Congenital Diaphragmatic Hernia

Nutritional: Feeding aversion, gastroesophageal reflux, failure to thrive
Pulmonary: Frequent bronchitis, asthma
Neurologic: Developmental delay, hearing loss
Cardiac: Pulmonary hypertension
Musculoskeletal: Scoliosis, chest asymmetry
Recurrent CDH (especially if patch necessary)

The severity of sequelae correlates with the severity of pulmonary hypoplasia/hypertension.

FUTURE DIRECTIONS

Fetal Surgery

Intuitively, CDH should be amenable to fetal therapy. By reducing the hernia contents, repairing the defect, and allowing the lung to grow while the fetus still derives oxygen and nutrients from the placental circulation, the pulmonary hypoplasia should reverse, allowing for normal postnatal lung function. An enormous body of experimental work, mainly in animals, has allowed the evolution of fetal therapy for CDH to progress to clinical trials.[410-413]

Early experimental work in animal models of CDH revealed that the creation of a diaphragmatic hernia in fetal sheep led to pulmonary hypoplasia, vascular maldevelopment, and clinical symptoms of respiratory distress that were similar to that observed in newborns with CDH.[414] From a clinical standpoint, the survival of infants with a prenatal diagnosis of CDH during this time period was dismal despite optimal neonatal care.[398] When the in utero correction of the hernia defect in animal models led to postnatal survival and normal lung function,[415] there was much optimism that these same results could be reproduced in human fetuses. The first successful fetal surgical procedure in humans for CDH was reported in 1990.[416] Although this first patient had an excellent outcome, subsequent patients fared less well. Indeed, only 5 of 21 fetuses undergoing surgery survived despite improvements in tocolysis and perioperative fetal care.[417] The main obstacle to successful repair occurred in those patients who had "liver up" in the chest, where replacement of the liver back within the abdominal cavity led to kinking of the sinus venosus, subsequent obstruction to umbilical vein flow, and fetal death.[418] A clinical trial evaluating the efficacy of open surgical repair for fetuses with "liver down" demonstrated that the outcome of these infants was no better than

infants cared for by conventional means.[419] Thus, the optimism for open fetal surgical repair for CDH diminished, and other modalities were investigated.

Tracheal Occlusion

It was also well known during this time that the amount of fetal lung fluid present affected fetal lung growth. If lung fluid was allowed to accumulate, the lung would grow.[420] Subsequently, open tracheal occlusion in fetal lambs with CDH was noted to prevent pulmonary hypoplasia.[421,422] These findings led to a prospective study[413] evaluating tracheal occlusion in 15 human fetuses, with "liver up," and a low LHR (<1.0), criteria suggestive of severe pulmonary hypoplasia. All fetuses underwent tracheal occlusion and were delivered by the exutero intrapartum technique (EXIT).[423] The EXIT procedure allowed the fetus to remain on placental support while airway control was established and the tracheal occlusion (clip) was removed. Unfortunately, only five patients survived to discharge and most of the deaths in this series were secondary to respiratory insufficiency.[413] However, all matched control patients who did not receive tracheal occlusion died, thus suggesting a clinical role for tracheal occlusion in a specific subpopulation of fetuses with CDH.

Advances in the technique of tracheal occlusion, particularly via endoscopy, which circumvented the need for large hysterotomy incisions and the ensuing risks of preterm labor, were then developed.[423,424] Animal models utilizing this technique were able to demonstrate significant lung growth and the reversal of pulmonary hypoplasia.[425] Further studies also revealed that the length and timing of tracheal occlusion[426] affected the morphology of the lung, surfactant synthesis, type I and type II cell balance, as well as the lung compliance and the ventilatory characteristics of the lung.[427-429] Endoscopic techniques were then further refined such that tracheal occlusion using either clips,[430] inflatable balloons,[431] or foam plugs[432] could be easily accomplished with less risk to the mother and fetus. Initial clinical results using the "Fetendo" clip[433] revealed a much improved 90-day survival for high-risk infants with CDH ("liver up" and LHR < 1.4). Unfortunately, the long-term survival of these patients was reduced secondary to tracheal complications and recurrent laryngeal nerve injury. Nonetheless, the enthusiasm for tracheal occlusion in high-risk infants with CDH led to a National Institutes for Health–sponsored randomized clinical trial in the United States.[411] After 24 patients were recruited for study, the trial was stopped prematurely because of an unexpectedly high survival rate for infants in the control group. An ongoing, prospective study from Europe (FETO group)[412] evaluating fetal tracheal occlusion by inflatable balloon has presented preliminary results that are encouraging, but its limitations are the lack of a randomized design as well as standardized postnatal care.[418]

Perfluorocarbon

These clear, odorless liquids are capable of carrying large amounts of oxygen and act as surfactant surrogates since they are also able to lower surface tension. Liquid ventilation with perfluorocarbon (PFC) has been assessed in neonates and infants with respiratory failure. Despite an ability to improve oxygenation and reduce arterial-alveolar gradients and the oxygen index in small series,[434-436] prospective studies failed to demonstrate any difference in morbidity or mortality compared to conventional gas ventilation.[437] The use of liquid ventilation in infants with CDH has also been assessed, with results demonstrating an improvement in oxygenation indices and lung compliance.[438] However, prospective studies have been halted until safety issues with PFC have been thoroughly evaluated. Nonetheless, PFC may have a role as an adjunct to tracheal occlusion. Indeed, PFC-induced lung growth has been evaluated in animal models[439] and in infants[440] with CDH with encouraging preliminary results.

MORGAGNI HERNIA AND DIAPHRAGMATIC EVENTRATION

Foramen of Morgagni hernias occur in a retrosternal location and usually contain a hernia sac. These hernias are rarely symptomatic at birth, are rarely accompanied by pulmonary hypoplasia, and are often identified on imaging studies for unrelated reasons (Fig. 64-28). An association has been noted with Down syndrome, with Morgagni hernias representing 3% of malformations in this group of patients.[441,442] The transverse colon is the most common viscera contained in the hernia, but other parts of the gastrointestinal tract and part of the liver may also be found. Complications such as bowel obstruction and segmental volvulus may occur and warrant urgent surgical repair. In recent years, laparoscopic techniques have emerged as the preferred approach for repair.[443]

Congenital diaphragmatic eventration accounts for less than 5% of diaphragmatic anomalies. It is due to incomplete muscularization of the membranous diaphragm. The involvement of the diaphragm is more commonly partial than total. As with Bochdalek hernia, it is thought to result from a congenital anomaly of the pleuroperitoneal membrane but occurring at a slightly later stage.[216] Clinically, it is difficult to differentiate between a diaphragmatic hernia with a sac and eventration, because both represent a spectrum of the same anomaly. Microscopically, one expects to find some fibrous tissue within the thinned portion of the eventrated diaphragm instead of only pleura and peritoneum in a diaphragmatic hernia sac. This entity should not be confused with *diaphragmatic paralysis*, which may be secondary to a traumatic delivery or to postnatal phrenic nerve injury (most often after cardiac surgery). Brachial plexus injuries (Erb's palsy) are associated in 75% of patients with diaphragmatic paralysis from traumatic deliveries.[216] The whole diaphragm is involved and noncontractile. Spontaneous recovery may occur but diaphragmatic plication is indicated if the patient remains ventilator dependent after 4 weeks.

Congenital diaphragmatic eventration rarely may present with severe neonatal respiratory distress and pulmonary hypoplasia. More often, it is discovered incidentally, but it may lead to respiratory or gastrointestinal symptoms, including gastric volvulus. Surgery is indicated for symptomatic patients and those in whom a true congenital diaphragmatic hernia cannot be excluded based on imaging alone. This difficulty occurs mainly on the right side, where the smooth contour of the herniated liver cannot be differentiated from a thinned area of the diaphragm; the diagnosis can be clarified by thoracoscopy.

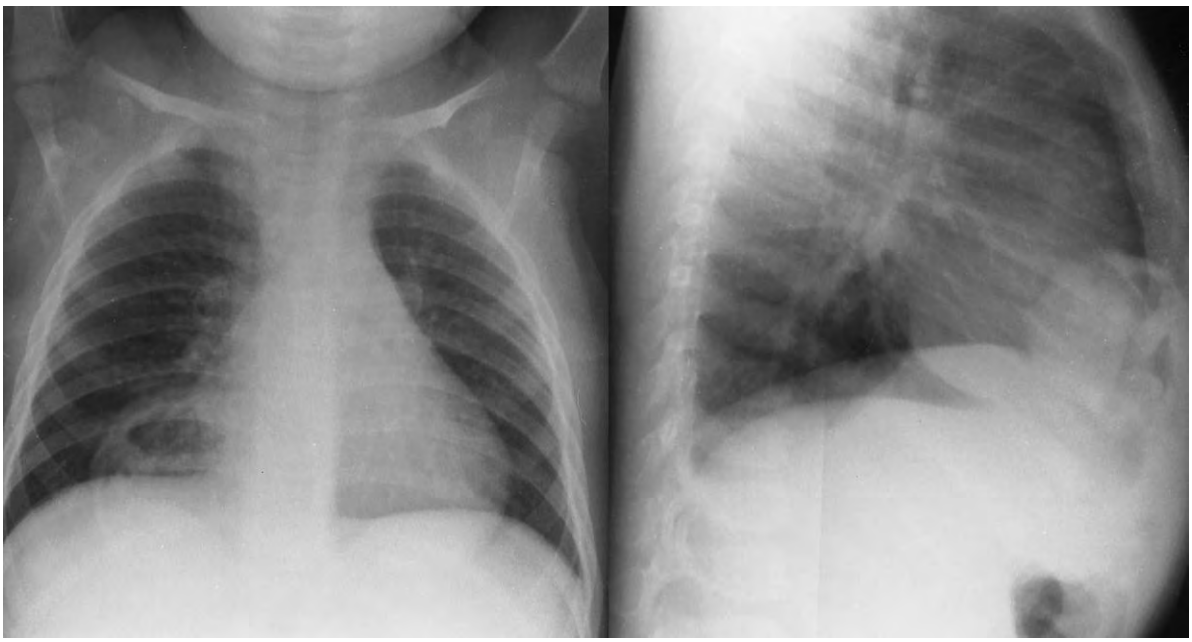

Figure 64-28 Anterior (Morgagni) diaphragmatic hernia. Anteroposterior chest radiograph showing a rounded shadow at the right heart border *(left)*, which on the lateral view appears multiloculated. This shadow represents loops of bowel entering the chest through a defect in the anterior foramen of Morgagni, and surgery is recommended in order to avoid the risk of bowel strangulation.

PITFALLS IN LUNG MALFORMATIONS

- Prenatally diagnosed lesions are not all CCAM/CPAM, and a histologic subtype should not be assigned on imaging.
- Regressing fetal lung lesions may not be apparent on postnatal chest radiography; CT scan is necessary.
- A systemic arterial supply may be encountered with any parenchymal malformation.
- Cystic pleuropulmonary blastoma often presents with spontaneous pneumothorax in infants and cannot be distinguished from CCAM/CPAM on imaging.

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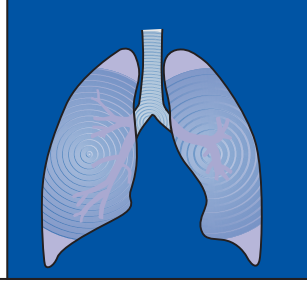

CHAPTER 65 Sleep-Disordered Breathing

Karen Ann Waters

TEACHING POINTS

- Obstructive sleep apnea is the most common sleep-associated breathing disorder in children.
- Pathologies underlying obstructive sleep apnea include airway structure and obesity.
- Physiologic changes that occur during sleep contribute to the associated respiratory dysfunction.
- Other respiratory disorders often deteriorate in sleep due to loss of accessory muscle activity, especially in rapid eye movement sleep.
- Disorders of respiratory control (e.g., congenital central hypoventilation syndrome) show most serious blood gas derangements in slow wave sleep.
- Treatments for obstructive sleep apnea include medical, surgical, and noninvasive pressure support.

OVERVIEW

Airway collapse and hypoventilation are conditions that are potentiated during normal sleep. Pediatric sleep units undertake comprehensive diagnostic studies during sleep to evaluate these and other forms of respiratory dysfunction. Interpretation of these studies requires an understanding of the dynamics of the upper airway and of respiratory control along with their developmental interactions with sleep. Accurate evaluation of sleep-associated respiratory abnormalities in children, using detailed clinical and investigative procedures, should include an assessment of the underlying pathology.

Obstructive sleep apnea (OSA) is the most common sleep-associated breathing disorder in children. A number of syndromes and malformations are associated with particular sleep-associated diagnoses, including increased risk for OSA. The other major diagnostic group is children with congenital and acquired hypoventilation syndromes. Respiratory failure during sleep is common in association with complex airway abnormalities, chronic lung disease, neuromuscular disorders, as well as congenital or acquired neurologic conditions leading to central hypoventilation.

Treatment of these sleep-associated respiratory disorders ranges from medical therapy to invasive ventilation. Treatment of childhood OSA includes medical and surgical therapies. Perioperative assessment and management is an important component of the therapeutic intervention. Pressure support therapies, including nocturnal ventilation to treat hypoventilation, can now be routinely delivered by nasal mask interfaces that are gaining wide application in pediatrics.

This chapter examines the current knowledge of OSA and sleep-associated hypoventilation in children. The normal pathology and the pathophysiology underlying sleep-related respiratory abnormalities are explored. Methods for identifying these disorders and their complications are discussed. The final section describes treatment modalities available for these disorders, with discussion of the circumstances in which various treatments should be implemented.

PREVALENCE

OSA can occur in all age groups from infancy to adulthood. The best studies of the prevalence of childhood OSA include questionnaires that are combined with some overnight monitoring (most commonly oximetry). The reported prevalence of habitual snoring in children varies from 3.2% to 15% of children.[1-3] Although the age groups included and the criteria for diagnosing OSA vary among studies, approximately 25% of children who snore habitually have clinically significant OSA. Prevalence estimates for OSA in children range from 0.6% to 10.3%.[4,5]

Hypoventilation is less common, but among children younger than 18 years, the causes of hypoventilation published from France include neuromuscular disease (34%), OSA and/or craniofacial abnormalities (30%), cystic fibrosis (17%), congenital hypoventilation (9%), scoliosis (8%), and other disorders (2%).[6] All studies that have reviewed the problem conclude that the number of patients currently ventilated is an underestimate of those who require the therapy. The best estimate of the incidence of sleep associated hypoventilation is a Swedish study, showing an overall incidence of 6.6 to 9.6 per 100,000.[7] However, independent studies suggest that congenital central hypoventilation syndrome (CCHS) has an estimated incidence of 1 per 200,000.[8] Assuming that CCHS comprises 9% of all ventilated children in France, the upper incidence of children requiring ventilation should be closer to 22.2 per 100,000.

PATHOPHYSIOLOGY

Upper Airway Muscles and Mechanisms of Obstruction

The upper airway extends from the nares to the larynx. From the nasopharynx to the glottis, it is a pliable tube, with walls made up of soft tissue supported only by muscle so that the

caliber of the airway can change with simple events, such as a change in head position.[9] Most postnatal changes in the size of the airway occur during the first year of life and during the pubertal growth spurt. However, during growth the airway soft tissue maintains proportionality with the facial skeleton.[10] Genioglossus activity is important in maintaining airway patency during sleep and responses vary between children with OSA compared to those without.[11-13] Upper airway reflexes protect airway patency by adjusting various muscle activities to suit the prevailing respiratory needs, and the importance of their activity in children with sleep apnea is demonstrated by changing responses after the application of topical anesthetic.[11] As reflected by these studies of genioglossus activity, the process of maintaining airway patency requires continuously responsive muscle function and upper airway patency is maintained by the dynamic interaction of muscle activity and airway size in both wakefulness and sleep. With sleep onset, there is relaxation of all postural muscles, including those of the upper airway. The activity of these muscles and the reflexes controlling them are blunted dramatically by onset of sleep, although the changes are least in slow wave sleep (SWS) and greatest in rapid eye movement (REM) sleep.[14]

Neural Control of the Upper Airway

Respiratory rhythm arises in the brainstem. The cells controlling respiration have been isolated in the medulla to the region of the pre-Bötzinger complex and the associated dorsal and ventral respiratory neuronal groups.[15,16] The dorsal respiratory group has primary output. Output from the ventral respiratory group is modulated within the dorsal group before the final integrated output. Neurons that drive the muscles of both the respiratory pump (diaphragm and accessory muscles) and the upper airway are intimately connected with those producing respiratory rhythm.[17] These respiratory centers also have intimate connections with the reticular activating system, with pontine influences particularly relevant during REM sleep.[18] The rates of development and myelination are not uniform among these neural centers, and the changing physiologic correlates during development are not well delineated.

The muscles of the upper airway are dynamically controlled throughout the respiratory cycle through coordination of these respiratory neuronal connections. Phasic activity of upper airway muscles can be demonstrated during normal respiration. The genioglossus is the major upper airway dilator muscle and is active during inspiration.[19] During infancy, there is active braking at the larynx during expiration.[20,21] Increased respiratory demand results in augmentation of normal respiratory activity, along with the additional recruitment of accessory muscles including the sternomastoid and the abdominal muscles.[22]

Reflexes Protecting the Upper Airway from Obstruction

During sleep, upper airway responses to negative pressure and to hypercapnia are preserved in normal children, although infants appear to have a different pattern of upper airway activation than older children.[23] In infants, the airway is generally stable, but the tendency to close with experimental occlusions reflects the occurrence of spontaneous occlusions.[24]

Intact brainstem reflex pathways are vital for the prevention and/or rapid recovery from sleep-associated airway obstruction. These reflex pathways involve many interconnections between sensory inputs from the oropharynx and chemoreceptors, the respiratory drive, the reticular activating system, and the motor neurons of the upper airway musculature.[25] The afferent supply to the upper airway and larynx is mostly provided by the trigeminal, glossopharyngeal, and vagus nerves.

Arousal is an important culmination of these protective intercommunications.[26] This may be in response to chemoreceptor, mechanoreceptor, or local upper airway reflex responses during sleep or simply due to increased ventilation whatever the primary stimulus.[27] Children with sleep apnea have increased arousals, but can also respond to airway obstruction with increased motor activity without the need for cortical arousal to occur, as they show an apparent lack of cortical arousal in response to airway obstruction.[28,29] It is possible that arousal occurs but at a level that is not seen on traditional investigative procedures, and a pattern of hierarchical noncortical arousals has been demonstrated in infants.[30] Prior sleep deficit, such as may occur with sleep apnea, also increases arousal thresholds, even in infants.[31]

Local and brainstem reflexes act to protect upper airway patency.[19] Laryngeal receptors respond directly to increased CO_2 and temperature. Rapidly adapting receptors have been identified within the oropharynx that produce increases in both upper airway and diaphragm muscle activity in response to vibration with frequencies similar to snoring.[32] Local receptors in the distribution of the trigeminal nerve respond specifically to respiratory stimuli.[33] The laryngeal chemoreflex and other local airway reflexes may contribute to the protective responses preventing upper airway obstruction.[34]

Muscle activity from the upper airway muscles (particularly hypoglossal) may increase or decrease in the presence of airway obstruction, depending on the timing of the stimulus during inspiration.[19] Increased activity is seen during both inspiratory and expiratory phases of the respiratory cycle, although the level of response is dependent on sleep/wake state and is increased when there is increased CO_2.[35] This increase in the electromyogram (EMG) signals may be used to quantify the severity of the obstruction in children and infants where recruitment of the genioglossus during airway occlusion is preserved during sleep, including REM/active sleep.[22]

Developmental Aspects of Respiratory and Airway Control; Age-Related Disorders

In infants, reflex responses to upper airway obstruction may produce apnea rather than respiratory stimulation. Laryngeal reflexes can produce life-threatening apnea in young animals, particularly in the presence of infections that damage the upper airway epithelium.[36] Infants have a predominance of inhibitory reflexes, and prolonged apnea has been documented in infants in the presence of nasopharyngitis and common sedatives.[36,37] It is likely that there is associated

inflammation or damage to sensory pathways within the epithelium or damage within the carotid bodies. Central apnea may also occur in response to upper airway obstruction, rather than increased respiratory effort. Hypercapnia is associated with recruitment of accessory muscles during non-REM (NREM) sleep, so ventilatory responses are less effective in REM sleep.[38] Although the initial apnea is mediated via vagal reflex pathways, for example, following a sigh, other factors contribute to the ongoing respiratory rhythm oscillation.[39]

Brainstem chemoreceptors change with development and are made more unstable by environmental changes such as altered ambient temperature. Ventilatory response testing in infants shows variability of the ventilatory response to hypoxia, although it tends to be biphasic and consistent between sleep states.[28] Ventilatory responses to changes in CO_2 levels mature faster than responses to hypoxia, where inconsistent responses are frequently observed, and a large number of apparently normal infants fail to arouse during hypoxia, especially during SWS.[28,40]

RELATIONSHIP OF AIRWAY OBSTRUCTION TO SLEEP

Tone changes associated with sleep are a critical factor in the pathophysiology of OSA. Both tonic activity and reflex responses of upper airway muscles are reduced in sleep, with the most dramatic effects in REM sleep.[22] Sleep onset is associated with reduced upper airway tone (and therefore reduced airway dimensions) and blunted reflex responses to acute events[23] (Fig. 65-1).

Characteristics of Normal Sleep

Normal sleep can be divided into five clearly distinguishable sleep states, with predictable sleep-state progression during the night. Mature human sleep is divided into stages I through IV and REM sleep.[41] Stages III and IV, also called deep sleep, or SWS, are characterized by large-amplitude, low-frequency electroencephalogram (EEG) activity. REM sleep is characterized by low-amplitude, high-frequency EEG activity, rapid (conjugate) eye movements (REMs), and loss of tonic muscle activity seen clearly in the chin (genioglossus) EMG. Once circadian rhythms are established, SWS is concentrated during the first hours of sleep, with most REM sleep occurring later, through the early morning hours. Stages I and II, also called light sleep, are interspersed throughout the night (Fig. 65-2A [infant]). Daytime sleep periods are dominated by light sleep with little, if any, REM sleep or SWS.

Infant sleep is relatively undifferentiated until the age of 6 months, and sleep stages are divided only into quiet, active, and indeterminate.[42] Active sleep is the equivalent of REM sleep in older individuals, and quiet sleep equates with SWS. During these first months of life, maturation involves the emergence of five clear sleep states and stabilization of circadian rhythms along with the distinction between day and night sleep (Fig. 65-2B [child]). The ongoing maturation of

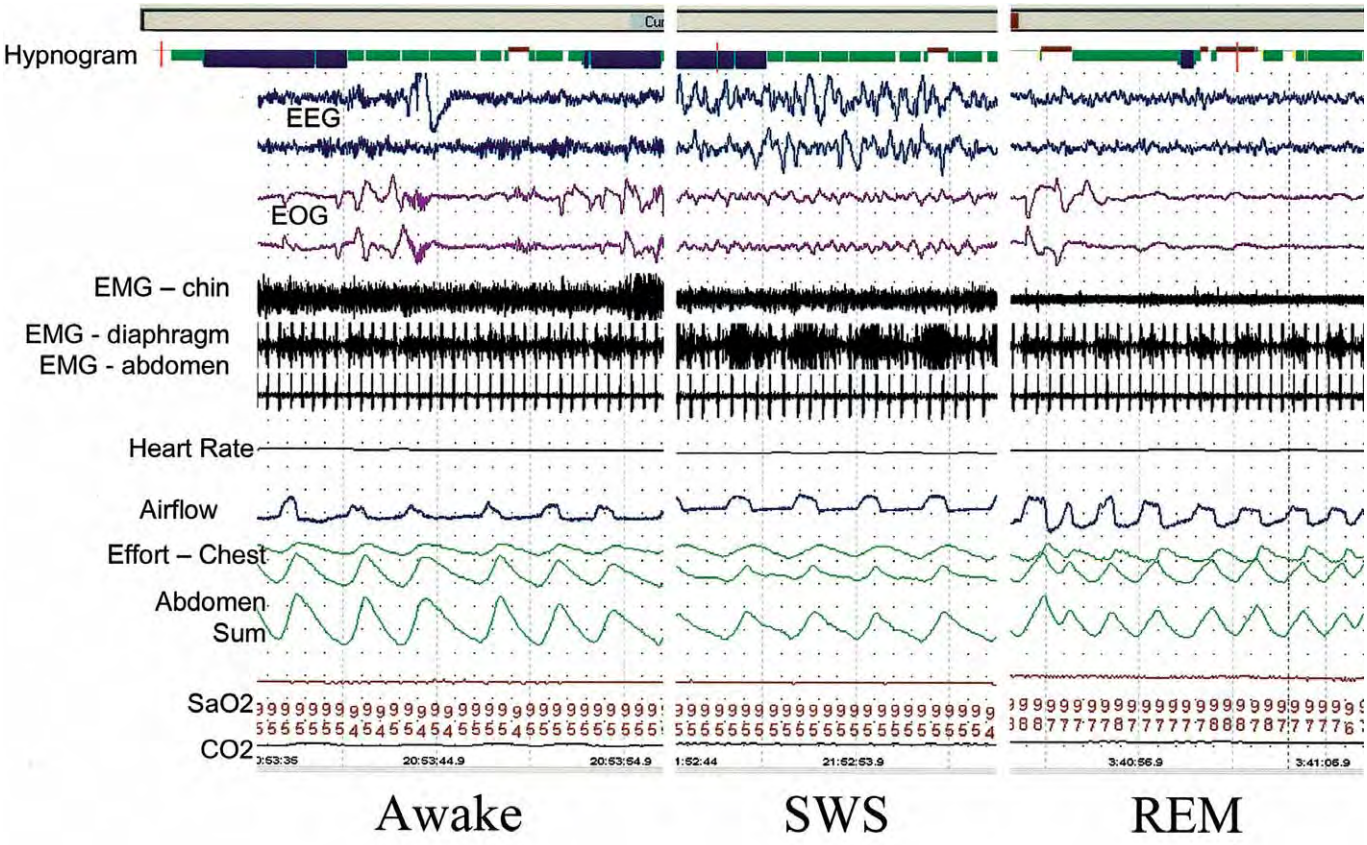

Figure 65-1 Changes in muscle tone between awake, slow wave sleep (SWS), and REM sleep.

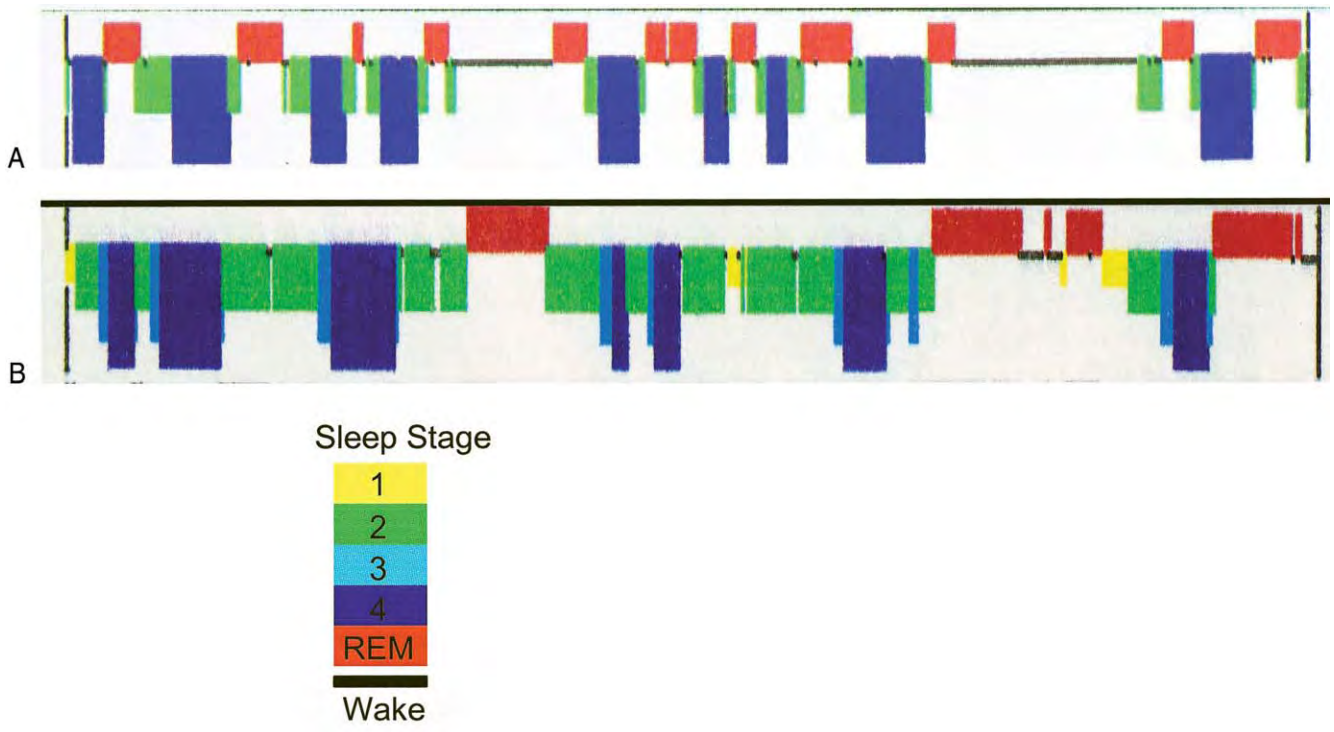

Figure 65-2 Differences in sleep architecture between an infant **(A)** and a child **(B).**

sleep states during later childhood involves substantial changes in the proportions of the different stages observed.[43]

Sleep-Associated Changes in Cardiorespiratory Patterns

SWS is associated with dampening of the arousal response, and respiration is almost completely under automatic control.[28] Respiratory control is under chemoreceptor control, and there is essentially no behavioral modification of respiratory drive. While muscle tone is maintained, arousal responses are relatively poor, and disorders of central respiratory control are most pronounced in this sleep state.

SWS is characterized by remarkable regularity of cardiorespiratory parameters, with little variability in cardiac or respiratory rate and rhythm and stable tidal volumes.[44] SWS periods in children with OSA are often characterized by prolonged periods of stable, partial upper airway obstruction demonstrated on polysomnogram (PSG) by increased phasic activity of the accessory muscles, especially during SWS. The accessory muscle activity includes chin, abdominals, and sometimes expiratory diaphragmatic activity. This can then convert to distinct periods of obstruction in REM sleep. Examples of EMG activity in normal and obstructed sleep are shown in Figure 65-3, A and B, respectively.

REM sleep is a characterized by marked variability in cardiorespiratory parameters, with behavioral control of respiratory output dominating. One of the hallmarks of REM sleep is the loss of muscle tone in peripheral muscles, including the accessory muscles and the muscles of the upper airway. Respiratory rhythm is irregular during REM sleep.[44] There is still some controversy about the degree to which there is damping of arousal and ventilatory responses (to hypoxia and hypercapnia) during REM compared to non-REM sleep.[28,44] One reason for the controversy is that the ultimate effect of any damping is lessened because of the overriding behavioral control of ventilation that also occurs. Conditions with reduced respiratory reserve can show hypoventilation in concert with reduced upper airway dilator muscle activity during (phasic) REM sleep.[44,45]

Activity of the respiratory accessory muscles is markedly reduced during REM sleep in normal subjects,[46] and, in infants, FRC may fall as a result of the loss of intercostal muscle activity.[46] Studies in infants have not consistently found the same fall in lung volumes as those that occur in adults during REM sleep. Infants and young children show persistence of phasic muscle tone in response to airway obstruction during REM sleep, and this gradually reduces with age.[47] This may be caused by persistence of some immature reflexes or due to a difference in the nature of REM sleep in the developing brain.

Respiration during light sleep (stages I and II) is associated with relative instability of respiration which can accompany transition between wakefulness and sleep. Perturbation of central control mechanisms, including drive to the upper airway, may be unmasked during this phase. An early sign of disordered breathing in sleep is prolongation of the transition time from wakefulness to sleep because of this instability of the airway.[48]

Minute ventilation is reduced in sleep, compared to wake states.[49] There is lower CO_2 responsiveness, minute volume is less for any given CO_2 level, and a rise of 2 to 8 mm Hg CO_2 is normal. Hypoxic responses are also affected. Normal oxygen saturation (Sa_{O_2}) variability with sleep is 2% or less, with P_{O_2} changing by 2 to 11 mm Hg.[50] There may be significant augmentation of this blood-gas variability in the

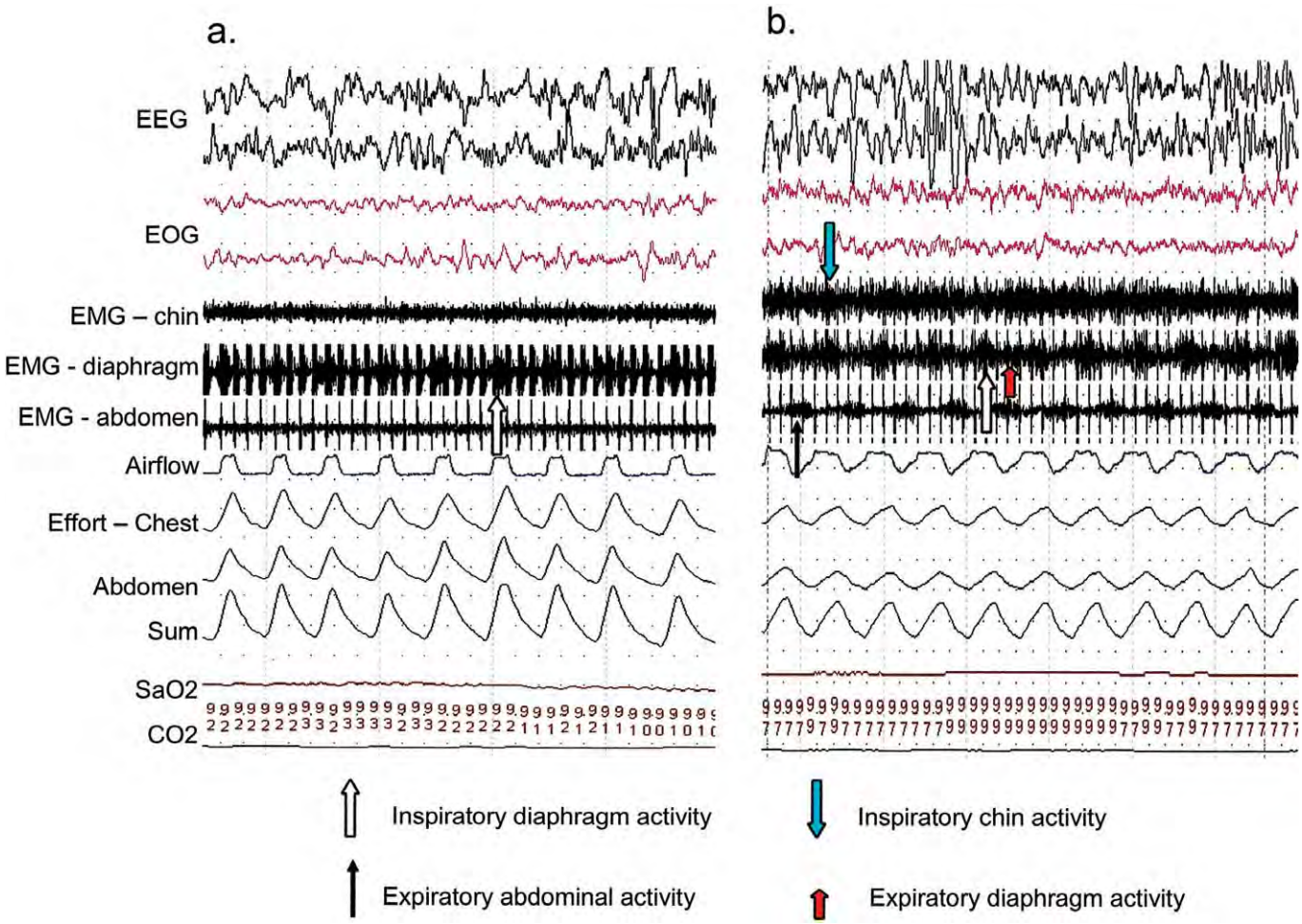

Figure 65-3 Accessory muscle activity during normal **(a)** and prolonged partial upper airway obstruction **(b)** with breathing in slow wave sleep.

presence of chronic lung disease.[50] Respiratory variability is greatest during REM sleep.

Sleep-Associated Changes in the Upper Airway

During sleep, the upper airway muscles are relaxed compared to awake, so the upper airway can be critically compromised at sleep onset because of the general fall in muscle tone and reflex functions which occurs. Sleep also alters reflex control of the upper airway, respiratory drive, and sensitivity to a variety of respiratory feedback mechanisms. The most pronounced mechanical differences are seen during REM sleep compared to the awake state. Abnormalities in chemical and respiratory drive responses are most pronounced in SWS.

Apneic events during sleep of normal children tend to be central in type, infrequent, and of short duration. These central events occur predominantly in REM sleep, although central apneas may also be seen in NREM sleep following sighs. Studies in normal children commonly show few central or obstructive apneas with indices of 0.08 ± 0.14 per hour and 0.01 ± 0.03 per hour, for central and obstructive apnea events, respectively.[51] In infants, brief central apneas (which may be called pauses) are also common, especially during stable periodic breathing. The frequency of these brief events can be up to 13.4 per hour, with periodic breathing very common in infants who were born prematurely and occupying a mean of up to $5.6 \pm 7.9\%$ of the night.[52] For monitoring purposes, apneas in infants are considered prolonged if they are longer than 20 seconds and/or if they are associated with other sequelae such as bradycardia or severe desaturations.[52]

UNDERLYING ABNORMALITIES IN OBSTRUCTIVE SLEEP APNEA

Structural abnormalities causing reduced airway dimensions, including the presence of enlarged tonsils and adenoids, have been highlighted as the underlying cause of OSA in children.[9,53] Other abnormalities associated with increased respiratory effort or more rapid oxygen desaturations may be associated with worsening of airway obstruction or its sequelae. Obesity also plays a significant role in childhood OSA.[54] Relatively small facial structure or abnormal upper airway function may be an inherited characteristic, but while there is general agreement that a genetic component exists, the origins of OSA are also thought to be multifactorial.[55,56] It is probable that some underlying abnormality in respiratory and/or upper airway control exists in many cases of sleep-associated obstructive apnea and hypoventilation.[57]

Small Upper Airway

Demonstration of structurally small airways as a mechanism underlying upper airway obstruction is easier than demon-

strating abnormal function in children. The dynamic function of the airway is likely to play a significant part in the pathophysiology of all cases of pediatric OSA.[23] Most recent studies of children's airways use technologies such as cine-MRI.[58] These have demonstrated that children with OSA have different dynamic function of the airway as well as significant compromise of airway size associated with the adenoids and tonsils.[9,58] Narrowing of the upper airway can occur at any point from the anterior nares to the larynx. This narrowing may be static or dynamic. Laryngomalacia and subglottic stenosis both increase the negative thoracic pressures required to generate inspiratory flow. Both of these types of airway narrowing predispose the affected individual to airway collapse during sleep. Children with malformations tend to have recalcitrant apnea. Persisting OSA after adenotonsillectomy may also be attributable to persisting airway abnormalities such as lingual tonsils.[59]

Some children clearly have a structurally small upper airway, for example, in Down syndrome, or craniosynostoses.[60-62] A structurally small airway, no matter what the underlying cause, may also be further compromised by adenotonsillar hypertrophy. Several studies have identified abnormal facial structure associated with OSA,[63,64] but in children who are otherwise normal, chronic airway obstruction has been associated with abnormal craniofacial structure that is reversible after treatment.[65] In others, with mucopolysaccharidoses or adenotonsillar hypertrophy, the airway lumen is crowded by extra soft tissue.[66] In the presence of reduced airway dimensions, upper airway muscles tend to maintain increased activity even in the awake state to maintain a patent airway. In this situation, the loss of muscle tone that occurs with sleep onset may be the critical factor that precipitates complete or incomplete airway obstruction.[13]

Abnormal Neurologic Control of Breathing

Abnormalities may occur in the central respiratory drive to the upper airway, or any site along the reflex pathways, the neural input of the upper airway reflexes, the central neural integration of these reflexes or the motor (output) pathways. Although abnormal upper airway reflex pathways have been postulated to cause OSA, when these reflex pathways are disrupted in conditions such as neuromyopathies or Moebius syndrome, it is generally not an isolated defect.[67-69] The processes involved with maturation of neurologic pathways, including the pathways controlling upper airway reflexes, is proposed as a potential cause of the sudden infant death syndrome (SIDS).[34] Abnormal neurologic control of the upper airway has been implicated in OSA, but this can also result from episodic hypoxia resulting in exacerbation of the disorder. Studies in adults with chronic snoring and OSA suggest that these patients have abnormal reflex control of the airway lumen, although it is not clear whether these abnormalities are the cause or the effect of the disorder.[70]

The pattern of abnormality in children with OSA tends to be preservation of the general architecture of sleep,[71] but their arousal responses to respiratory stimuli are dampened compared to controls.[72] Observed in its extreme form, children preserve sleep architecture at the expense of oxygenation and CO_2 clearance. Occasionally, children also show the converse response, of repetitive arousal in response to airway obstruction resulting in normal patterns of oxygenation and CO_2, but disrupted sleep architecture. Depressed ventilatory responses have been documented in subgroups of the pediatric population with OSA.[73] No studies to date have confirmed that arousal in response to OSA correlates with the ventilatory response activity of children, although it has been suggested that the rate of spontaneous arousals decreases as the apnea index increases.[74] These data provide some explanation as to why screening studies that measure only oxygen saturation (and/or CO_2) do not indicate the level of sleep disturbance present in those cases with vigorous arousal in response to upper airway obstruction.[75]

The congenital central hypoventilation syndrome (CCHS) occurs as a result of a genetic mutation and exemplifies the most extreme form of abnormal neurologic respiratory control.[76] This disorder results from genetic defects in the Phox-2B pathway and is associated with varying degrees of hypoventilation; the majority of affected individuals only have sleep-associated hypoventilation, but the most severely affected have hypoventilation during wakefulness and during sleep. Now that genetic testing is available, it appears that some may only present with later onset.[77] The respiratory defect is associated with abnormal autonomic function and may also be associated with Hirschsprung's disease.[78,79]

The prototypical cause of hypoventilation is the CCHS, in which central chemoreceptor responsiveness is absent due to a genetic defect in the PHOX-2B pathway. However, acquired forms of central hypoventilation may be secondary to demonstrable anatomic lesions of the brainstem, or posterior fossa.[80] Abnormal central control may coexist with or may be secondary to an anatomically small airway.[73,81] Structural lesions in the brainstem or other causes of respiratory failure, such as a muscular dystrophy, may also present with hypoventilation during sleep.[6] In the Arnold-Chiari malformation, or syringobulbia, hypoventilation may occur secondary to abnormal motor control of the cranial nerves or due to abnormal central control of respiration.[80,82,83]

It is widely theorized that the likely underlying cause of SIDS deaths is delayed maturation or abnormalities of the neural cardiorespiratory-control pathways, causing these children to be at risk of death from an otherwise inconsequential insult.[84] Such abnormal neural control may also be expressed as, or occur secondary to OSA, and studies may be able to detect a number of those children at risk for SIDS.[85,86] The abnormality may become apparent only during an upper respiratory tract infection or other acute event.[87]

Dysfunctional Upper Airway

Most children with abnormal neuromuscular control of the airway appear to have normal airway size. Palatal muscle function is abnormal in association with cleft palate, and this remains abnormal even after surgery, so that children with cleft palate appear to be at increased risk of sleep-associated airway obstruction.[88] When airway dimensions are reduced, these muscles may not be able to prevent airway obstruction.[89] Presumably the local sensory perception would also be affected, although central respiratory control is not usually affected in this disorder.

Generalized motor hypotonia contributes to upper airway obstruction and is more common in younger children and in those with disorders such as Down syndrome.[90] Sleep-disordered breathing can be precipitated or exacerbated by confounders such as obesity or scoliosis.[91] Muscular dystrophies and neuromuscular disorders are generally progressive. In Duchenne muscular dystrophy, this deterioration eventually results in respiratory and cardiac failure. However, treatment intervention when the respiratory dysfunction is critically altered during sleep will dramatically improve the quality and prolong the lives of these patients.[92,93]

OSA may occur where there is abnormal soft tissue function without demonstrable muscle weakness. In Marfan syndrome, in which the only apparent abnormality is poor connective tissue integrity, there is also a high incidence of OSA, which may then be responsible for causing or exacerbating further abnormalities such as dilation of the aortic root.[94,95] Although it seems likely that other diagnostic groups with connective tissue disorders, such as Ehlers-Danlos syndrome, would also have a high incidence of OSA, the groups affected with airway obstruction appear to be those with associated anatomical abnormalities such as micrognathia in rheumatoid arthritis or depositions causing airway narrowing in the mucopolysaccharidoses.[96,97] The skeletal abnormalities in achondroplasia cause a small foramen magnum. OSA in this group is thought to be on the basis of compression of the brainstem and upper cervical spinal cord at the level of the foramen magnum.[98]

Mechanisms of Complications

Complications of severe OSA include failure to thrive (FTT) and pulmonary hypertension. Growth failure may be caused by disturbance of growth hormone secretion, increased energy expenditure, or more generalized metabolic responses to hypoxia.[99] Obesity is associated with OSA, and there appears to be a higher risk for metabolic complications of obesity if OSA is also present.[100,101] The neurologic and behavioral sequelae of OSA have been highlighted over recent years, although many of these appear to be reversible with treatment.[102,103]

PRINCIPLES OF ASSESSMENT

To date, the diagnosis of OSA in children requires monitoring during sleep. The aim of such studies is to find the abnormalities (sleep-associated respiratory dysfunction) and classify them by criteria which are discriminatory between studies and indicate the likelihood of detrimental effects in both the short and long term.

The gold standard for assessing sleep-related respiratory dysfunction is overnight polysomnography, and these detailed overnight studies provide the most detailed diagnostic information. It can be, however, an expensive and time-consuming procedure. Some form of screening needs to be used to determine which children should undergo such studies. Clinical assessment is the start of this screening process.

CLINICAL CHARACTERISTICS

Questionnaires initially looked promising, but it is now clear that history cannot distinguish OSA from primary snoring.[104] Standardized questionnaires have been developed to assist in the process of symptom identification and prioritization.[105] The most discriminatory symptoms are breathing difficulty during sleep, witnessed apnea, snoring, and restless sleep.[106] Witnessed apneas are typically brief. Disturbed sleep, rhinorrhea, excessive sweating during sleep, and mouth breathing in the awake state are frequent but not universal features. Other features such as enuresis are reported anecdotally but may not be sufficiently discriminatory to help distinguish individual children with OSA.[107,108] Upper respiratory tract infections appear to be an infrequent cause for the acute precipitation of obstructive apnea.[109,110] Reports are inconsistent regarding reduction in the frequency of respiratory tract infections after adenotonsillectomy, but overall they appear to show a slight reduction in the frequency of events.[111,112]

There is consensus that even mild disease can have significant negative impact on the development and behavior of infants and children, although many of these effects also appear to be reversible.[103,113] This has led to increased screening of children who are otherwise deemed to have attention deficit-hyperactivity disorders (ADHDs). For individual cases, it is not generally possible to screen for developmental or behavioral abnormalities that are specifically attributable to OSA, nor is it currently possible to predict the improvement an individual might achieve after surgery.[114]

As children get older, their parents are less likely to witness children's sleep, so history appears to become more unreliable. However, factors such as a history of associated lower respiratory tract disease, secondary enuresis, or daytime sleepiness may be available. Daytime sleepiness is an infrequent complaint among children with sleep apnea, although measures have shown that children with OSA are objectively more sleepy compared to controls.[115] Less-common presentations are reported anecdotally or as "associated symptoms," such as developmental delay, night seizures, costochondritis, cyclic vomiting, hyperactivity or inattentiveness, and morning headaches.[116] OSA may also lead to exacerbation of conditions such as seizures, although this may not be apparent until there is improvement after treatment.[117]

Past history may give an indication of the severity of obstruction. There may be a history of anesthetic difficulties.[118,119] Sedative drugs or muscle relaxants may contribute to upper airway problems, and children with OSA appear to be particularly sensitive to opiates.[120] Young infants may have symptoms of noisy breathing and sweating in sleep, and some children who present as near-miss SIDS have been demonstrated to have obstructive events on subsequent sleep studies.[121] Children who have subsequently died of SIDS have had obstructive apneic events demonstrated on sleep studies performed prior to death.[86] With better access to appropriate screening studies, it is possible that children who have these abnormalities can be detected and treated.

Despite recognition that history is not able to accurately identify the presence or severity of OSA in children, surveys continue to show that most ENT surgeons use only history to make the diagnosis; objective testing for OSA occurs only in 10% to 12% of cases that proceed to surgery with a diagnosis of OSA.[122]

Underlying Conditions

Unless there has been a clear precipitating event or specific questioning for a history of sleep-disordered breathing is sought, the symptoms of obstructive apnea may not be distinguished from the developmental history of children where an underlying condition is associated with increased risk for airway obstruction. With research now demonstrating that some syndromes have an increased or high incidence of obstructive apnea, there is better screening of children with such disorders for this disease. Any cause of airway narrowing may contribute to sleep-associated obstruction, including rhinitis or nasal abnormalities.[123] Other predisposing factors include choanal stenosis, laryngeal palsy (congenital or acquired), and tracheobronchomalacia.[118,119] Infants with a history of prematurity have facial features predisposing to obstruction.[23,124] Symptoms affecting both daytime and nighttime function, including intellectual dysfunction and sleepiness, may be considered part of the inherited syndrome rather than secondary sequelae.

Studies suggest that there is a familial incidence of OSA; children with OSA often have one or more parents who are also affected. A genetic link has been proposed.[125] It is possible that there is also a link with SIDS deaths.[126,127] Further studies are required to confirm these associations.

Examination

It is increasingly rare for children with OSA to present with complications of the disease, although the link between behavioral and neurologic abnormalities has meant that children with ADHD or other behavioral disturbances may need to have a diagnosis of OSA excluded.[102] Nonetheless, vigilance is required among those groups at highest risk.

Careful daytime examination can potentially reveal a wide range of physical features associated with obstructive apnea in children or a variety of medical conditions that have now been associated with the disorder.[128] Increased upper airway (nasal) resistance can result in mouth breathing when awake.[129] The patency of the nasal airway should be assessed, including endoscopy if required.[129,130] Syndromes and malformations may be associated with other airway abnormalities,[131] as well as those specifically linked to OSA such as hypoplastic mid-face or mandible.[119] Syndromes and malformations may be present in more than a quarter of children diagnosed with OSA.[132]

The oropharynx must always be examined for enlarged tonsils, the extent of the tonsillar extension behind the tongue, and the presence and quantity of upper airway secretions. A characteristic "snorer's throat" includes edema and petechiae in the soft tissues of the oropharynx, although petechiae can also occur with recurrent tonsillitis.[133] The palate should specifically be examined for clefts and other clues of submucosal clefts, such as a bifid uvula. The presence of lymphadenopathy may support a history of recurrent tonsillitis.[133]

Respiratory examination may reveal chest deformities; Harrison's sulci are common where there is significant upper airway obstruction. Restrictive chest deformities are another common cause of respiratory decompensation in sleep, although not necessarily associated with OSA.[128]

Weight abnormalities are associated with OSA. Obesity is increasingly common and increases the risk for OSA even in childhood, and weight loss can be associated with improvement in OSA.[134] FTT occurs secondary to OSA, and may occur in up to 21% of young children (<6 years) or infants where there is also a clear growth response following effective treatment.[99] The incidence of FTT is now reported to be quite low, although it appears to be more common in infants than in older children with OSA.[121] Features of pulmonary hypertension are uncommon, except in the most severe cases and tend to be more subtle than can be observed on clinical examination.[118] Cardiologic assessment by CXR and ECG can be used, but echocardiographic examination is the most sensitive test for evaluating cardiac complications in children with severe OSA.[135,136]

Clinical features of hypoventilation vary. For children with congenital central hypoventilation, the most common presentation is apnea or respiratory failure soon after birth, although other common features may be associated with their exposure to recurrent hypoxia.[137] Where hypoventilation is secondary to neurologic abnormalities, the problem may be silent until the time of a sleep study, or it may present with other symptoms that relate to the neurologic abnormality.[82,138] Increased awareness that children with neuromuscular diseases and thoracic deformities are at risk of respiratory failure has led to increased use of anticipatory monitoring to evaluate respiratory deterioration in sleep. Although transcutaneous and end-tidal measurements are helpful, blood gases should also be measured when there is suspicion of respiratory failure. As arterial blood gas samples may be difficult to obtain in children, capillary or venous sampling and transcutaneous monitoring are valuable aids in this assessment.

FURTHER STUDIES

Initial investigations are appropriately directed toward finding the underlying cause for, or complications of, OSA. Lateral airway radiographs can show airway-occluding soft-tissue (masses) including the tonsils and adenoids. They are more readily available, although not as precise as MRI for determining the static size of the airway and the relative size of the tonsils and adenoids.[9,139] If linked to the respiratory cycle, dynamic differences in airway dimensions can also be determined by these imaging modalities.[140] Nasendoscopy is useful for a dynamic assessment of airway size and to assess space-occupying lesions.[141] CT scan is useful for determining a three-dimensional, static image of airway size. MRI, reconstructed CT images, and acoustic reflection can be used to determine an absolute volume for the airway. MRI is the most useful imaging technique for examining the brainstem, posterior fossa, and upper cervical cord.

Now that the genetic defect for CCHS has been identified, genetic testing is appropriate if CCHS is suspected and parental testing should also be undertaken for newly diagnosed cases. Ongoing research will clarify how the phenotypic features of the disease relate to the genotypic expression and it is clear that genetic mosaicism can produce less severe phenotypes.[8,78] In addition, autonomic dysfunction, as previously suspected and as is consistent with the pathways where the mutation has been identified, does appear to coexist in the majority of cases.[142]

Screening Studies

The most well-studied testing modality to screen for sleep apnea in children is oximetry.[75,143] The major difficulty with this test is that although it is specific, it is not a sensitive test for sleep apnea. As with questionnaires of clinical symptoms, a significant proportion of the results lead to a need for subsequent sleep studies, therefore limiting the cost-effectiveness of the screening.

Sleep Study Methods

Overnight sleep studies provide information about respiration during a period of sleep and, despite some controversies, they are still considered the gold standard for diagnosis.[5,144,145] These studies are usually performed because the history and/or examination suggest a diagnosis of OSA, but there are not enough facilities to provide full sleep studies for all children where OSA is suspected because of snoring. Therefore some form of screening is generally required in order to prioritize which children will have full sleep studies and which children should have surgery with adenotonsillectomy to treat upper airway obstruction.[143]

Polysomnography is the name given to a multiple-channel, physiologic recording performed during sleep. In its complete form, more than 16 variables are measured during the normal period of nighttime sleep. The clear benefit is the amount of information provided. The corollary in pediatrics is the highly demanding process of preparing children with all the attachments necessary for such a recording. Leads need to be placed accurately and firmly in order to provide good quality recordings for an 8- to 10-hour study. Sleep state is recorded by a combination of EEG, eye movements, and muscle (usually genioglossus) tone. The combination of these signals is required to differentiate all sleep stages, particularly REM. To record sleep stage, a minimum of one, but usually two to four, EEG leads are used. Eye movements and EMG signals are recorded via surface electrodes. This is costly because it is both time and labor intensive, but it provides accurate diagnoses with no significant detrimental effects on first compared to subsequent studies.[146]

Respiratory recordings include measures of both the effort exerted and the resulting effects. Effort can be recorded using EMG signals or chest/abdominal displacement. Plethysmography is the most popular measure, as the signal recorded is proportional to volume and has the potential to be calibrated. Impedance recordings are another common alternative.[147]

Respiratory-outcome measures include the presence or absence of airflow at the nose and mouth, and indicators of the blood gases (P_{O_2} and P_{CO_2}). Airflow may be measured by several methods, including pressure transducer, thermistors, and thermocouples. Oxygenation is usually measured by saturation. Transcutaneous P_{AO_2} may be recorded, but is associated with a wide margin of error and is not routine. CO_2 levels are most commonly recorded by transcutaneous and/or end-tidal monitors. More accurate measures require blood-gas analysis; these are generally used when noninvasive methods indicate abnormalities. An example of the blood gas abnormalities in OSA as recorded by Sa_{O_2} and transcutaneous CO_2 monitors is shown in the lower panel of Figure 65-4.

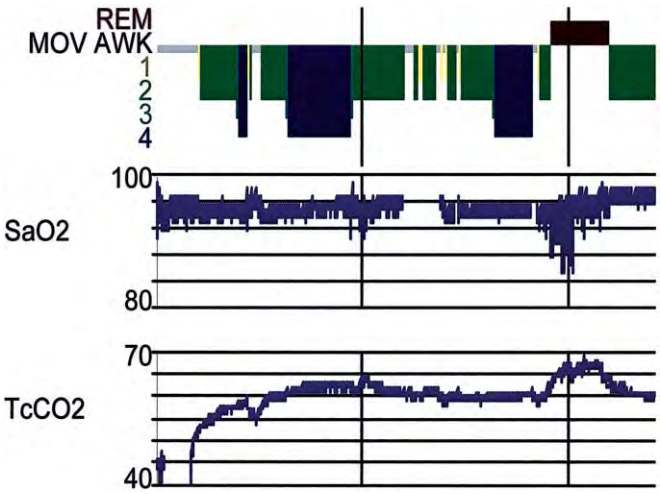

Figure 65-4 Hypnogram showing sleep stages, including REM sleep, with oxygen saturation and transcutaneous CO_2 measurements, illustrating the changes observed during REM sleep in association with obstructive sleep apnea.

The data recorded in these studies, including digital video, are virtually unlimited as storage capacities increase.

Sleep Study Interpretation

The principal aim of a sleep study is to evaluate the patterns of respiration in sleep and to quantify the changes in blood gases, levels of arousal, and sleep stage which occur in response to respiratory or other events. Criteria for sleep-stage scoring have been established across the age spectrum, although absolute EEG amplitudes (in microvolts) tend to be greater in younger age groups. Separate, specific criteria have been defined for infants. Commercial packages are increasingly accurate in the analysis of sleep and respiratory parameters, although all studies need to be manually checked for accuracy and the medical interpretation/report takes features other than the raw variables into account when evaluating the record (for example, quality of recording, nonrespiratory events and composite measures of respiratory effort).

Wakefulness is characterized by low-amplitude high-frequency EEG, the presence of conjugate eye movements, and high muscle tone. Sleep onset is heralded by rolling eye movements, associated with slowing of EEG signal frequency and a fall in muscle tone. SWS is associated with high-amplitude, low-frequency EEG, absent eye movements, and decreased muscle tone. REM sleep is characterized by low-amplitude, high-frequency EEG, the presence of eye movements, and loss of postural muscle tone. Light sleep stages have the additional characteristics of sleep spindles and K complexes. These are distinctive EEG patterns seen particularly in stage 2 sleep. Sleep spindles and K complexes are characteristic of stage 2 sleep. Sleep spindles are fast (7-10 Hz) bursts lasting 3-5 seconds and recurring at 30-second intervals. K complexes are well-delineated negative sharp waves immediately followed by a positive component. The duration of a K complex is no longer than 0.5 seconds. Detailed descriptions of each sleep scoring system are provided in the relevant reference manuals.[41,42]

Discrete respiratory events are defined as obstructive or central, depending on whether respiratory efforts continue during the apnea. An obstructive apnea indicates ongoing respiratory effort without airflow being achieved. During a central apnea there is no effort and no diaphragmatic activity. During mixed apnea airflow is absent, with diaphragmatic effort present for only a portion of the event. Criteria for scoring respiratory events in children need to account for the change in respiratory rate with age. In Australia, agreed criteria score respiratory events which disturb two or more consecutive respiratory cycles. The fall in oxygen saturation most commonly used to define a significant event is 3% to 4%. Values for normal children have now been published by several authors.[51]

The frequency of arousal and the levels of oxygen desaturation seen during the night in children with OSA are higher than in age-matched controls, but do not approach those seen in adult patients. The tolerance in children of "stable" partial obstruction does not appear to circumvent all symptoms or sequelae of obstructive apnea.[148] Detailed studies do suggest that there is an altered duration and distribution of sleep states in these children as a group.[103,134] Not all studies show consistent changes in sleep architecture since there is a tendency for children to preserve sleep architecture despite OSA.[149,150] Infants appear to have significant attenuation of REM sleep with respiratory disorders, including obstructive apnea.[151,152] REM sleep deprivation increases neuronal excitability and facilitates seizure activity, and deprivation of REM sleep during development has been shown to result in permanent behavioral changes and brain morphologic and biochemical abnormalities in animals.[153]

Children tend to have long periods of partial upper airway obstruction with minimal sleep disruption. Carbon dioxide retention can be marked during these periods, and some degree of hypoventilation occurs quite commonly in children with OSA. Sleep studies should include some measurement of CO_2 wherever possible.[154]

Studies demonstrating central hypoventilation, including central nervous system abnormalities other than CCHS, are characterized by marked blood gas disturbances in SWS. Children with CCHS fail to respond with either ventilatory or arousal responses to severe desaturations or CO_2 retention[155] although in our experience there does appear to be recovery of arousal in response to hypoxia after a period of treatment with adequate ventilation. Hypoventilation in response to neuromuscular or thoracic abnormalities is most marked during REM sleep when there is loss of accessory muscle activity, and a clinical history, examination, and detailed sleep study are required to distinguish this from upper airway obstruction.[156]

MANAGEMENT OPTIONS

Introduction

Treatment is first directed by accurate characterizations of the sleep-breathing abnormality. In the immediate sense, the significance of an apnea is determined by the physiologic changes it produces. During an obstructive event, these are the consequence of reduced or absent airflow despite sustained or increased respiratory efforts. Immediate effects include hypoxia and increased amplitude of negative intrathoracic pressure swings as well as arousal and increased sympathetic outflow.[157] Hemodynamic changes include bradycardia or tachycardia and can progress to systemic and pulmonary hypertension.[158] In contrast to OSA, central hypoventilation disorders are characterized by lack of effective effort in response to blood gas disturbances.[155]

Public Awareness

Awareness of the syndrome of OSA appears to be increasing among the public and medical communities.[159,160] Support group networks have been one effective way of disseminating information to the public. A high percentage of children with syndromes and malformations are thought to suffer with OSA, and their families frequently belong to such support associations. Increased education of clinicians as well as the public about the symptoms and signs of the disorder has been helpful in identifying children so that they reach medical attention. Most support groups have newsletters, which are an effective means of distributing such information. Surveys reveal that the majority of children present through parental action, despite their primary physician being aware of their symptomatology.

Medical Therapies

The role of pharmacologic options for the treatment of OSA in children is still being clarified. Nasal steroids are effective to reduce the severity of disease.[161] Allergic rhinitis may require topical nasal therapy whether these children have surgery or not.[162,163] Sedating agents, such as the benzodiazepines, may contribute to upper airway discoordination and increase upper airway secretions:[73] In some cases it may be possible to reduce these medications to minimize this component of the obstruction.

OSA is common in obese children.[101,164] The treatment of obesity is a difficult problem, usually involving the whole family in long-term intervention. The severity of the OSA is likely to improve after weight loss, but it is often necessary to treat the OSA acutely by other means, while commencing such a weight-control program.

Other chronic respiratory disorders may exacerbate sleep-disordered breathing. Attention should be paid to diagnosing and treating such specific problems as nasal polyps in cystic fibrosis, or frequent coughing, which will cause arousals and disturb sleep.[128] Maximizing lower respiratory tract function, including aggressive treatment of acute exacerbations will minimize the additional impact of sleep. Additional treatment, such as nocturnal nasal oxygen, CPAP, or ventilation may be necessary during sleep periods. The clinical reasons cited for commencing noninvasive mechanical ventilation (NIMV) include nocturnal hypoventilation (67%), acute exacerbations of lung disease (28%), and/or failure to thrive (21%).[6]

Nasal CPAP and Nasal Mask Ventilation

Nasal mask CPAP has been used for the treatment of adult OSA since 1981,[165] with exponential increase in the number of adult patients using this therapy since that time. Major centers acquire experience with the use of nasal CPAP in

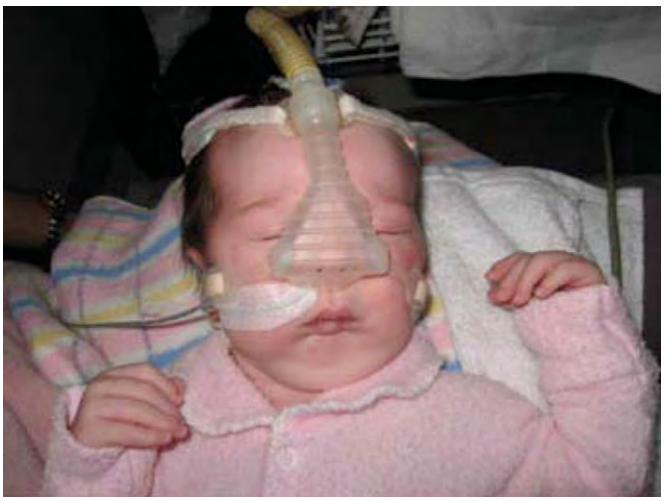

Figure 65-5 Nasal CPAP in an infant with Robin sequence (Maskmedic Concept Mask).

children quickly and with high success rates, confirming that CPAP is a practical treatment alternative for those children who do not achieve relief of their obstruction by adenotonsillectomy.[132,166,167] Although the use of CPAP in children has been less widespread than in adults, it is now a useful alternative to tracheotomy even for palliation.[168] Two important factors have been the development of a widely applicable pediatric nose mask (Fig. 65-5), and the use of a behavioral program to introduce the therapy to children.[169,170] Children often return quickly to their previous overnight sleep requirements after the implementation of successful treatment strategies. Compliance with noninvasive treatment regimens can become difficult, although the predictors of noncompliance are not well defined.

Nasal masks can also be used for the delivery of nocturnal volume or pressure cycled ventilation in children who present with congenital or acquired central hypoventilation.[171] Again, this mode of treatment delivery circumvents the need for tracheotomy, and it has been successfully used in the home environment from infancy on.[93] Side effects may occur both acutely and in the long term, particularly the development of mid-face hypoplasia.[172] Overnight nursing assistance is usually required as with tracheostomized children who are ventilated in the home environment.[173]

Surgical Options

The mainstay of treatment for OSA is adenotonsillectomy. The proportion of adenotonsillectomies performed to treat upper airway obstructive symptoms has shown a fairly steady increase.[174] Recent rates for tonsillectomy in Australia are 2.7% of children by the age of 5 and 8.9% by the age of 15 years.[174] Adenotonsillectomy results in significant improvement in most children with OSA.[175] Reported results of surgery to relieve upper airway obstruction include relief of symptoms, catch-up growth in those who have been FTT, marked reduction in the work of breathing, improved neurocognitive function, and improved quality of life.[102,121,175,176]

It is important to be aware that the complications of adenotonsillectomy surgery are higher in children for whom the surgery is being undertaken for OSA.[177] Children with OSA have increased anesthetic risk from sensitivity to opiates,[73,120] as well as increased risks for respiratory complications of the surgery.[143,178] Associated complications are more common in the younger age groups, with those younger than 2 to 3 years particularly affected.[179] Nonetheless, this surgery is recommended as the first-line treatment of OSA in children even if there are other underlying factors such as a small airway.[122,145]

It is now also clear that surgery is not always curative.[180] It is estimated that around 10% to 20% of children have persisting OSA after adenotonsillectomy.[53,181] There is increased risk for persisting disease in children with an anatomically small or dysfunctional upper airway, obese subjects, children with a history of prematurity, and those with more severe disease before surgery.[181-183] The role for adenoidectomy alone, particularly when the tonsils are not large, is not clear because of the perceived increased risk for subsequent tonsillectomy.[184,185] Until further studies clarify this issue, these children should have follow-up monitoring. Particular syndromes may have a very high incidence of OSA, with those documented including children with Down syndrome, Crouzon, other craniostenoses, or skeletal dysplasias such as achondroplasia.[186,187] Airway obstruction has been reported after surgery to correct cleft palate.[88] Children with such syndromes or malformations can constitute a high proportion of those requiring ongoing treatment, indicating that they are more likely to have severe apnea than their counterparts with normal facial structure.[132] Other groups requiring ongoing supervision and intervention are those with progressive infiltrative diseases such as mucopolysaccharidoses.[97]

Other surgical procedures may be used to treat OSA including mid-face or mandibular advancement and rapid mandibular expansion.[188] These surgical procedures may be implemented on the basis of the cosmetic benefits expected but will also alter the character of the upper airway. Where this surgery is undertaken, there should be careful perioperative attention to the upper airway.[188,189]

Uvulopalatopharyngoplasty (UPPP) has relatively low success rates (≈50%) and will be mentioned only to caution against its application in children.[190] UPPP has very limited application in adults, and even less in children for the treatment of obstructive apnea. This surgery is associated with poor long-term response and may have significant complications, in particular, velopharyngeal incompetence.[191]

Tracheotomy remains a surgical option. This has been demonstrated to be effective in treating obstructive apnea and characteristically results in relief of sleep-associated obstruction. Catch-up growth and relief of right-heart failure have been seen in children where adenotonsillectomy alone was not successful.[188] This surgery is associated with its own morbidity and complications and is not a first-line therapy.

Diaphragmatic Pacing for Hypoventilation

Electrical stimulation of the diaphragm, using a small implantable electrode and receiver, can successfully support ventilation in children with inadequate central respiratory drive or high quadriplegia.[192] The signal is transmitted by an antennae placed on the skin, overlying subcutaneously implanted receivers. An electrical impulse is then transmitted to the thoracic phrenic nerve, resulting in diaphragmatic

contraction. The stimulus parameters that are most appropriate for children are a low stimulus frequency, short inspiratory time, and moderate respiratory rate.

A tracheotomy is required in all young children up to school age and older in order to prevent pacing-related upper airway obstruction (the larynx does not dilate during inspiration). Bilateral diaphragmatic pacing is required in children in order to achieve a sufficient level of ventilation. Due to the risk of permanent diaphragmatic and phrenic nerve injury any additional support (more than 12 to 15 hours per day) requires alternative modes of delivery. The biggest advantage of this mode of treatment is the increased mobility that it permits, although backup forms of ventilation should be available at all times. The most significant complications are infection (reported rate 6%), component failure, and mechanical nerve injury. The disadvantages of this mode of ventilation (high cost, the need for a tracheotomy, and for an external transmitter) mean that, for patients who require ventilation only at night, mask ventilation is preferable.[193]

CONCLUSION

Ongoing studies will determine the relationships between SIDS, the childhood syndrome of OSA, and the adult syndrome. With more refined studies, the precise implications of OSA in children will be elucidated. It is possible that some causative genetic or neurodevelopmental factor will be isolated in some cases of this syndrome. Current developments mean that automatically responsive pressure devices will soon be available for all age groups, making both CPAP and nasal mask ventilation more precise and therefore more comfortable to use.

Challenges in the field include development and validation of confirmatory and discriminatory testing regimens that are more easily applied than full overnight sleep studies. For each test, there is a need to determine the cutoff levels at which treatment should be instituted as well as where special perioperative precautions need to be introduced. This includes refinement of treatment intervention for mild disease that may only have behavioral or developmental, rather than significant blood gas, respiratory, or long-term cardiac complications. While recognizing the enormous practical benefit of noninvasive interfaces for CPAP and ventilation, it is also important to define the role of more definitive treatment options in children.

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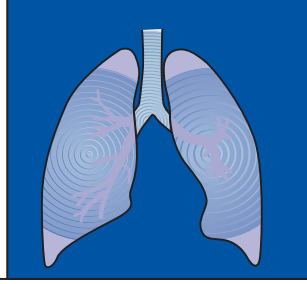


CHAPTER 66 Neuromuscular and Chest Wall Disorders

Oscar Henry Mayer, Karen Webster Gripp, Julian Lewis Allen, and Mary Ellen Beck Wohl

TEACHING POINTS

- There is a decrease in chest wall compliance from infancy through adulthood due to both ossification of the ribs and an increase in chest wall muscle mass.
- The component of tidal volume from rib cage excursion relative to the abdominal excursion increases from infancy through adulthood.
- The inspiratory action of the diaphragm includes decreasing intrapleural pressure, expanding the lower rib cage, and increasing intra-abdominal pressure.
- The fatigue resistance of the diaphragm can change based on the mechanical load of the respiratory system.
- Although respiratory muscle training can be useful in conditions of deconditioning, it is not recommended in patients with progressive neuromuscular disease.
- While surgery for pectus excavatum can correct the visual defect, it often does not produce a significant improvement in lung volumes or forced expiratory flows.
- Early diagnosis and treatment of scoliosis are very important in minimizing the impact on lung function.
- Congenital diaphragmatic hernia is often associated with pulmonary hypoplasia of both the affected and the unaffected sides.
- Progressive neuromuscular disease can cause both chronic respiratory failure and poor airway clearance, which can put further load on the respiratory system.

The chest wall serves as a protective cage for the heart, lungs, and great vessels of the thorax and as the respiratory pump that drives respiration. This chapter discusses normal developmental chest wall structure and function, as well as the causes and treatment of chest wall and neuromuscular disorders.

GROWTH AND DEVELOPMENT OF THE CHEST WALL

Structural Changes with Growth

Major structural changes occur in the chest wall with growth, and these changes have important functional implications for respiratory pump efficiency and function. In infancy, the orientation of the ribs is horizontal, but with growth they slowly rotate downward in a caudal declination until the normal adult pattern of downward-sloping ribs occurs at about 10 years of age[1] (Fig. 66-1). Chest wall muscle mass increases progressively with development. Ossification of the chest wall begins in utero and continues to approximately the 25th year. Progressive calcification of the costal cartilages can continue into old age.

Functional Consequences of Developmental Structural Changes of the Chest Wall

MECHANICAL PROPERTIES

Specific chest wall compliance decreases progressively with growth. In the infant, compliance of the chest wall is three to six times that of the lung.[2-5] Chest wall compliance is greater in preterm infants[3] than in full-term infants and decreases further during the first 2 years of life.[6] In school-age children, chest wall compliance is approximately twice that of the lung[7]; in the mature adult, it is equal to that of the lung, and in the elderly, it may be half that of the lung[8] (Fig. 66-2).

These changes in chest wall compliance are in part due to increasing ossification of the chest wall with development and increasing calcification with aging. Increasing muscle mass also contributes to the decrease in chest wall compliance with age.[9-11]

Although it is advantageous to have a highly compliant chest wall during the birthing process, functional disadvantages occur in infancy. With diaphragm contraction and downward diaphragm motion pleural pressure becomes negative. In a fully mature ribcage, the external intercostal muscles also contract as the ribs rotate superiorly and laterally, increasing the cross-sectional area of the thorax and expanding the lungs effectively. However, in a young or premature infant with higher chest wall compliance, due to the absence of full rib ossification and full intercostal muscle activity, the negative pleural pressure during inspiration may cause inward motion of the ribcage.[12] In addition, with the ribs rotated out in a more horizontal orientation, the diaphragm may be more flat with a smaller area of apposition to the chest wall, causing lower rib cage inward motion with diaphragm contraction, because the plane of contraction will be more horizontal.[12]

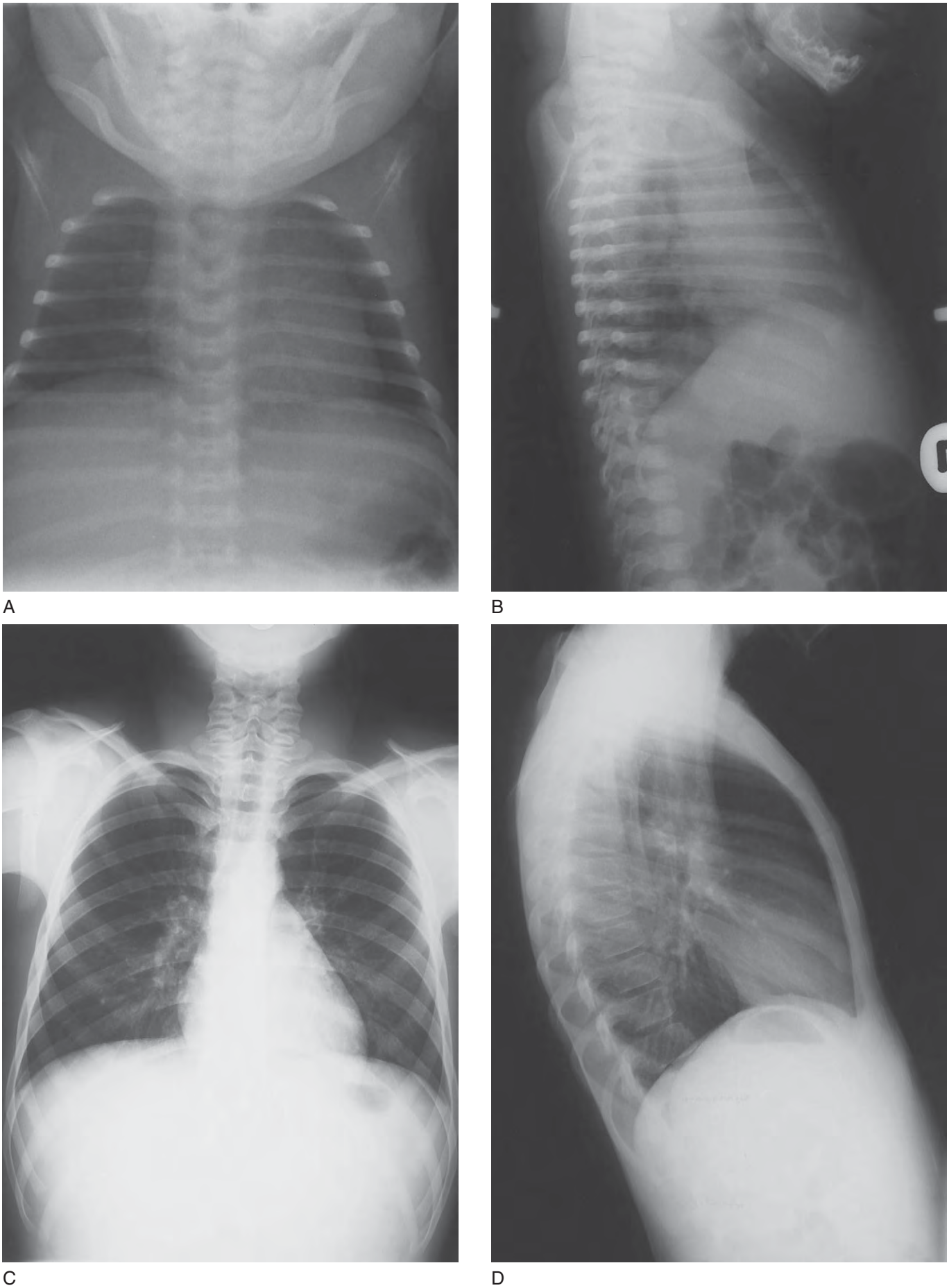


Figure 66-1 Changes in ribcage morphometry with growth. **A and B,** Posteroanterior (PA) and lateral chest radiographs of a 4-month-old infant. **C and D,** PA and lateral chest radiographs of a 14-year-old boy. In the infant, the slope of the ribs is nearly horizontal, whereas in the 14-year-old, there is a downward declination of the ribs. Progressive ossification of the sternal ossification centers can be seen in the lateral radiograph.

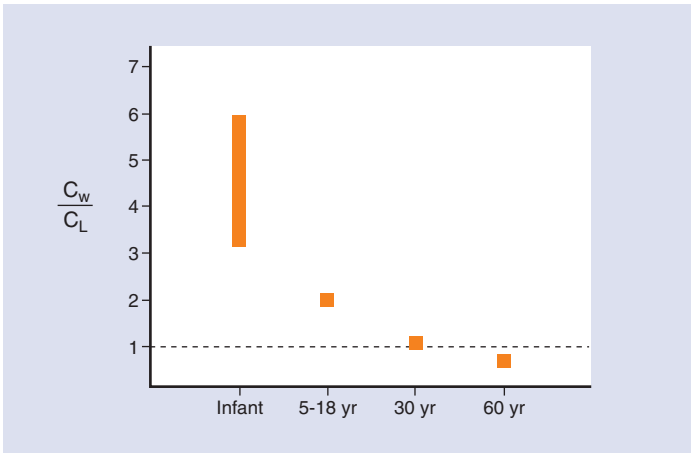


Figure 66-2 Changes in the ratio of chest wall to lung compliance with aging. Data for infants represent a range from several studies. In infants and children, the chest wall is more compliant than the lungs; in adults the chest wall compliance is close to that of the lungs, and in the elderly it is less than that of the lungs. C_W, wall compliance; C_L, lung compliance.

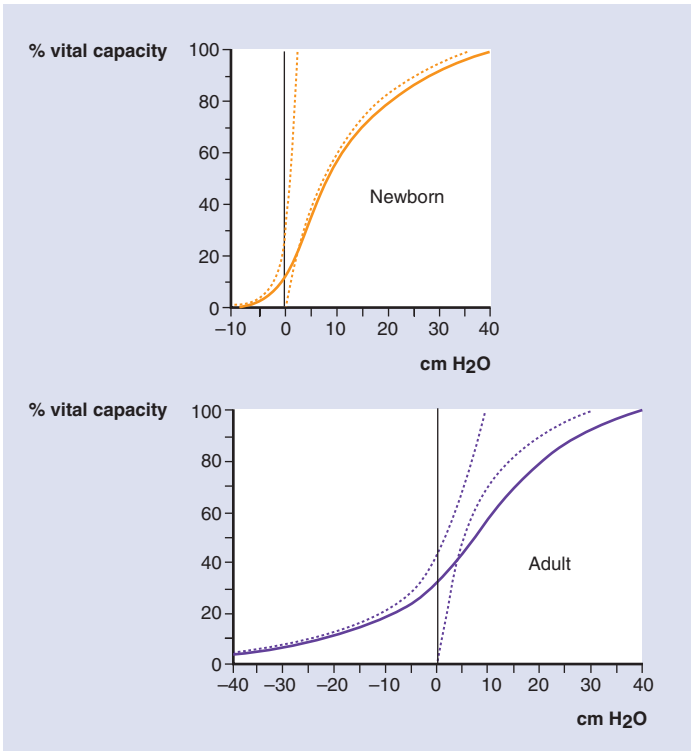


Figure 66-3 Respiratory system PV curves in the newborn and adult human. The *x*-axis represents pressure and the *y*-axis represents volume. The slope of each curve at a given lung volume represents the compliance at that volume. The *solid curve* in each diagram is the PV curve of the respiratory system. At a given lung volume, it represents the sum of the pressures resulting from the chest wall PV curve (*left dashed line*) and the lung PV curve (*right dashed line*). Passive end-expiratory lung volume is represented by the point at which the solid curve crosses the volume axis. It is lower in the newborn than in the adult because of the high compliance of the newborn chest wall curve. (Redrawn from Agostoni E, Mead J: Statics of the respiratory system. In Fenn WO, Rahn H [eds]: Handbook of Physiology, Respiration, Section 3, Volume 1. Washington, DC, 1964, American Physiological Society, p 401.)

Few studies have been done on developmental changes in chest wall resistance. The chest wall accounts for approximately 30% to 35% of total respiratory system resistance in adults[13] and 20% to 25% in infants.[6,14]

MAINTENANCE OF FUNCTIONAL RESIDUAL CAPACITY

The passive relaxation volume of the respiratory system (V_r) is determined by the balance of two opposing forces: the outward recoil of the chest wall and the inward recoil of the lung[15] (Fig. 66-3). The highly compliant chest wall of an infant provides less outward recoil and produces a low V_r. If V_r falls below the volume at which airway closure occurs, atelectasis can occur. Furthermore, during inspiration, additional energy needs to be expended to open these closed airways before inspiratory airflow occurs. This mode of breathing places an unnecessary metabolic burden on a patient.

Instead, full-term infants adopt a strategy of active maintenance of end-expiratory lung volume (EEV), consisting of an active prolongation of expiration. This phenomenon can be observed by comparing the active tidal breathing flow-volume curve with the passive flow-volume curve elicited by relaxing the respiratory muscles with a brief end-inspiratory occlusion, which activates the Hering-Breuer reflex[16] (Fig. 66-4). The active and passive time constants are represented by the slopes of the expiratory limb of these curves. The EEV can be maintained above V_r by increasing the expiratory time constant, τ, of the respiratory system relative to the time actually available for expiration.[17] This slower exhalation interrupts expiratory flow at a lung volume above the relaxed level (see Fig. 66-4) and will minimize airway closure. Preterm infants also maintain EEV above V_r, but their ability to do so is markedly sleep-state dependent, being less effective in active than in quiet sleep.

The neonate accomplishes active prolongation of expiration via two mechanisms: post–inspiratory activity of the inspiratory muscles, such as the diaphragm,[18] and expiratory "braking" by the upper airway muscles,[19,20] or vocal cord adduction. In infants with hyaline membrane disease, the more poorly compliant lungs predispose a child to an even lower V_r, and expiratory braking is clearly manifested as "grunting." Normal active maintenance of EEV diminishes with age and during the second year of life disappears,[21] likely as a result of progressive stiffening of the chest wall allowing a higher passively determined EEV.[6,22,23]

DEVELOPMENT OF THE RESPIRATORY MUSCLES

Structural and Functional Changes

The diaphragm has three major inspiratory actions.[24,25] First, the diaphragm decreases intrapleural pressure by acting as a piston, thereby creating a gradient of pressure that favors air flow from the airway opening to the alveoli. Second, the diaphragm increases intra-abdominal pressure. Because a substantial portion of intra-abdominal contents actually resides within the ribcage (Fig. 66-5), this increased abdominal pressure causes the lower ribcage to expand. Third, the diaphragm increases lower ribcage dimensions by acting through its area of apposition (see Fig. 66-5) to the inner ribcage wall to elevate the lower ribs, the "fulcrum" effect. This elevation

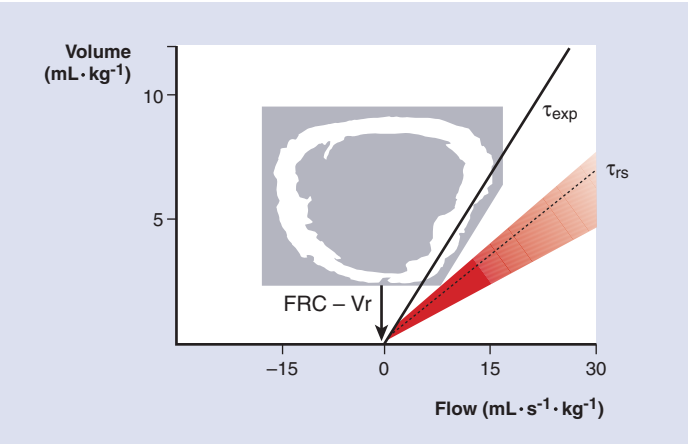


Figure 66-4 Elevation of EEV by active prolongation of the respiratory system time constant, t. A tidal flow volume curve is shown on the oscilloscope tracing. The slope of the expiratory limb of this curve ([volume, mL/kg]/[flow, mL/{sec • kg}]) has the units of seconds and represents the active expiratory time constant, t_{exp}. The slope of the dotted line represents the passive time constant of the *respiratory* system (t_{rs}) following an end-inspiratory occlusion that activates the Hering-Breuer reflex and relaxes the respiratory muscles. The lines intersect at the passive relaxation volume (V_r). The volume difference between V_r and the active flow-volume curve EEV represents the difference between functional residual capacity (FRC) and V_r and reflects active maintenance of FRC. (Reprinted with permission from Mortola JP, Saetta M: Pediatr Pulmonol 3:123-130, 1987.)

of the lower ribs also expands the lower thoracic cross-sectional area by causing the downward-sloping ribs to assume a more horizontal position, the "bucket handle" effect (Fig. 66-6).

In addition, there are a number of other factors that impact on the mechanical efficiency of diaphragm contraction. Less of the ribcage's contents are intra-abdominal and the area of apposition is smaller in the infant than that in the older child and adult. Furthermore, diaphragmatic mass is less in the infant.[11] Theoretically, these differences should

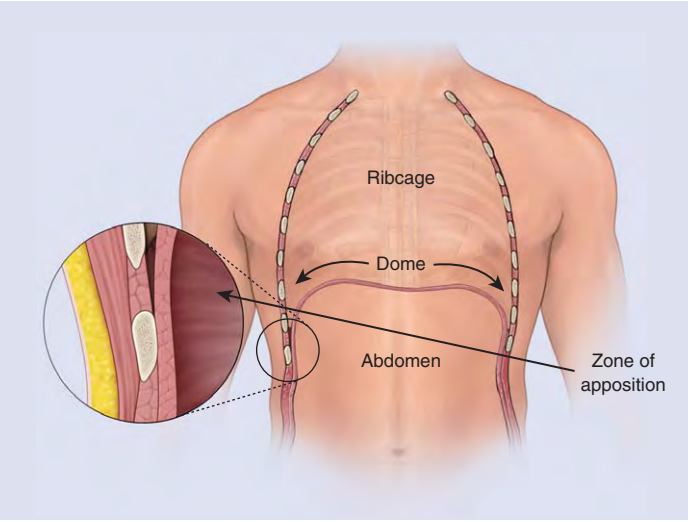


Figure 66-5 Zone of apposition. Whereas there is a substantial portion of the abdomen that is within the ribcage, there is apposition of the diaphragm and the inner chest wall (see circled area). (Reprinted with permission from DeTroyer A, Loring SH: Clin Chest Med 9:175-193, 1988.)

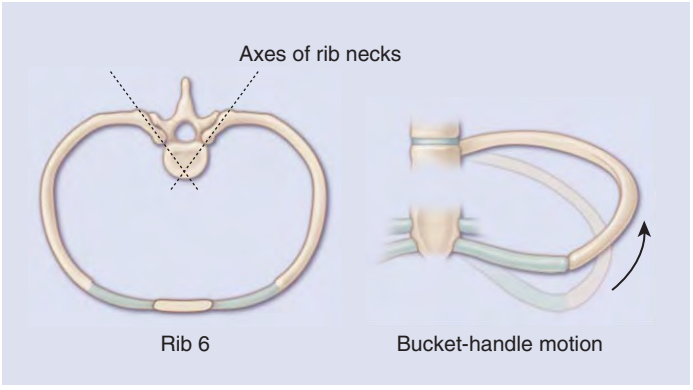


Figure 66-6 Bucket handle effect. [Reprinted with permission from DeTroyer A, Loring SH: Action of the respiratory muscles. In Macklem PT, Mead J [eds]: Handbook of Physiology. The Respiratory System. Mechanics of Breathing, Section 3, Volume III, Part 2. Bethesda, MD, 1986, American Physiological Society, p 453.)

impair the infant diaphragm's inspiratory action. On the other hand, by the law of Laplace, the smaller radius of curvature of the infant's diaphragm relative to the adult should improve its pressure-generating ability at a given level of tension.

Tidal expiration is primarily driven by the passive elastic recoil of the respiratory system. Neonates, like adults, can recruit abdominal muscles to promote active expiration,[26,27] although this is highly sleep-state dependent and is much less effective in rapid eye movement (REM) than in non-REM sleep.

Developmental Cell Biology of the Respiratory Muscles and Implications for Fatigue Resistance

It has been suggested that the mechanical disadvantage imposed by a highly compliant chest wall will predispose the premature and newborn infant to respiratory muscle fatigue and respiratory pump failure.[28-30] However, there are molecular and contractile properties that impart a certain fatigue resistance in newborn and young infants.

Developmental Changes in Respiratory Muscle Fiber Type Determined by Histochemistry

The relative proportion of type I (slow twitch, fatigue resistant) and type II fibers (fast twitch, fatigable) in respiratory muscles changes with development. The percent composition of type I fibers in the diaphragm of human premature infants, newborns, and older children (older than 2 years) is 10%, 25%, and 55%, respectively,[28] and there is a similar developmental pattern with the intercostal muscles.[28] Therefore, it would be reasonable to conclude that premature and newborn infants would be more susceptible to respiratory muscle fatigue than older children. Le Souëf and associates[29] found a paucity of type I fibers in the newborn rabbit diaphragm and an impaired ability to maintain occlusion pressure during sustained activation of the diaphragm by phrenic nerve stimulation. However, Maxwell and associates[31] found that the respiratory muscles of premature baboons were highly oxidative and fatigue *resistant*. Therefore there are other factors to consider than muscle fiber types.

Sieck[32] and Watchko[33] and associates have demonstrated that although specific force (peak tetanic force output normalized for muscle cross-sectional area) of diaphragmatic fibers increases with postnatal age, fatigue resistance decreases with age. They also found that fatigue resistance is related not only to oxidative capacity of the muscle (indexed by succinic dehydrogenase [SDH] activity), but also to myosin heavy chain (MHC) phenotype.[34] The neonatal MHC phenotype seems to impart a greater degree of fatigue resistance than do the adult isoforms. Therefore, fatigue resistance of respiratory muscle during development may relate to a balance between the energetic demands of the muscle contractile proteins (reflected by MHC isoform composition) and its oxidative capacity (reflected by SDH activity).[34] However, high oxidative capacity, while promoting fatigue resistance, may lead to oxidative damage if not balanced by increased antioxidant enzymes, such as superoxide dismutase (SOD).[35]

Recently, it has been determined that the fatigue resistance of respiratory muscles is plastic, and can change in the face of increasing resistive loads. Patients with chronic obstructive pulmonary disease (COPD) have diaphragms with an increased proportion of fatigue resistant type I fibers and an increased percentage of slow MHC isoform I compared with control subjects' diaphragms, which have fewer type I fibers and an increased percentage of fast MHC isoforms IIa and IIb.[36] Furthermore, fatigue-resistant developmental (embryonic and neonatal) MHCs have been reported in the diaphragms of patients with COPD, but their numbers are actually reduced compared with controls.[37] This may reduce the effectiveness of type I fibers in combating fatigue.

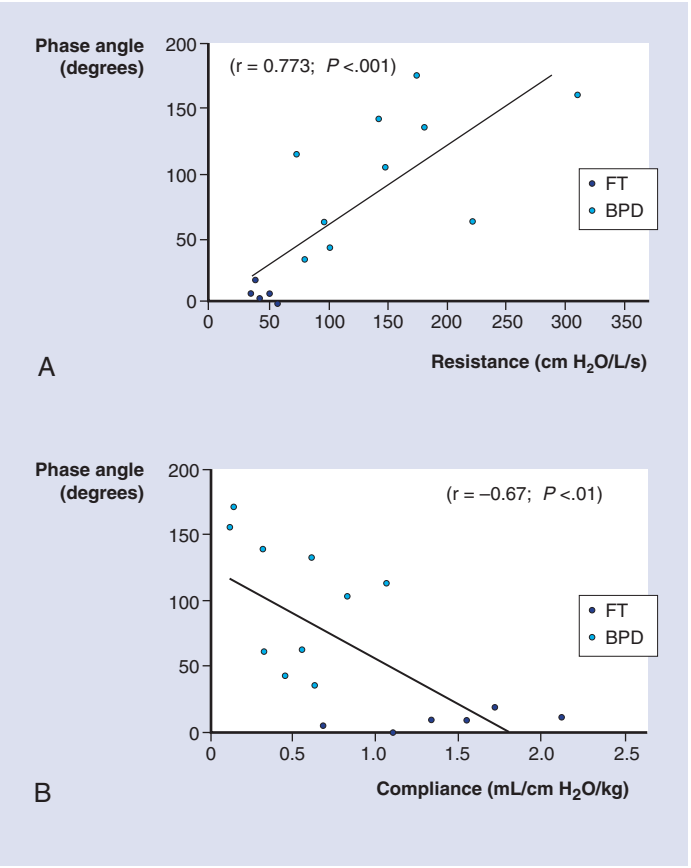


Figure 66-7 Relationship between thoracoabdominal asynchrony, quantitated by RC-AB phase angle, and lung mechanics. **A,** Phase angle versus resistance. **B,** Phase angle versus compliance. FT, full-term control; infants. BPD, bronchopulmonary dysplasia. (Redrawn from Allen JL, et al: Pediatr Pulmonol 11:37-43, 1991.)

METHODS FOR ASSESSING CHEST WALL FUNCTION

Chest Wall Motion

The quantitation of chest wall motion gives information about both chest wall and underlying lung function. The most widely used method to assess chest wall motion is respiratory inductive plethysmography; although video motion capture, strain gauges, and magnetometers have been used as well.[38]

Thoracoabdominal motion is more asynchronous with decreased or increased chest wall compliance and with increased airways resistance[39-41] (Fig. 66-7). In patients with increased chest wall compliance, the contraction of the diaphragm during inspiration produces a drop in pleural pressure and increase in abdominal pressure. The highly compliant ribcage may have inward motion at the same time the highly compliant abdomen has outward motion.[23] With increased airways resistance or decreased chest wall compliance, the diaphragm will have to contract more to generate the negative pleural pressure needed for adequate air flow and ventilation. The diaphragm motion will cause outward abdominal motion and the delay to outward chest wall excursion is dependent on the work needed to overcome chest wall compliance and/or airways resistance.

In the different situation of increased chest wall compliance as seen in premature infants and children with neuromuscular weakness such as spinal muscular atrophy, progressive increase in negative pleural pressure will cause *inward* as opposed to *outward* ribcage motion. Even at rest, to maintain adequate ventilation there will be increased outward abdominal motion.

Timing relationships between ribcage (RC) and abdomen (AB) excursion can be quantitated by measuring the period delay between maximal RC and AB excursions on a scalar tracing. This can also be measured by plotting RC versus AB motion in a Lissajous, or Konno-Mead figure[42] and calculating the phase angle based on the shape of the resultant figure (Fig. 66-8). The phase angle is an index of thoracoabdominal motion (TAM). This phase angle can range from 0 degrees (synchronous RC-AB motion) to 180 degrees (paradoxical RC-AB motion).

Premature infants normally display asynchronous or paradoxical breathing during quiet sleep (mean phase angle 58 degrees, range 0 to 157 degrees).[43] In different studies, the normal phase angle is 8 to 13 degrees in awake full-term infants,[39] 15 degrees in preschool-age children,[44] and 8 degrees in adolescents.[45] However, there are no longitudinal data through childhood to evaluate the variation of phase angle with age. There is significant variability with position, with phase angle being higher when supine than when sitting or standing and lowest in the sitting position.[44]

The magnitude of the contribution of the ribcage (RC) and abdominal (AB) compartments to tidal volume can also

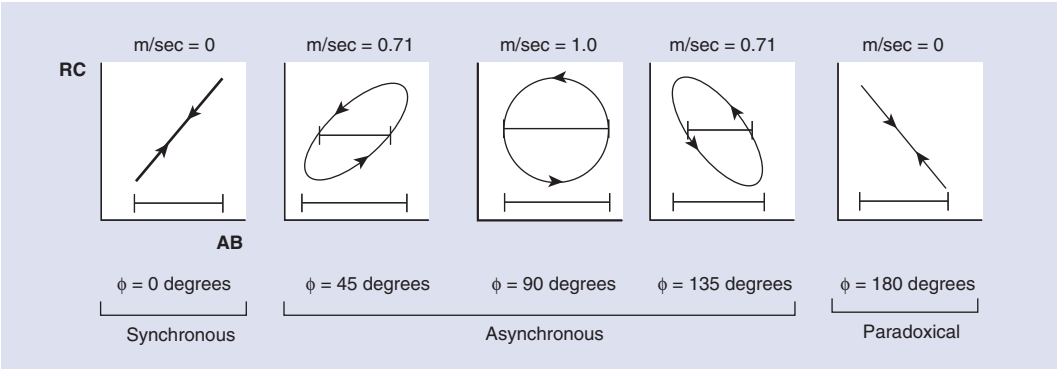


Figure 66-8 Lissajous figures of ribcage (RC) and abdominal wall (AB) motion. Phase angle, ϕ, is an index of thoracoabdominal asynchrony. Increasing thoracoabdominal asynchrony is seen as increasing width of the figure up to a phase angle of 90 degrees and then by a change from a positive to a negative slope between 90 and 180 degrees. For phase angles $0 < \phi < 90$ degrees, $\sin \phi = m/sec$; for $90 < \phi < 180$ degrees, $\phi = 180 - \mu$, where $\sin \mu = m/sec$ (see text). (Redrawn with permission from Allen JL, et al: Am Rev Respir Dis 141:337-342, 1990.)

be quantitated. Newborn infants breathe predominantly with their abdominal compartments, as opposed to adults, who are primarily ribcage breathers. The ribcage's contribution to tidal breathing during quiet sleep in the newborn is 35% of tidal volume (range 20% to 50%), increasing gradually over the first year to the normal adult value of 65%.[46]

Clinical Assessment of Respiratory Pump Function and Fatigue

PHYSICAL EXAMINATION OF THE CHEST WALL

Paradoxical motion of the ribcage and abdomen is easy to identify, although lesser degrees of thoracoabdominal asynchrony may be more difficult to discern. However, determining the amount of thoracoabdominal asynchrony relative to the phase of respiration can be very useful. Although chest wall paradox can be observed visually, the phase of respiration may be ascertained by a fingertip held at the mouth to feel airflow, a hand on the chest to feel chest wall excursion, or by chest auscultation. Inspiratory inward RC motion with outward AB motion occurs in patients with increased ribcage compliance, such as premature infants, and in some normal infants during REM sleep. It also occurs in patients with neuromuscular disease with intercostal muscle weakness but intact diaphragmatic function, such as spinal muscular atrophy (SMA) and quadriplegia. Inspiratory outward AB motion significantly ahead of outward RC motion is present in infants and children with increased airway resistance or decreased ribcage compliance. Inspiratory outward RC and inward AB motion is seen in patients with diaphragmatic dysfunction. It can also be seen in adults with severe airflow obstruction and impending diaphragm fatigue.

Roussos and associates[47] described a pattern of "respiratory alternans" during inspiratory resistive loaded breathing, in which breathing alternates between using the diaphragm and intercostal muscles, possibly postponing the onset of or attenuating respiratory muscle fatigue. One would expect this to be reflected in an alternating pattern of RC and AB motion, with outward motion primarily in the RC on one breath followed by primarily AB motion in another breath, with each compartment's displacement alternating in magnitude. Asynchronous RC/AB motion may also merely reflect the magnitude of the load itself, rather than respiratory muscle fatigue per se.[39,48,49]

Although the driving pressure for exhalation is the inward elastic recoil of the respiratory system, the abdominal muscles (particularly the rectus abdominis) may contract during active exhalation. This occurs in patients with severe obstructive lung disease, in whom passive recoil of the respiratory system may provide insufficient pressure to overcome expiratory airflow obstruction. Active expiration occurs normally during exercise. Alternately, it can be seen in some patients with inspiratory muscle weakness who may "actively" exhale below their functional residual capacity (FRC); the succeeding inspiration is then augmented by the outward elastic recoil of the chest wall from below FRC to FRC.

ASSESSMENT OF RESPIRATORY MUSCLE STRENGTH

Normal adults can develop maximal inspiratory and expiratory pressures against an occluded airway in excess of −100 and 200 cm H_2O, respectively. Occlusion pressures can be measured during crying in infants as young as one month of age. Changes in maximal inspiratory and expiratory pressures with age are shown in Table 66-1.

The gender difference in Pe_{max} and Pi_{max} is thought by some to be due to the difference in muscle mass with gender.[50] Pi_{max} has been measured and reported from both residual volume (RV) and FRC, so it is important to make note of the volume at measurement for appropriate comparisons.[50,51]

Alternately, sniff inspiratory pressure (sniff Pi) through a single nostril, with the contralateral nostril occluded and mouth closed, was shown to be a useful surrogate in patients with neuromuscular disease, some of whom may not be able to perform an adequate Pi_{max} via mouthpiece.[52] While the sniff inspiratory pressure in a cohort of children and adults with neuromuscular disease was similar to Pi_{max},[52] there was a significant difference in a separate study of healthy children.[53] However, there was a significant correlation between sniff inspiratory pressure and Pi_{max} in both studies.[52,53]

Maximal inspiratory force is an index of inspiratory muscle strength that is used by some clinicians in weaning a patient

Table 66-1
Measurements of Respiratory Muscle Strength in Childhood

Age	Gender	Point of Measurement	Sniff Pi (cm $H_2O \pm SD$)	Pi_{max} (cm $H_2O \pm SD$)	Pe_{max} (cm $H_2O \pm SD$)	Citation
3-36 mo	M & F	RV; TLC (crying)		−118 ± 21	125 ± 35	(1)
4-11 yr	M	FRC	−83 ± 26	−73 ± 28		(2)
	F	FRC	−79 ± 29	−62 ± 28		(3)
8-10 yr	M	RV; TLC		−79 ± 31	95 ± 34	(3)
	F	RV; TLC		−68 ± 24	82 ± 29	(3)
11-14 yr	M	RV; TLC		−111 ± 31	147 ± 34	(3)
	F	RV; TLC		−89 ± 27	115 ± 33	(3)
15-17 yr	M	RV; TLC		−129 ± 24	180 ± 43	(3)
	F	RV; TLC		−97 ± 24	133 ± 35	(3)

From (1) Shardonofsky F, Perez-Chada D, Carmuega E, Milic-Emili J: Airway pressures during crying in healthy infants. Pediatr Pulmonol 6:14-18, 1989; (2) Rafferty GF, Leech S, Knight L, et al: Sniff nasal inspiratory pressure in children. Pediatr Pulmonol 29:468-475, 2000; and (3) Domenech-Clar R, López-Andrev JA, Compte-Torrero L, et al: Maximal static respiratory pressures in children and adolescents. Pediatr Pulmonol 35:126-132, 2003.

from mechanical ventilation, although its utility is not universally accepted.[54] Transdiaphragmatic pressure (Pdi) is a measure of the pressure output of the diaphragm and is an index of diaphragmatic strength; however, it is more difficult to measure, requiring the placement of both gastric and esophageal pressure monitors.

Inspiratory muscle force is sometimes measured following either electrical or magnetic stimulation of the phrenic nerves.[55] While these techniques eliminate the variability inherent in volitional efforts, they are not widely clinically applied in pediatrics.[56,57]

ASSESSMENT OF RESPIRATORY MUSCLE FATIGUE

Measurement of the tension time index and frequency pattern assessment of diaphragmatic electromyogram (EMG) activity have been proposed as indicators of impending respiratory muscle failure.

Respiratory muscle fatigue can be defined as an inability of the respiratory muscles to maintain the force required to sustain minute ventilation in the presence of a mechanical load. The development of fatigue is closely linked to the force and duration of muscle contraction. The tension time index of the diaphragm (TTI_d) is a dimensionless product of the ratio of developed Pdi to maximal transdiaphragmatic pressure (Pdi_{max}) and the ratio of the inspiratory time (Ti) to the respiratory cycle time (T_{tot}), also known as the "duty cycle."

$$TTI_d = Pdi/Pdi_{max} \bullet Ti/T_{tot} \qquad \text{Eq 66.1}$$

The TTI_d has been used in adults to predict the development of fatigue. When the TTI_d exceeds 0.2, it is highly likely that fatigue will occur. The measurement of the TTI_d requires the ability to assess Pdi and Pdi_{max}, which can be technically difficult, because these measurements require both esophageal and gastric pressure transducers to measure the pressure generated across the diaphragm. A few studies have been done in infants and children to determine whether the same values of the tension time index are applicable.[58]

In a test analogous to the TTId, termed the TTmus, the tension time index of all the inspiratory muscles and not just the diaphragm is measured without the use of catheters. An inspiratory occlusion pressure measured at the mouth 100 milliseconds after the onset of inspiration is extrapolated to end inspiration. The mean inspiratory pressure (Pi) is calculated, and divided by the maximal inspiratory pressure measured at the mouth at FRC (MIP). The TTmus is then calculated as

$$TTmus = Pi\ (mean)/MIP \bullet Ti/Ttot \qquad \text{Eq 66.2}$$

This test has the advantage of being noninvasive and has been used to assess susceptibility to respiratory muscle fatigue in children with cystic fibrosis and neuromuscular disease[59-61] (Fig. 66-9).

Spectral frequency analysis of the surface diaphragmatic EMG during fatiguing loads has been shown to indicate diaphragmatic muscle fatigue in adults.[62] Similarly, in infants diaphragmatic fatigue produces a decrease in the high-frequency power and an increase in the low-frequency power of the EMG.[63] During weaning from mechanical ventilation, the EMG power spectrum remained normal in infants who were able to be weaned successfully, whereas in infants who failed extubation and in whom mechanical ventilation had to be reinstituted, a decrease in the high/low power spectrum ratio occurred before CO_2 retention and clinical deterioration. Because shifts in the diaphragmatic EMG power spectrum may occur in the absence of fatigue,[64] this technique has limited clinical use. Accurate placement of electrodes is critical to adequate recording of power spectra and at present this technique is seldom used for clinical purposes.

A joint statement of the American Thoracic Society and the European Respiratory Society[57] addresses many of the technical aspects of the measurement of both respiratory muscle strength and fatigue in children.

TREATMENT OF RESPIRATORY PUMP FATIGUE

General Principles

Respiratory pump fatigue can result from three mechanisms: intrinsic pulmonary disease (e.g., COPD or interstitial lung

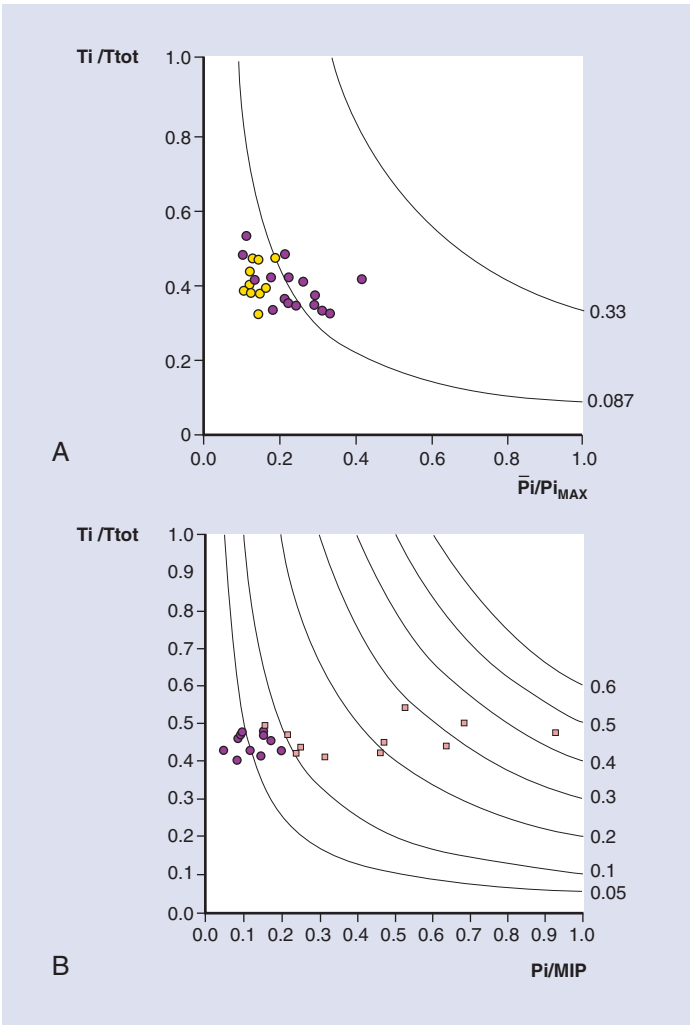


Figure 66-9 **A,** TTmus in normal children (*yellow*) and children with cystic fibrosis (*purple*). (Reprinted with permission from Hayot M, et al: Pediatr Pulmonol 23:336-343, 1997.) **B,** TTmus in children with neuromuscular disease (*square*) and healthy children (*circles*). (Reprinted with permission from Mulreany LT, et al: J Appl Physiol 95:931-937, 2003.)

disease) that increases the resistive or elastic work of breathing, muscle failure (e.g., neuromuscular disease), or chest wall deformity (e.g., scoliosis or flail chest) that decreases pump efficiency. All these mechanisms may be thought of in terms of Pdi/Pdi_{max}, the first term of the TTI. Whereas an increased work of breathing increases the quantity (Pdi/Pdi_{max}) by *increasing* Pdi, respiratory muscle weakness and inefficiency increases the quantity (Pdi/Pdi_{max}) by *decreasing* Pdi_{max}. Respiratory pump fatigue can be treated by respiratory muscle rest, respiratory muscle training, and the use of pharmacologic agents, all of which can increase Pdi_{max}. Obviously, reducing the work the diaphragm has to do (Pdi) by treating the underlying disorder is crucial in treating respiratory fatigue as well.

Respiratory Muscle Rest

Assisted ventilation is the most common form of respiratory muscle rest therapy. It can be done noninvasively via nasal, oral, and oronasal interfaces and also using negative pressure ventilation in subjects without upper airway obstruction. Although the technology for noninvasive ventilation was developed for adults, there are a few interfaces that are made specifically for children, but a larger number of adult masks that come in sizes small enough to use in children. Even though there are no noninvasive ventilators approved for use in children, they can be used effectively in children. Alternately, ventilation can also be done invasively via a tracheostomy tube using invasive ventilators designed for outpatient use. Ventilation can be used on an intermittent basis, on demand by mouthpiece or by nasal mask at night or during naps, for the majority of the day, or continuously with progression of disease or during periods of illness.

There are many modes of chronic ventilation used for muscle rest. Support can be full, giving complete respiratory muscle rest, or partial, with the respiratory muscles still doing some work. What is used is based both on patient need and desire.

Assisted ventilation can improve gas exchange, and the results can persist after discontinuation of ventilation.[65] This improved gas exchange can be due to improved respiratory muscle strength or may be due to a "resetting" of the respiratory control center to a lower P_{CO_2} during the period of assisted ventilation.[66,67] In addition, although brief periods of intermittent positive-pressure breathing do not alter lung mechanics,[68] the increase in tidal volume during nocturnal assisted ventilation can reexpand areas of atelectasis that had developed during nonassisted breathing.

While nocturnal ventilation can reduce respiratory muscle fatigue by effecting respiratory muscle rest, continual mechanical ventilation may actually reduce respiratory muscle endurance, probably by a "deconditioning" effect. Patients in intensive care units requiring mechanical ventilation for greater than 48 hours have reduced respiratory muscle endurance immediately after weaning, and the degree of reduction is worsened by longer duration of mechanical ventilation.[59]

Respiratory Muscle Training

Training can increase the strength and endurance of skeletal muscle. Strength and endurance training differ, as do the cellular changes that occur during each type of training. Strength training involves few repetitions of a high-intensity stimulus, and the major cellular response is muscle fiber hypertrophy. Endurance training involves frequent repetitions of a low-intensity stimulus, and the major cellular response is increased oxidative capacity, with increases in oxidative enzymes,[69] capillary density,[70] with a decrease in cross-sectional area.[71]

In normal adults respiratory muscle strength and endurance can be increased by specific training.[72] Respiratory muscle strength training has been performed using repetitions of maximal forced respiratory maneuvers and resistive loaded breathing with high inspiratory resistive loads. Endurance training has been accomplished with nonspecific (i.e., total body exercise) conditioning and specific conditioning. Specific endurance programs include voluntary isocapneic hyperventilation, resistive loaded breathing, and inspiratory threshold loading. In one recent study, athletes who underwent specific inspiratory muscle training increased strength by 25% and endurance by 27%.[73]

Respiratory muscle training has been shown to increase respiratory muscle strength and endurance in patients with quadriplegia.[74-76] A major unresolved question is when respiratory muscles should be exercised and when they should be rested. A general principle is that weak muscles should be exercised and fatigued muscles should be rested.[77,78] In Duchenne muscular dystrophy, the results of muscle training are varied from positive results that persist for a period of time after training ceases to no significant change.[79-84] It remains controversial, however, whether respiratory muscle training in patients with neuromuscular disease may lead to further muscle damage due to a decreased capacity to recover from the stress on the muscles from training.[56] Some have suggested that this risk can be minimized with endurance, limited load, high frequency training.[84] The American Thoracic Society currently does not recommend respiratory muscle training in patients with Duchenne muscular dystrophy.[56] There is some thought that other cytoskeletal components might be able to be upregulated to make the muscles of patients with Duchenne muscular dystrophy more tolerant of exertion and training.[85]

Pharmacotherapy of Respiratory Muscle Fatigue

Theophylline is the most studied pharmacologic agent for respiratory muscle fatigue. In vitro, theophylline produces a dose-dependent increase in peak twitch tension of the diaphragm[86] and can attenuate fatigue if used prophylactically.[87] In animal models, theophylline increases maximal transdiaphragmatic pressure[88] and improves diaphragmatic force generation after fatigue has developed.[89,90] In experimental spinal cord transection theophylline pretreatment as an adenosine type 1 receptor antagonist preserved diaphragm function and improved recovery, and the effect persisted after the theophylline was stopped.[91] This effect was increased with pretreatment with adenosine type 2 agonist.[91] Other work has demonstrated that sepsis-induced diaphragm fatigue may be mediated through NO-mediated lipid peroxidation of diaphragm myofibrils and that pharmacologic inhibition of inducible NO in this model prevented much of the contractile dysfunction.[92-94] Other work has shown that pretreatment with lidocaine can have a similar antioxidant effect.[95,96] However, in humans, there is only published experience with theophylline.

In healthy patients, theophylline has a potent effect on diaphragmatic contractility[97] and in patients with COPD, theophylline increases diaphragmatic strength and postpones the onset of diaphragmatic fatigue induced by resistive loaded breathing. Aminophylline increases diaphragmatic excursions in preterm infants,[98] but whether this is a central or peripheral effect is unclear.

STRUCTURAL ABNORMALITIES OF THE CHEST WALL INCLUDING THE DIAPHRAGM

Thoracic Dystrophies

A number of disorders of development of the chest wall exist, many of which are uncommon and result in early death from associated pulmonary hypoplasia, respiratory mechanical inefficiency, and respiratory pump failure.[99] If the defect occurs early enough in gestation to affect mesenchymal development it will negatively impact both airway and vascular development. If the thoracic defect occurs late in gestation or post-partum, then it may cause vascular and airway derecruitment that may be reversible after correction of the defect.

The etiologies of a number of these disorders have recently been elucidated as the genetic control of bone and cartilage growth and development becomes more clearly understood[100] and can replace classifications based on radiographic and morphologic characteristics[101,102] (Table 66-2).

Genetic Mechanisms

Congenital anomalies of the chest wall can occur due to embryologic anomalies or due to underlying gene mutations. The VATER (vertebral, anal, tracheoesophageal fistula, radial and renal anomalies) association is an example of an embryologic anomaly without a known genetic cause and no significant recurrence risk.[103] In contrast, disorders caused by gene mutations may have a recurrence risk and may be present in family members. It is therefore important to understand the inheritance pattern and to discuss this with family members at risk.

Osteogenesis imperfecta (see Table 66-2) is an example of autosomal dominant conditions that act via a dominant negative mechanism. Osteogenesis imperfecta results from a mutation in one of the genes encoding a procollagen chain.[104-107] Mature collagen molecules consist of three procollagen chains forming a triple helical structure. Incorporation of a single structurally abnormal component disrupts this complex structure and leads to the abnormal connective tissue properties and brittle bones. Another example of a disease acting by dominant negative action is Marfan syndrome, in which an abnormal fibrillin-1 gene causes abnormal fibrillin to be incorporated into extracellular microfibrils.

A second mechanism by which autosomal dominant mutations result in abnormal phenotypes is gain of function of the gene product. Achondroplasia is caused by a recurrent specific heterozygous point mutation in the fibroblast growth factor receptor 3 gene (*FGFR3*). This membrane-bound receptor has an intracellular tyrosine kinase domain that is activated upon ligand binding and ultimately regulates cell proliferation. The function of the normal receptor is negative regulation of endochondral growth, as demonstrated by skeletal overgrowth seen in mice lacking both functional copies of the gene.[108] The pathogenesis of the mutation involves constitutive activation of FGFR3, inhibiting proliferation of growth plate chondrocytes and causing short limb dwarfism.

A third pathogenic mechanism that causes autosomal dominant skeletal disorders is haploinsufficiency for the functional gene product. This mechanism most often affects protein products acting as transcription factors that control the expression of other genes. A 50% decrease of the functional protein is disease-causing in dosage-sensitive pathways, as seen in campomelic dysplasia and cleidocranial dysostosis (see Table 66-2).

A fourth pathogenic mechanism causing autosomal dominant disorders is that in which loss of function mutations in one gene copy are not functionally restored by a second,

Table 66-2
Chest Wall Disorders, Their Thoracic and Respiratory Presentation, Inheritance Pattern, and Gene Mutations

Category	Disorder	Major Findings	Thoracic Involvement	Respiratory Complications	Inheritance Pattern	Gene	Mutation
Dominant negative action	Osteogenesis imperfecta	Multiple fractures; joint laxity; blue sclera; dentinogenesis imperfecta	Rib fractures	Pulmonary hypoplasia in severe forms; unstable thorax after multiple rib fracture	Autosomal dominant	*COL1A1* or *COL1A2* (procollagen molecules)	Multiple
Dominant negative action	Marfan syndrome	Dolichostenomelia arachnodactyly; joint laxity; aortic dilatation	Scoliosis, kyphosis, and pectus excavatum or carinatum	Rarely respiratory distress due to abnormal thorax	Autosomal dominant	*FBN1* (Fibrillin 1)	Multiple
Dominant negative action	Beals syndrome	Dolichostenomelia camptodactyly; arachnodactyly; crumpled ears	Kyphoscoliosis	Rare	Autosomal dominant	*FBN2* (Fibrillin 2)	Multiple
Gain of function	Achondroplasia	Rhizomelic dwarfism; macrocephaly	Small ribcage; kyphosis	May occur in infancy; upper airway obstruction possible	Autosomal dominant	*FGFR3* (Fibroblast growth factor receptor 3)	Gly380Arg
Gain of function	Thanatophoric dysplasia	Short limbs, lethal dwarfism	Narrow thorax due to shortened ribs; flat vertebral bodies	Lethal shortly after birth, often due to respiratory insufficiency	*Sporadic cases due to new mutation*	*FGFR3*	Arg248Cys; Lys650Glu; others
Haploinsufficiency	Camptomelic dysplasia	Bowing of long bones; male to female sex reversal; micrognathia	Small thoracic cage with slender ribs or decreased number of ribs. kyphoscoliosis	Respiratory insufficiency may cause death in early infancy; failure to thrive in survivors	Autosomal dominant	*SOX9* (transcription factor)	Multiple
Haploinsufficiency	Cleidocranial dysplasia	Wide anterior fontanel with delayed closure; excess teeth; mild short stature	Partially or completely absent clavicle; narrow chest	Rare	Autosomal dominant	*CBFA1* (transcription factor)	Multiple
Loss of function	Marfan syndrome 2(1)	Dolichostenomelia arachnodactyly; joint laxity; aortic dilatation	Scoliosis, kyphosis and pectus excavatum or carinatum	Rarely respiratory distress due to abnormal thorax	Autosomal dominant	*TGFBR2* (TGF-beta receptor 2)	Multiple
Loss of function	Loeys-Dietz syndrome (2)	Joint laxity; aortic dilatation; hypertelorism; bifid uvula; micrognathia; patent ductus arteriosus; arachnodactyly;	Scoliosis, pectus excavatum or carinatum	Rarely respiratory distress due to abnormal thorax	Autosomal dominant	*TGFBR1* or *TGFBR2* (TGF-beta receptor1, 2)	Multiple
Loss of function	Ellis-van Creveld syndrome (chondroectodermal dysplasia)	Short distal extremities; polydactyly; nail hypoplasia; cardiac defects	Small thoracic cage with short ribs	Respiratory distress may occur due to the small thorax or the cardiac defect	Autosomal recessive	*EVC*	Multiple
Loss of function	Hypophosphatasia (neonatal form)	Undermineralized, hypoplastic and fragile bones; rachitic rosary; hypercalcemia	Short ribs and small thoracic cage	Death due to respiratory insufficiency in neonatal period common	Autosomal recessive	*ALPL* (alkaline phosphatase)	Multiple
Loss of function	Jarcho-Levin syndrome (spondylothoracic dysplasia; spondylocostal dysostosis)	Short neck; long digits with camptodactyly	Short thorax with multiple vertebral defects and abnormal ribs	Respiratory distress due to small thoracic volume causes death in infancy	Autosomal recessive; most cases of Puerto Rican ancestry	*DLL3* (delta-like 3)	Multiple
Unknown	Jeune syndrome (asphyxiating thoracic dystrophy)	Short limbs; polydactyly; cystic renal lesions or chronic nephritis	Small, bell-shaped ribcage; hypoplastic lungs	Usually fatal neonatal asphyxia	Autosomal recessive	Unknown	Unknown
Unknown	Cerebro-costo-mandibular syndrome	Severe micrognathia; prenatal growth deficiency	Small, bell-shaped thorax; gaps between posterior ossified and anterior cartilaginous ribs	Respiratory insufficiency may cause neonatal death	Possibly autosomal recessive or autosomal dominant	Unknown	Unknown

From Mizuguchi T, Collod-Beroud G, Akiyama T, et al: Heterozygous TGFBR2 mutations in Marfan syndrome. Nat Genet 36:855-860, 2004; and Loeys BL, Chen J, Neptune ER, et al: A syndrome of altered cardiovascular, craniofacial, neurocognitive and skeletal development caused by mutations in TGFBR1 or TGFBR2. Nat Genet 37:275-281, 2005.
Additional references: http://www.geneclinics.org and http://www.ncbi.nlm.nih.gov.

normal copy of the gene. While similar to the haploinsufficiency mechanism, these mutations do not usually affect transcription factors. For example, mutation in the transforming growth factor β receptors 1 or 2 (*TGFBR1* or *TGFBR*2) can cause Loeys-Dietz syndrome if only one copy of the gene is abnormal (see Table 66-2).

In contrast, autosomal recessive disorders are due to loss or function mutations in both alleles of the respective gene, causing loss of function protein products with enzymatic or transport function. Examples of these disorders include diastrophic dwarfism, achondrogenesis type 1B, and Jarcho-Levin syndrome. For example, achondrogenesis type 1B causes a clinical syndrome of extreme short stature, poor ossification of the skull and vertebral bodies, severe micromelia of the limbs, extremely short ribs, and stellate long bones.[103] The mutation resides in the diastrophic dysplasia sulfate transporter (*DTDST*) gene,[109] leading to decreased or absent sulfate transport[110] and abnormalities in cartilage proteoglycan sulfation.

Clinical Syndromes

Achondroplasia, an autosomal dominant skeletal dysplasia, is one of the most common forms of short-limbed dwarfism. It results from a mutation in the transmembrane domain of FGFR3.[100] Phenotypically, it is associated with developmental abnormalities of the ribs, thorax, long bones, and cranium. The ribs are short and flared, and the anteroposterior diameter of the thorax is narrowed, which can compress the intervening structures such as the trachea.[111] This compression may be related to the posterior ribs bowing around the transverse processes of the spine, thus "pushing" the vertebral bodies anteriorly.

The respiratory complications of achondroplasia include disordered sleep and obstructive apnea in about three quarters of subjects,[112] due to brainstem compression causing disorders in the control of breathing and midface hypoplasia. In addition to obstructive apnea, in part related to the midface hypoplasia, brainstem compression may lead to disorders in the control of breathing.[112-114] The small lung volumes mean that airways are narrower than normal and more likely to be occluded by secretions, thereby predisposing the patient to recurrent pneumonia and hypoxemia due to atelectasis and ventilation-perfusion mismatch. Related spinal cord compression can also cause respiratory muscle weakness and "pump" failure.

Despite the 10% of infants and young children with these complications, most patients with achondroplasia survive into adulthood. In contrast to the heterozygous mutation causing achondroplasia as an autosomal dominant trait, the skeletal abnormalities of homozygous offspring are so severe that most die in the first year or two of life.

Two other heterozygous mutations in the *FGFR3* gene account for the findings in thanatophoric dysplasia, which, like homozygous achondroplasia, is lethal in very early life. These are the most severe phenotypes caused by mutations in the *FGFR3* gene; achondroplasia is less severe and hypochondroplasia (HCH) is the least severe.[115]

Jeune syndrome, or asphyxiating thoracic dystrophy, is a rare autosomal recessive abnormality of endochondral bone formation characterized by a very small, shallow thoracic cage, abnormalities of the pelvis, polydactyly, and abnormal teeth. The thoracic cage does not grow normally, with ribs having a very low radius of curvature that produce a poorly compliant thorax that can only expand caudally during respiration (Fig. 66-10A). Without intervention, severe respiratory failure occurs and patients can die early in life.[116] There is the additional mechanical disadvantage of a flat low diaphragm with a lower force generating capacity due to the increased radius of curvature. In a 4-month-old child who died with Jeune syndrome, pathologic examination showed that there was a normal complement of preacinar arterioles, airways, and minimal impact on alveolar growth; however, there was evidence of vascular remodeling consistent with pulmonary hypertension.[117]

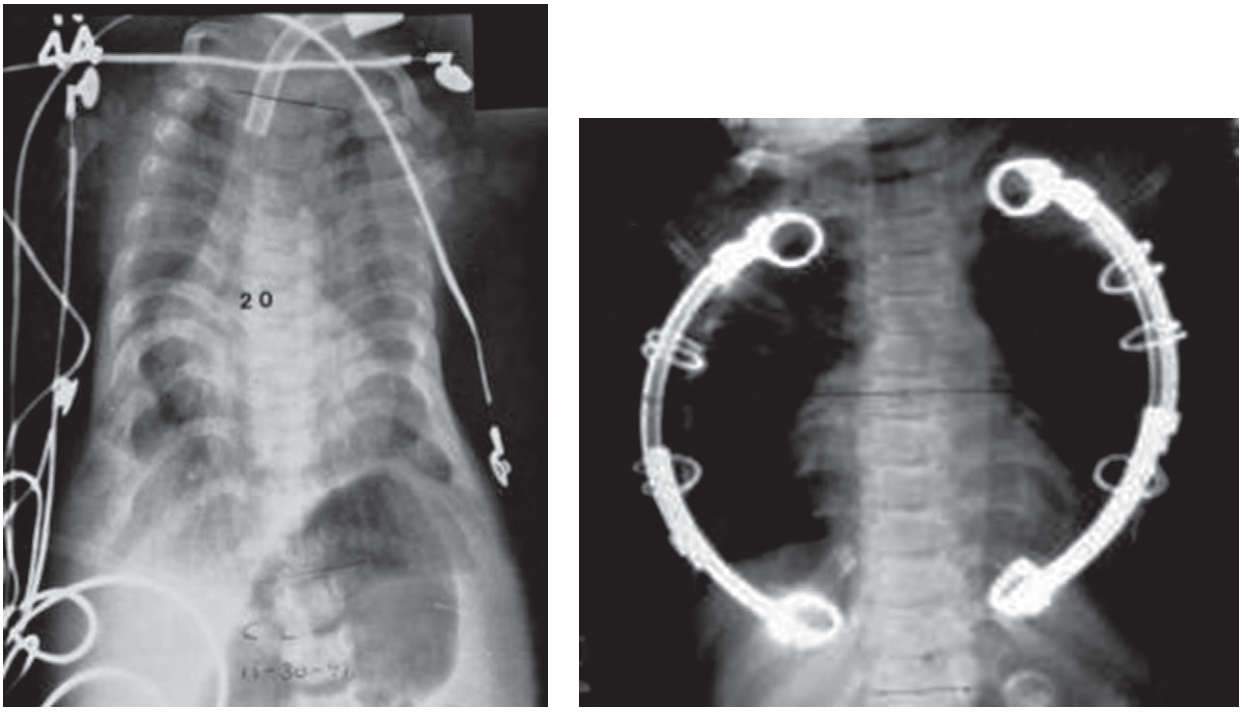
There are a number of different surgical interventions that are available to correct the thoracic limitation from Jeune syndrome, and both involve lateral expansion.

In one procedure, a vertical expandable prosthetic titanium rib (VEPTR) is placed across a thoracotomy and a series of sequential osteotomies made through the middle ribs. The VEPTR has a radius of curvature much smaller than the ribcage and when the freed ribs are sutured in place, they are moved outward from their original position (see Fig. 66-10). In time, the thoracic cage heals, with a greater thoracic cross-sectional area shown on chest CT scan (Dr. Robert Campbell, personal communication).

A separate technique, lateral thoracic expansion,[118] also uses a thoracotomy with sequential osteotomies and lateral expansion. The osteotomies are offset from each other and the periosteum is left in place and the "long" ends of adjacent ribs are attached using titanium supports for reinforcement (Fig. 66-11*A*). This expands the chest outward and leaves large gaps at every other rib level; however, within 3 weeks postoperatively, there is evidence of bone growth from the periosteum (Fig. 66-11*B*). Both techniques have been used successfully over the last decade.

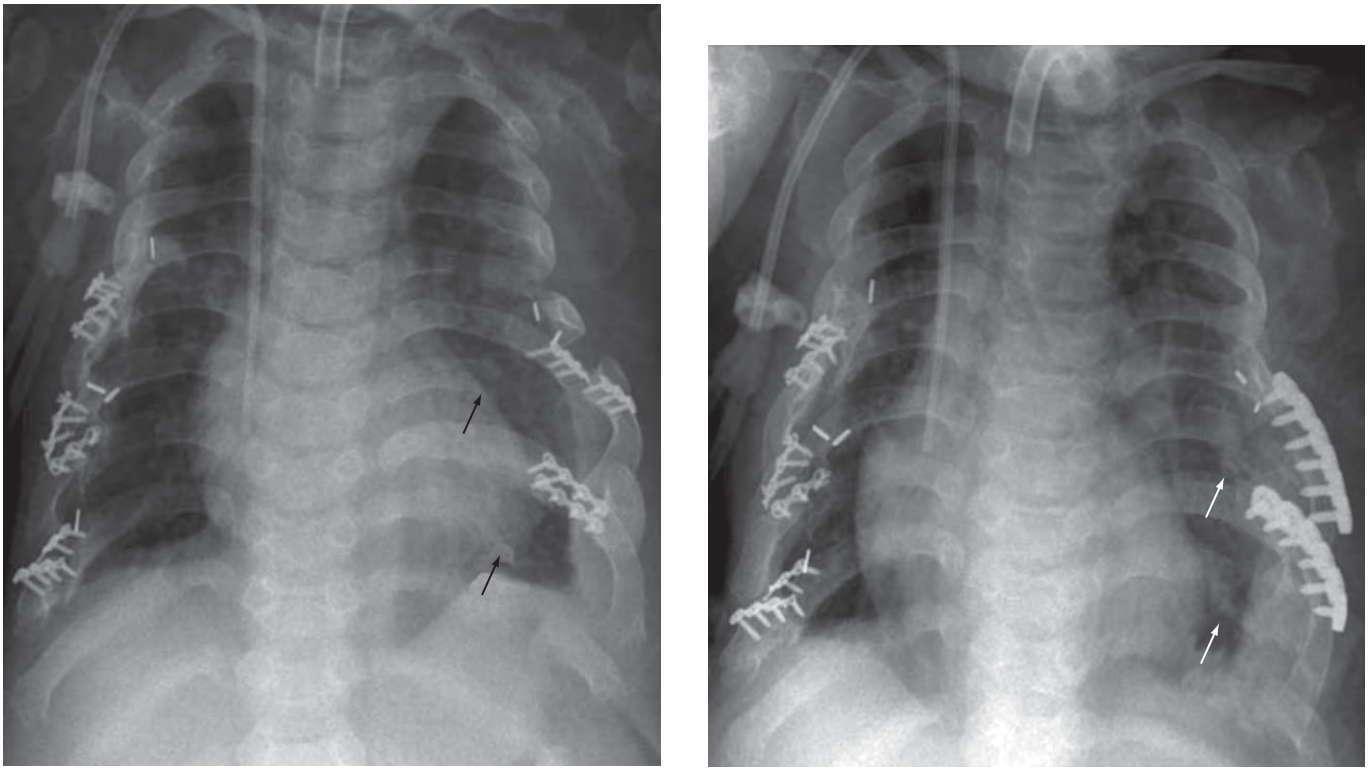
Osteogenesis imperfecta, an inherited disorder of bone formation, usually results from mutations in the genes encoding type I collagen. It is associated with fractures of the bones including the ribs. The common respiratory problems relate to the fractures of the ribs produced by minimal trauma. This may cause a rapid-shallow breathing pattern, because deeper breaths are painful. The inflammatory response to fractures may cause febrile episodes that clinically are difficult to distinguish from respiratory tract infections but will increase the metabolic demand on the patient. Chest radiographs are often of no help in defining absence or presence of infiltrates because the lung parenchyma is obscured by bone and callus formation.

Jarcho-Levin, or spondylothoracic dysplasia, syndrome is an autosomal recessive disorder in which there is a combination of spinal and rib cage abnormality with truncation of normal spinal growth and a fan-shaped appearance of the ribs (Fig. 66-12). The abnormality begins with the spine, with multiple vertebral anomalies at all levels with hemivertebrae, and fused, hypoplastic vertebrae.[119] Because of the restrictive thorax, patients with Jarcho-Levin syndrome can experience chronic respiratory failure early in life. In one series, mortality was 44% by 6 months of age.[119] In addition, there also can be secondary pulmonary hypertension and congestive heart failure. Although death can occur during infancy, in a



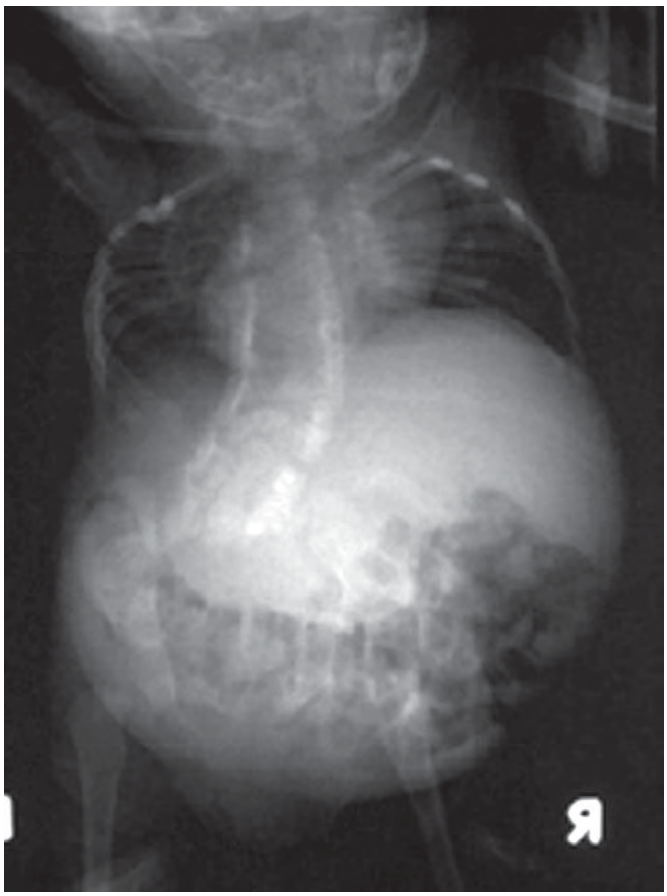
A B

Figure 66-10 Jeune syndrome before **(A)** and after **(B)** repair using bilateral lateral expansion using the VEPTR. (Courtesy of Dr. Randall Betz.)



A B

Figure 66-11 **A,** Jeune syndrome with repair using the lateral thoracic expansion technique, with titanium supports, immediately after initial repair, with *black arrows* indicating rib ends from osteotomy. **B,** After 3 weeks with evidence of ossification of periosteum at rib ends. (Reprinted with permission from Davis JT, et al: Ann Thorac Surg 77:445-448, 2004.)



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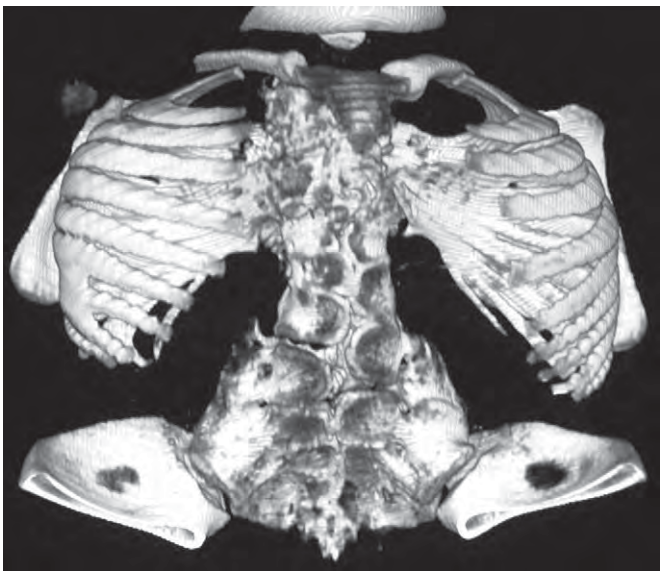


B

Figure 66-12 Jarcho-Levin syndrome on PA view **(A)** and on chest CT scan reconstruction **(B)** demonstrating the shortened thorax and "fan-shaped" orientation of the ribs relative to the spine. (Courtesy of Dr. Randall Betz.)

Puerto Rican cohort those who survived infancy had an almost 3-fold decrease in hospitalizations for respiratory tract infections after 24 months of age.[119]

Surgical interventions to treat the thorax of patients with Jarcho-Levin syndrome are similar to those for Jeune syndrome and may prevent the need for or complement ventilatory support. Anterior and/or posterior spinal fusion have been performed in patients with progressive scoliosis.[120] In other situations, lateral thoracic reconstruction has been performed.[121] Chest wall expansion using VEPTR has been performed in two general patterns: lateral rib-to-rib chest wall distraction using the VEPTR after a series of thoracotomies and osteotomies to open the medial bone mass or with a rib-to-spine or rib-to-iliac crest traction spanning the defective region if there is significant scoliosis (Dr. Robert Campbell, personal communication). Outside of stabilization from the initial surgery, subsequent expansions to maintain traction on the spine can encourage spine growth.

Pectus Excavatum

Pectus deformities are among the most common abnormalities of the thorax. There are no recent data on incidence; however, in older data the incidence was 6 to 8 per 1000 children.[122] Although the causes of pectus are not clearly defined, they may be linked to upper airway obstruction during chest wall growth, overgrowth of costal cartilage, thoracic cage muscle weakness, and underlying mesenchymal abnormalities, such as connective tissue disease.[123] If pectus excavatum is discovered, a comprehensive patient and family history and physical examination should be performed to evaluate for other associated disease processes such as other skeletal abnormalities, mitral valve prolapse, and Marfan syndrome.

The nature and extent of physiologic abnormalities associated with pectus deformities are controversial.[124,125] There have been studies demonstrating that pectus excavatum produces no pulmonary function abnormalities,[126] whereas others demonstrated a mild to moderate restrictive defect,[122,127] which correlates only loosely in severity to radiographic measurements of the magnitude of the pectus. However, others have demonstrated that though restrictive defects occur, they are less common than obstructive defects.[128-130]

There are two basic approaches to pectus excavatum surgical correction. The first is the classic Ravitch procedure that involves a sternotomy and bone resection with remodeling of sternal cartilage.[131] In a minority of patients receiving the Ravitch procedure, there was a significant asphyxiating restrictive defect that occurred in the years postoperatively,[131,132] and alterations were made to correct this defect and minimize the occurrence.[131,133] The second is the Nuss procedure in which a titanium bar, bent to the expected contour of the chest after surgery, is inserted beneath the ribs laterally and rotated anteriorly to apply outward pressure on the internal edge of the sternum.[134] The bar remains in place for 2 to 4 years and the sternal remodeling remains permanent in most cases.[135]

There is wide variation in pulmonary outcomes after corrective surgery. In some patients, there is actually a decrease in lung function after surgery.[131,132] This has been related to the severity of the pectus, with the less severe patients having less improvement or a decrease in lung function.[135] The group that developed the Nuss procedure has outcome data in a cohort of 43 patients that demonstrated a statistically significant improvement of 5% of predicted value in FVC and FEV_1 and of 8% in $FEF_{25-75\%}$ after the bar was removed at a mean of 2.9 years after insertion.[135] Interestingly, the patients who were under 11 years of age had no significant improvement in pulmonary function, whereas the patients over age 11 all had significant improvement.[135] There is increased oxygen consumption at high levels of exercise before and after pectus repair, although the improvement in exercise capacity after pectus repair appears to be modest.[126]

For the vast majority of subjects who receive pectus repair there is minimal cardiac dysfunction.[136,137] However, there is some evidence for increased stroke volume after repair, increased ventricular filling, increased oxygen pulse resulting in a decreased heart rate at the same workload, and increased duration and level of exercise.[136,138]

Scoliosis

In the United States, approximately 1 in 1000 persons has a scoliotic curve greater than 35 degrees and 1 of 10,000 has a curve greater than 75 degrees, which can put them at risk for chronic respiratory failure.[139,140] This places about 30,000 patients at risk for chronic respiratory failure caused by scoliosis in the United States.[139] Patients with infantile or juvenile scoliosis typically have greater morbidity and mortality compared with patients with adolescent onset scoliosis, who can have very little morbidity if the degree is mild and/or it is detected early.[141,142] Therefore, early diagnosis and aggressive intervention are critically important.

There are a number of different causes of scoliosis. Although scoliosis is visualized on examination or on radiograph as a spinal curvature, it goes well beyond just the spine. The scoliosis can be a primary spinal defect with hemivertebra and fused or absent vertebra that alters the normal spinal growth pattern. Alternately, the curve can be secondary to lateral rib tethering from rib fusion (Fig. 66-13*A*-C) or to rib absence (Fig. 66-13*A*,*B*) with inadequate lateral support. With rib fusion, the contralateral spine grows at a faster rate than the ipsilateral spine and the curve increases with growth (Fig. 66-13C). Absence of ribs causes an incompetent thorax with adequate support on only one side, and with growth, there is a curve convex to the side with the rib absence (Fig. 66-13*A*,*B*). Patients with intercostal muscle weakness can develop scoliosis due to inadequate ribcage support with scoliosis and a more downward rotation of the ribs in a "Christmas tree" appearance, as is seen in spinal muscular atrophy (Fig. 66-14).

Scoliosis can cause a restrictive defect in which the magnitude of the restriction is related to the angle of scoliosis (Cobb angle), the location of the curve, and loss of normal thoracic kyphosis. Although the amount of the curve can be linked to respiratory compromise, the correlation is not direct or consistent. The level of curve and the amount of spinal rotation are also important in determining the amount of respiratory compromise. The more cephalad the curve, the more severely the lung on the convex side is compressed. Spinal rotation shifts the ribs laterally so that the midpoint of the sternum is lateral to the midpoint of the spine (Fig. 66-15). This further compresses or distorts the lungs by flattening them in the lateral plane and puts torsion on the diaphragm.[143] The torsion on the diaphragm may increase the radius of curvature of the diaphragm, thereby decreasing the force-generating capacity and making it less efficient.

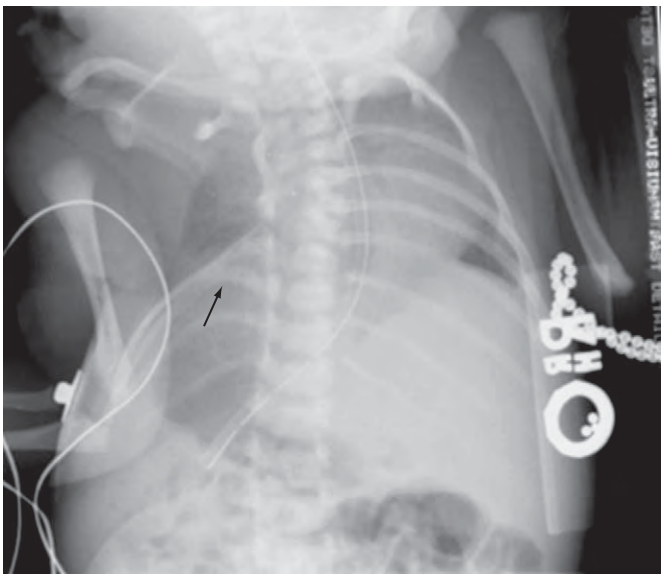
The compliance of the respiratory system and, in particular, the chest wall is decreased in patients with scoliosis. This decrease in compliance correlates closely with the severity of scoliosis and with the decrease in FVC[140] that is well described in scoliosis. In addition, as might be expected in the convex lung, there can be peripheral airway obstruction and air trapping,[140,144] demonstrated by plethysmography; as one might expect, this has not been consistently demonstrated using the helium dilution technique. Some patients have demonstrated a significant postbronchodilator decrease in the RV/TLC ratio and an increase in FEV_1, which was thought to indicate increased airway smooth muscle tone to resist the compressive force from the scoliosis[144]; however, airway hyperreactivity was not independently assessed.

Scoliosis in certain circumstances can have a profound influence on lung development. Congenital scoliosis that is allowed to progress and significantly limit lung growth within the first few years of life can impact lung growth during the period of rapid alveolar development and limit alveolar number, although the alveolar size is appropriate for age.[145]

There are a number of different ways to intervene in treating children with congenital scoliosis. In milder cases, bracing may prevent or decrease progression of the curve through adolescence, after which time further progression should be minimal. For more severe cases, it is generally accepted that spinal fusion using instrumentation such as Harrington rods is the most reliable final solution in that it stabilizes the spine well with some correction and prevents further progression. The disadvantage of spinal fusion is the lack of potential for future growth of the fused segment, which limits its utility in younger patients.

There are two alternate methods of spinal correction that allow for spinal growth: "growing rods" and the vertical expandable prosthetic titanium rib (VEPTR). Growing rods are placed along the lateral edges of the spinal column and attached intermittently along the stabilized region (Fig. 66-16). As the patient grows, the rods can be lengthened at the connection points or replaced with longer rods to allow normal spinal growth. Whereas some believe that the advantage of this construct is that it prevents any limitation of the outward ribcage motion during respiration and keeps the correction in the perispinal region, others believe that invading the perispinal region makes the definitive spinal fusion performed later more difficult.

The VEPTR has been used in patients with congenital scoliosis with rib fusion or rib absence (see Fig. 66-13*B*). The advantage of use in these two situations is that there is both correction of the curve, to the extent possible, and rib cage stabilization. Semiannually, the VEPTR is expanded to allow normal growth. Although some have expressed concern that the placement across multiple ribs will decrease rib cage



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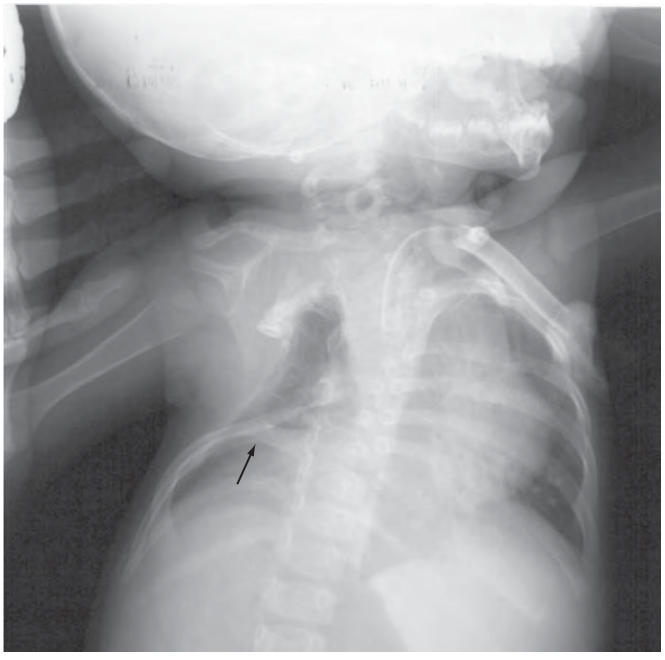

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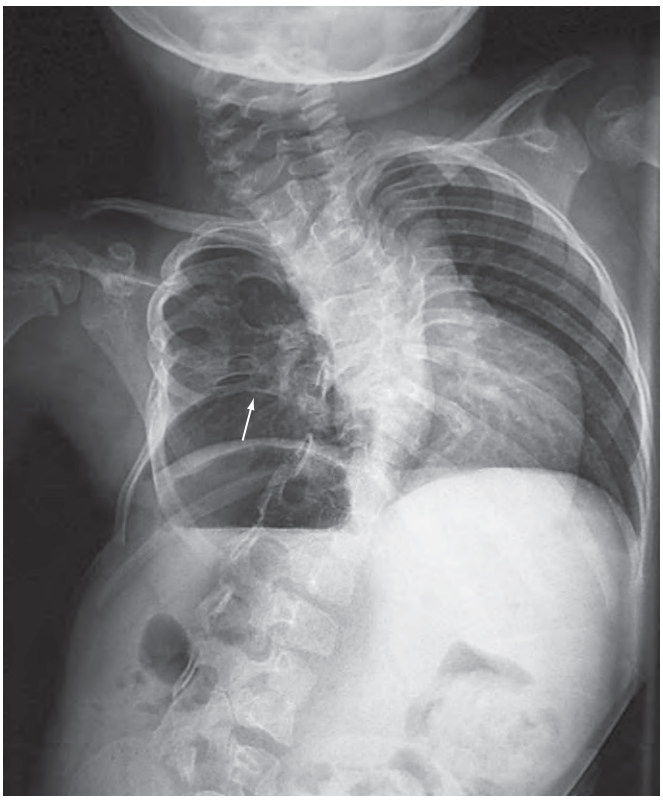


C

Figure 66-13 Absence of ribs 2 through 7 and fusion of ribs 8 and 9 (*arrow*) in a 1-week-old girl **(A)** and later at 10 months **(B),** demonstrating scoliocurve of 50 degrees. (Courtesy of Dr. John Flynn.) **C,** Rib fusion and scoliosis in a different 5-year-old girl. (Courtesy of Dr. Randall Betz.)

compliance and negatively impact respiration, there is no evidence to support this assertion. Importantly, there is minimal, if any, entry into the perispinal region that is thought to make any subsequent spinal fusion after growth has ceased much easier (Dr. Robert Campbell, personal communication). Unfortunately, there is a paucity of pulmonary function outcome data after insertion using either the growing rod or VEPTR.

Considerable controversy still exists over whether Harrington instrumentation improves lung function. A meta-analysis of 173 patients indicated a significant improvement of 2% to 11%.[146] The improvement may not be immediate, and there may be initial loss of vital capacity; however, the preoperative FVC is reached by 2-year follow-up.[147,148] Much of the variability in improvement in lung function may depend on at what point the intervention is performed. If performed after the curve is not correctible with traction, the likelihood of significant improvement is minimal; however, the patient may still benefit from preventing further progression of scoliosis and restriction.

Defects in Development of the Chest Wall Muscles

The chest wall is considered broadly as the respiratory pump and the structures bordering on the lungs, including the thorax, both inspiratory and expiratory musculature, and the abdominal wall. Congenital defects in the structure of the chest wall muscles can affect the function of the respiratory pump and the development of the lung.

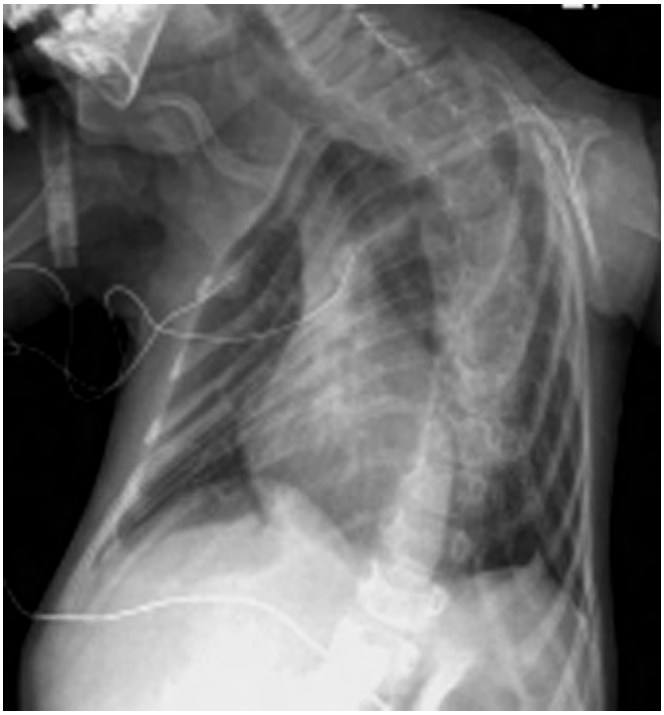
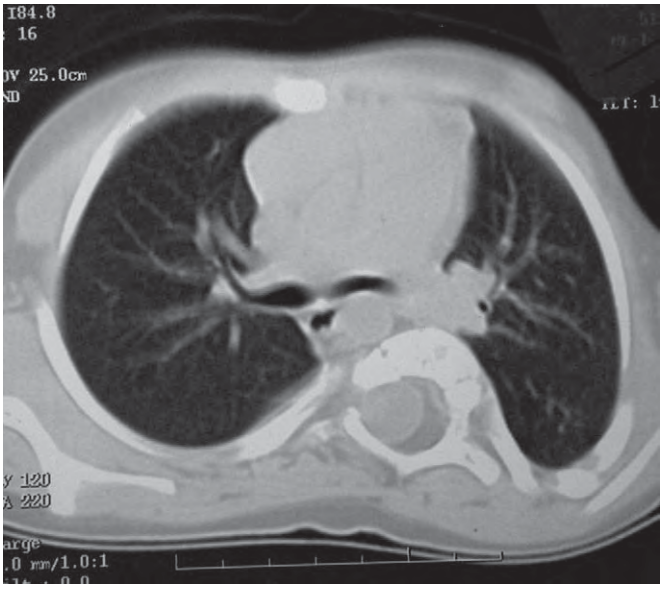


Figure 66-14 A chest radiograph of patient with spinal muscular atrophy type I (Werdnig-Hoffman disease) demonstrating the caudal collapse of the ribs due to intercostal muscle weakness. (Courtesy of Dr. Randall Betz.)



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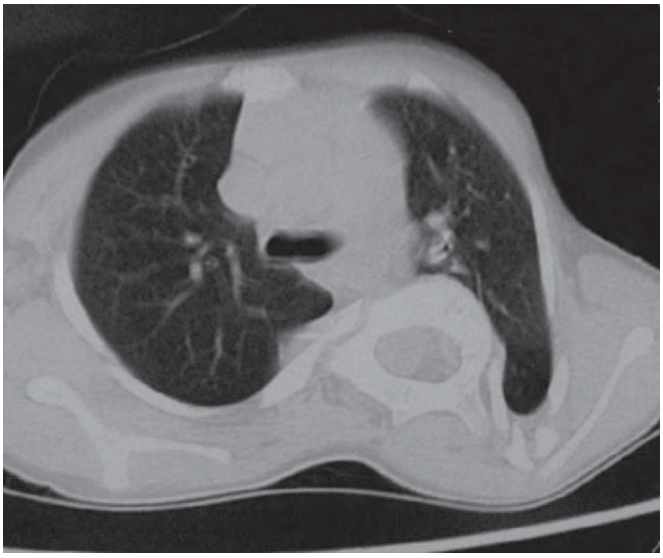

B

Figure 66-15 Chest CT scans at 2 years **(A)** and 7 years **(B)** of age demonstrating the progression of spinal rotation. (Courtesy of Dr. Robert Campbell.)

Congenital Diaphragmatic Hernia

Congenital diaphragmatic hernia (CDH) occurs in approximately 1 in 2500 live births,[149-151] and about 40% are associated with other congenital abnormalities (Table 66-3), including neural tube defects, cardiac anomalies, and skeletal, craniofacial, urinary, anterior abdominal wall, and other defects that may influence survival.[152,153] Of the 60% without other major congenital malformation, the magnitude of the pulmonary hypoplasia strongly influences survival.

The hernia defect is caused by a failure of the pleuroperitoneal canal to close during fetal development. Although the pulmonary hypoplasia has been attributed to mechanical compression from the herniated abdominal content, recent evidence suggests that there are a number of mesenchymal growth factors and signaling pathways that may be affected during diaphragm development.[154] These are believed to cause the abnormal branching pattern, which can leave the lung in the late canalicular or early saccular stage of development.[155] In fact, the contralateral lung itself is also smaller than normal.[155]

A number of investigators have studied lung function in school-age survivors of CDH. The data are remarkably consistent and demonstrate mild airway obstruction, normal total lung capacity, and some increase in RV/TLC ratios.[156-163] Although MIP is decreased (as would be expected), MEP is not significantly different from normal.[164] Of the flow measurements, $FEF_{25-75\%}$ is decreased proportionally to the perfusion defect[164] that probably reflects the developmental truncation of the vascular and airway tree. There is also bronchodilator sensitivity that may be due to the increased smooth muscle in the airways and small airway disease as part of the initial abnormality or as an iatrogenic effect from the early interventions and medical course.[164]

The status of the thoracic structures and the thoracic pump has not been extensively investigated. In one study of 25 subjects, there was a 46% incidence of pectus deformities and scoliosis.[164]

ABDOMINAL WALL DEFECTS (GASTROSCHISIS, OMPHALOCELE, PRUNE-BELLY SYNDROME)

The anterior abdominal wall is part of the respiratory muscle pump, and abdominal wall defects have potential influences on the developing lung. Omphalocele and gastroschisis occur in approximately 1 in 4000 to 5000 live-born children.[165] Prune-belly or Eagle-Barrett syndrome is less common and has absent or reduced abdominal wall musculature believed to be due to obstruction of the urinary outflow tract and

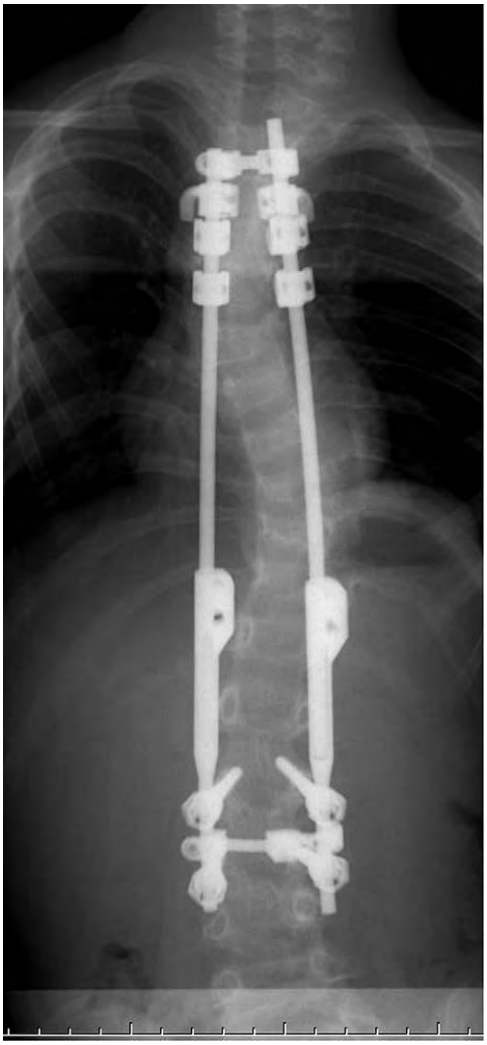

Figure 66-16 Bilateral growing rods. (Courtesy of Dr. Randall Betz.)

massive distention of the urinary tract and abdomen and abnormal mesenchymal development. Because of the increased abdominal compliance, these defects allow abdominal contents to extend beyond the usual borders of the anterior abdominal wall.

Mechanically, two problems can occur. With diaphragm contraction during inspiration, the abdominal contents will go outward more instead of serving as a "fulcrum" moving out the inferior rib cage. During forceful exhalation, there is less abdominal force generated to augment the passive recoil of the ribcage and maneuvers like coughing can be significantly compromised. In this situation, an abdominal binder can be useful.

Prune-belly syndrome presents a number of additional respiratory challenges. Some of these patients have generalized muscle weakness related to uremia and to corticosteroids administered following renal transplantation. As a result of the mechanical abnormalities, these patients have slightly reduced lung volumes, markedly reduced inspiratory and expiratory muscle strength, and impairment in exercise capacity.[166,167] The exercise impairment may be due to the marked thoracoabdominal asynchrony that occurs during exercise and may be related to abnormally large ribcage excursion during exercise.[166] Interpretation of tests of airway obstruction in these patients is difficult because expiratory muscle weakness probably contributes to reduced expiratory flow rates, particularly peak flow.

Patients with abdominal wall defects can have narrow chest walls, downslanting ribs, and reduced radiographic estimates of lung volume, suggesting a component of pulmonary hypoplasia. In fact, the radial alveolar count, an index of alveolar number, is reduced in children with giant omphaloceles as can be the lung weight–to–body weight ratio.[168]

Closure of abdominal wall defects presents both respiratory and cardiovascular challenges. Although the size of the entire coeloemic cavity has not been estimated in these conditions, the peritoneal cavity is thought to be small. Thus, when the defect is closed, abdominal pressure increases. This can be an advantage to the infant in that increased abdominal pressure may elevate and lengthen the diaphragm and decrease the radius of curvature, which puts the diaphragm at a more favorable length-tension relationship. Most artificial materials used to close the wall are nondistensible and skin is often under tension. Inspiration in these patients may be associated with large positive swings in intra-abdominal pressure, which may prevent venous return to the right side of the heart, compress the inferior vena cava, and impair cardiac output.

Lung function has been measured in some infants before and after surgical closure of abdominal wall defects. Lung volumes as measured by a forced deflation vital capacity maneuver were decreased by about 40%, and compliance of the respiratory system was reduced by about 50%, as might be expected.[169,170] In 18 adolescent patients who had a large omphalocele (>6 cm) or gastroschisis (>4 cm) repaired at birth, there was no abnormality in FVC or in cardiovascular function during exercise.[167] However, they reached their maximal heart rate sooner into exercise and had a lower maximal oxygen consumption than normal controls,[167] both of which were thought to be due to deconditioning.

NEUROMUSCULAR DISEASE

Classification of Neuromuscular Diseases

Although there are a wide variety of neuromuscular conditions with many different genetic and cellular etiologies, they are often unified by a morbidity and mortality due to respiratory failure (Table 66-4). This can result either from progressive chronic respiratory failure or from an acute event rapidly overwhelming the capacity of the respiratory system. Outside of the direct failure of the diaphragm or chest wall muscles, upper airway muscle failure, in particular the pharyngeal and laryngeal muscles, can also worsen respiratory dysfunction. Pharyngeal muscle weakness can lead to upper airway obstruction. The weakness can be exacerbated during sleep and add resistive load to the respiratory system. Laryngeal muscle weakness can decrease airway protection and put a patient at greater risk of aspiration. In addition, failure of the intercostal muscles can decrease thoracic support and cause a downward "collapse" of the ribs in a "Christmas tree" appearance (see Fig. 66-14), as in spinal muscular atrophy, or can lead to scoliosis if the weakness is asymmetric.

Table 66-3
Congenital Diaphragmatic Hernia with Respiratory Complications, Inheritance Pattern, and Genetic Abnormality

Syndrome	Major Findings	Thoracic Involvement	Respiratory Complications	Inheritance Pattern	Gene/Chromosome
Fryns	Large size; coarse face; digital and nail hypoplasia; heart and renal malformations	Diaphragmatic hernia (common)	Pulmonary hypoplasia	Autosomal recessive	Unknown
Donnai-Barrow	Hypertelorism, iris coloboma; agenesis of corpus callosum, omphalocele	Diaphragmatic hernia (common)	Pulmonary hypoplasia	Autosomal recessive	*LRP2*
Apert	Craniosynostosis, syndactyly; heart defect	Diaphragmatic hernia; anomalous tracheal cartilage	More likely from tracheal sleeve or choanal atresia/stenosis	Autosomal dominant; usually de novo mutation	*FGFR2* (one of two specific mutations)
Pallister-Killian	Coarse face; high anterior hairline; tall forehead	Diaphragmatic hernia		De novo	Mosaic tetrasomy 12p (in skin fibroblasts)
Craniofrontonasal dysplasia	Hypertelorism; craniosynostosis	Diaphragmatic hernia Pectus excavatum Clavicular pseudarthrosis		X-linked; females more severely affected	Ephrin B1
De Lange	Small stature, microcephaly; phocomelia; arched eyebrows with synophrys	Diaphragmatic hernia		Autosomal dominant	*NIPBL*
Wolf-Hirschhorn	Small stature, microcephaly, prominent glabella, cleft lip; coloboma; heart defect	Diaphragmatic hernia	Pulmonary isomerism	Chromosome deletion	Deletion 4p16.3
Chromosome anomalies	Intrauterine growth retardation; multiple congenital anomalies	Diaphragmatic hernia;		Unbalanced chromosome anomaly	Multiple, including trisomy 13, 18

Data from Slavotinek AM: Fryns syndrome: A review of the phenotype and diagnostic guidelines. Am J Med Genet 124A:427-433, 2004; Schinzel A: Tetrasomy 12p (Pallister-Killian syndrome). J Med Genet 28:122-125, 1991; Gripp KW, Donnai D, Clericuzio CL, et al: Diaphragmatic hernia-exomphalos-hypertelorism syndrome: A new case and further evidence of autosomal recessive inheritance. Am J Med Genet 68:441-444, 1997; Neri G, Gurrieri F, Zanni G, et al: Clinical and molecular aspects of the Simpson-Golabi-Behmel syndrome. Am J Med Genet 79:279-283, 1998; Tachdjian G, Fondacci C, Tapia S, et al: The Wolf-Hirschhorn syndrome in fetuses. Clin Genet 42:281-287, 1992; Wieland I, Jakubiczka S, Muschke P, et al: Mutations of the ephrin-B1 gene cause craniofrontonasal syndrome. Am J Hum Genet 74:1209-1215, 2004; Jelsema RD, Isada NB, Kazzi NJ, et al: Prenatal diagnosis of congenital diaphragmatic hernia not amenable to prenatal or neonatal repair: Brachmann-de Lange syndrome. Am J Med Genet 47:1022-1023, 1993; and Wilkie AOM, Slaney SF, Oldridge M, et al: Apert syndrome results from localized mutations of FGFR2 and is allelic with Crouzon syndrome. Nat Genet 9:165-172, 1995.
Additional references: http://www.geneclinics.org and http://www.ncbi.nlm.nih.gov.

Both thoracic defects will further add to the load on the respiratory system.

Neuromuscular disease can be localized anywhere from the corticospinal tract to the peripheral nervous system and the myoneural junction to the muscle itself.

The effects on the respiratory tract depend not only on the nature and location of the abnormality but also on whether it is acute or chronic. In general, lower motor neuron, myopathic lesions, and acute neurologic illness cause flaccid muscles and poor chest wall stabilization. However, upper motor neuron or cortical lesions and chronic neurologic illness often increase muscle tone and cause less mobile chest wall ligaments and joints. Although this stiffness can be treated or prevented to an extent with aggressive physical therapy to maintain range of motion, pharmacologic therapy with muscle relaxants is a common adjunct.

Spinal cord trauma is one example of the importance of lesion location. The respiratory effects of low thoracic cord lesions are minimal, although cough and forced expiratory maneuvers that rely on activation of abdominal wall muscles may be impaired. In high thoracic cord lesions, intercostal muscles are affected, causing breathing to be purely from the diaphragm. High cervical cord lesions (C3-5) affect the intercostal muscles and the phrenic nerve and diaphragm; therefore, patients with these lesions cannot breathe independently.

Pathophysiology

ALTERATIONS OF LUNG FUNCTION IN NEUROMUSCULAR DISEASE

Total lung capacity (TLC) and vital capacity (VC) may be normal in mild neuromuscular disease but are reduced in moderate to severe disease. The reductions in TLC and VC are caused by inspiratory and expiratory muscle weakness, scoliosis, and decreased lung and chest wall compliance due to a progressive decrease in lung and chest wall expansion.[169] RV may be normal or elevated as a result of expiratory muscle weakness. Therefore, an elevated RV/TLC ratio in patients with neuromuscular disease is not usually due to air trapping as is the case in obstructive lung disease.

Maximal expiratory flow rates in patients with neuromuscular disease are usually diminished as a consequence of both low lung volumes and decreased expiratory muscle strength, because both lung volume and driving force can impact maximal flow. Furthermore, patients with neuromuscular disease often have a characteristic shape of the flow-volume curve at low lung volumes, with a precipitous decrease in flows before reaching RV[171] rather than a linear decrease through lower lung volumes. This phenomenon is a result of the diminished ability of the expiratory muscles to overcome the outward recoil of the chest wall. As is the case in most

Table 66-4
Neuromuscular and Chest Wall Disorders, Their Thoracic and Respiratory Presentation, Inheritance Pattern, and Genetic Abnormality

Category	Disorder	Major Findings	Inheritance Pattern	Gene	Mutation
Muscular dystrophies	Dystrophinopathies: Duchenne	Progressive symmetric muscular weakness, proximal greater than distals, present before age 5 years Wheelchair dependency before age 13 years	X-linked	*DMD*	Multiple; lack of dystrophin expression
Muscular dystrophies	Dystrophinopathies: Becker	Progressive symmetric muscle weakness and atrophy, proximal greater than distal Activity-induced cramping (present in some individuals) Wheelchair dependency after 16 years of age	X-linked	*DMD*	Multiple; abnormal quality or quantity of dystrophin
Muscular dystrophies	Limb girdle MD: sarcoglycanopathies	Proximal limb weakness	Autosomal recessive	*SGCA* *SGCB* *SGCG* *SGCA*	R77C; Multiple Multiple Multiple Multiple
Muscular dystrophies	Limb girdle MD: calpainopathy	Proximal limb weakness	Autosomal recessive	*CAPN3*	Loss of function by multiple different mutations
Muscular dystrophies	Limb girdle MD: dysferlinopathy	Proximal limb weakness	Autosomal recessive	*DYSF*	Loss of function by multiple different mutations
Muscular dystrophies	Limb girdle MD	Proximal limb weakness	Autosomal dominant	*TTID* *LMNA* *CAV3*	Missense
Muscular dystrophies	Emery-Dreifuss	Joint contractures Muscle weakness Cardiac involvement	X-linked	*EMD*	Multiple null mutations; missense may cause milder phenotype
Muscular dystrophies	Emery-Dreifuss	Joint contractures Muscle weakness Tachyarrhythmia, dilated cardiomyopathy	Autosomal dominant	*LMNA*	Multiple missense
Muscular dystrophies	Facioscapulohumeral	Progressive muscle weakness of face, scapular stabilizers, upper arm, lower leg, and hip girdle	Autosomal dominant	D4Z4 (3.3-kb DNA repeat motif)	Deletion
Congenital and metabolic myopathies	Central core disease	Congenital myopathy; central cores on muscle biopsy	Autosomal dominant (autosomal recessive rare)	*RYR1*	Multiple missense
Congenital and metabolic myopathies	Nemaline rod myopathy	Congenital myopathy, progressive; rod-like structures in muscle fibers on biopsy	Autosomal dominant and autosomal recessive	*ACTA1* *TNNT1* *TPM2* *TPM3* *NEB*	Heterozygous missense; compound heterozygotes may show severe form
Mitochondrial disorders	Kearns-Sayre	Pigmentary retinopathy, muscle weakness, external ophthalmoplegia, cardiac conduction block, cerebellar ataxia	Maternally inherited, through mitochondrial DNA		mtDNA deletions (1.3-10 kb)
	MELAS	Mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes	Maternally inherited, through mitochondrial DNA	*MTTL1* *MTTQ* *MTTH* *MTTK* *MTTS1* *MTND1* *MTND5* *MTND6*	Point mutations
	MERRF	Myoclonus epilepsy associated with ragged-red fibers; myopathy	Maternally inherited, through mitochondrial DNA	*MTTK,* others as in MELAS	Point mutations

Continued

Table 66-4
Neuromuscular and Chest Wall Disorders, Their Thoracic and Respiratory Presentation, Inheritance Pattern, and Genetic Abnormality—cont'd

Category	Disorder	Major Findings	Inheritance Pattern	Gene	Mutation
Myotonic dystrophy	Thomsen disease	Myotonia; except in congenital form with hypotonia	Autosomal-dominant	*DMPK* (rarely *CLCN1*)	CTG expansion Normal: 5 to 27 copies Affected, Mild: 50-80 repeats Adult onset: 100-500 repeats Congenital: 500-2000 repeats (heterozygous CLCN1 mutations)
Channelopathies	Myotonia congenita: Becker disease	Myotonia	Autosomal recessive	*CLCN1*	Homozygous mutations
Spinal muscular atrophies	Types 0-IV	Progressive muscle weakness, onset from prenatal to adulthood	Autosomal recessive	*SMN1* (*SMN2* dosages impacts on type)	95% homozygous partial gene deletions; 5% compound heterozygote for deletion and point mutation

Additional references: http://www.geneclinics.org and http://www.ncbi.nlm.nih.gov.

restrictive lung disease, the FEV_1/FVC ratio is normal in patients with neuromuscular disease.

Lung compliance is reduced in patients with neuromuscular disease,[172] whereas specific compliance is usually normal.[173] This suggests that the decreased compliance is due to loss of lung units or alveolar number as opposed to an alteration of the tissue properties of the lung.

RESPIRATORY MUSCLE STRENGTH

Maximal inspiratory and expiratory pressures are reduced in patients with neuromuscular disease.[169,174,175] The degree of reduction does not seem to correlate with the reduction in general skeletal muscle strength.[174] Respiratory muscle strength is related, however, to the distribution of general muscle weakness, tending to be more severe in patients with proximal muscle weakness and less severe in patients with mainly peripheral muscle weakness.[171]

CHEST WALL ALTERATIONS

Infants and young children with neuromuscular disease often have a highly compliant chest wall,[176] although most adults with neuromuscular disease will have *reduced* chest wall compliance.[174] This suggests that intact muscle function is necessary for the development of normal intrinsic chest wall stiffness but that, with time, long-term diminished tidal chest wall excursions lead to costovertebral joint contractures and poor chest wall compliance.

CONTROL OF BREATHING

Patients with neuromuscular disease may have abnormalities of the respiratory control center as a primary or secondary event. Clearly, brainstem abnormalities can directly affect respiratory control and cause diminished ventilatory responses to hypercarbia and hypoxia, central and obstructive apnea, and excessive periodic breathing. As is the case with chronic lung disease of any sort, long-standing CO_2 retention can reset the respiratory control center to a higher CO_2 level and diminish the hypercarbic response. Furthermore, the chronic metabolic alkalosis compensating for long-standing CO_2 retention can blunt respiratory drive in response to increasing CO_2 levels by buffering hydrogen ion and reducing acidosis.

Whether patients with neuromuscular disease that is *not* of central origin, such as myopathies, have disordered control of breathing is difficult to ascertain, because most tests of respiratory control depend on intact respiratory system mechanics and muscle strength. For example, assessing the change in minute ventilation during CO_2 rebreathing assumes that such ventilatory changes are not limited by the mechanics of the system, an assumption that is not true in the presence of severe restrictive chest wall disease and muscle weakness. To overcome this limitation, the P_{100} has been suggested as a good index of respiratory drive in patients with lung mechanic abnormalities. By assessing the mouth pressure response to the first 100 milliseconds of an inspiratory occlusion, patients with neuromuscular disease can presumably reach normal values despite respiratory muscle weakness because the normal value of P_{100} (about 2 cm H_2O in adults) is well below the maximal pressures that can be generated by most patients with neuromuscular disease. Although few studies have been reported, it appears the patients with neuromuscular disease have normal P_{100} values, indicating intact respiratory drive.[177,178]

ABNORMALITIES OF COUGH IN PATIENTS WITH NEUROMUSCULAR DISEASE

A major factor predisposing to recurrent pneumonia in patients with neuromuscular disease is an ineffective cough due to weak inspiratory muscles, poor glottic closure, and weak abdominal and thoracic expiratory muscles. Patients with low thoracolumbar cord lesions and paraplegia can still maintain a fairly effective cough because of intact abdominal muscle strength. Patients with tetraplegia can use the clavicular head of the pectoralis major as a muscle of forced expira-

tion and often unconsciously adopt these muscles for coughing.[179]

Approach to the Patient with Neuromuscular Disease

In taking a history from a patient with neuromuscular disease, it is important to ask about chronic or recurrent pneumonias, gastroesophageal reflux, aspiration of secretions, snoring, and symptoms of sleep hypoventilation and obstructive sleep apnea such as morning headaches and daytime somnolence. Seizure control is important because uncontrolled seizures may predispose to aspiration pneumonias.

On physical examination, the spine should be carefully assessed for scoliosis as a possible contributing cause to lung dysfunction. Signs of cor pulmonale should be evaluated and the patient should be examined for clubbing as an indication of bronchiectasis from recurrent suppurative lung infections.

Pulmonary function tests including lung volumes and maximal inspiratory and expiratsory pressures should be performed on all patients who can do them. Chest radiographs and assessment of oxygenation and ventilation by arterial blood gas analysis, pulse oximetry, end tidal CO_2 measurement, and serum bicarbonate (as an index of the chronic CO_2 retention) should be done. A modified barium swallow, with a feeding specialist, to evaluate swallowing function and gastrointestinal anatomy and gastroesophageal reflux studies (scintiscan or pH probe) should be done in patients with histories suggestive of aspiration. Sleeping pulse oximetry or more formal polysomnography should be done in patients with histories suggestive of sleep apnea or in those at risk of sleep hypoventilation by virtue of marginal lung function (VC less than 50%, FEV_1 less than 40% of predicted). This can be a very valuable screening tool since the compensatory mechanisms that patients with neuromuscular disease develop to overcome their mechanical abnormalities may not be present or will be compromised during REM sleep. Electrocardiography and echocardiography should be done in all patients with baseline or sleeping hypoxemia to evaluate for the presence of cor pulmonale.

Respiratory Complications of Neuromuscular Disease and Their Treatments

POOR AIRWAY CLEARANCE

Poor lower airway clearance due to an ineffective cough puts patients with neuromuscular disease at increased risk of pneumonia. Once secretions have entered the lower respiratory tract, many patients are unable to clear them effectively and lower respiratory tract infections occur. In addition to standard airway clearance therapy with manual percussion with postural drainage and oropharyngeal suctioning, there are a number of other assisted airway clearance therapies available to compensate for inadequate cough.

A cough involves a deep inspiration, with a brief glottic closure during early exhalation, followed by glottic opening with explosive expiratory flow.[180] Each of these three phases can be abnormal in patients with neuromuscular disease.

Inspiration can be augmented by breath stacking with a mask with a one-way valve, glossopharyngeal breathing, manual insufflation, and using a mechanical insufflator.[181-183] This will increase elastic recoil pressure that can be used to augment exhalation.

There is no way to recreate the effect of glottic closure in patients with bulbar dysfunction or pharyngeal weakness.

Exhalation can be augmented manually with abdominal thrusts or compressions[78] or by applying negative pressure at the airway opening using a mechanical exsufflator.[182-184] Manual cough assistance can be challenging in patients with scoliosis or extremity contractures that can block access to the abdomen.[184] Exsufflation pressures above −40 cm H_2O may cause upper airway narrowing, especially in the younger patient or those with pharyngeal hypotonia. Together, mechanical insufflation and exhalation has been used successfully with pressures of up to +40 cm H_2O for insufflation and −50 cm H_2O for exsufflation in pediatric patients with neuromuscular disease.[185] Mechanical insufflation and exsufflation can be delivered through a mouthpiece, face mask, or endotracheal or tracheostomy tube, depending on the patient's situation.

Other alternatives to improve peripheral airway clearance include high-frequency chest wall oscillation (HFCWO) and intrapulmonary percussive ventilation (IPV). HFCWO is commonly used in patients with cystic fibrosis to decrease the viscosity of mucus and to shear it from airway walls, while the patient expels it with a cough or deep breathing maneuver. Although the inadequate cough in a patient with neuromuscular disease may limit its utility in this population, it has been successfully used in patients with quadriplegic cerebral palsy.[186]

IPV delivers small pulses of air at high frequency and variable pressures, with an aerosolized solution with saline or a bronchodilator delivered at the same time. IPV has been used successfully in pediatric patients with a variety of different neuromuscular conditions irrespective of their ability to cough.[56,187-189]

RECURRENT PNEUMONIA

Recurrent pneumonias are a common cause of morbidity in patients with neuromuscular disease. Other risk factors include aspiration due to excessive secretions, poor laryngeal-pharyngeal clearance, poor recognition, and poor airways clearance. Patients with a significant central nervous system dysfunction may have hypersalivation and be unable to properly recognize and clear upper airway secretions. Therefore, there can be an unfortunate combination of excessive volume and ineffective clearance that puts one at risk of aspiration.

Antibiotic coverage should include anaerobic oropharyngeal organisms in addition to gram-positive organisms (clindamycin, amoxicillin-clavulanic acid). For patients with a history of prolonged endotracheal intubation or tracheostomy, current or previous, coverage for *Pseudomonas aeruginosa* should be added. Finally, patients with neuromuscular disease are also susceptible to community-acquired organisms. For patients with recurrent aspiration, antibiotics to treat common anaerobic mouth organisms can be given either intermittently or prophylactically to prevent aspiration pneumonia.

In addition to antibiotic therapy appropriate to known or suspected pathogen, patients should get augmented airway clearance via manual chest physiotherapy or a raised volume device such as an intermittent positive breathing device or a

cough assistance device. These therapies can be used both on a prophylactic basis and in an acute care setting. Mucolytic agents such as dornase-α, hypertonic saline (3% or 6%), and acetylcysteine have been used clinically to help clear thick mucus in patients with recurrent or chronic pneumonia.

Inhaled β-agonist bronchodilators are of questionable utility in patients with neuromuscular disease without a coincident history of asthma, but they may be useful in combination with chest physical therapy, especially in the setting of acute atelectasis. They can also improve mucocilary clearance by increasing the ciliary beat frequency. CPAP or invasive or noninvasive mechanical ventilation can also be useful, both in compensating for the added load on the respiratory system from the infection and in augmenting airway clearance and providing distending pressure to maintain airway patency through a greater portion of the respiratory cycle.

SWALLOWING DYSFUNCTION AND GASTROESOPHAGEAL REFLUX

Aspiration is a major cause of recurrent pneumonia in patients with neuromuscular disease. Swallowing is a complicated mechanism involving precise timing between various pharyngeal, laryngeal, and esophageal muscles. Damage to any of these muscles or the neural pathways that support them can have a major impact on swallowing function. In brainstem or cortical injury, there may be little or no swallowing function due to the absence of proper neural signaling and coordination. With a more peripheral myopathy, swallowing dysfunction may not occur until much later in disease progression; however, swallowing efficiency may be impacted as patients have difficulty safely taking in enough calories to meet their nutritional needs.[190]

A speech therapy consultation may identify food textures that are not aspirated and modes of swallowing that can compensate for the abnormal swallow mechanism and can enable the patient to take at least part of his or her daily caloric intake by the oral route.[190] If this does not work, then a gastrostomy tube to bypass the oropharynx can be useful.

Although a tracheostomy tube with the cuff inflated can bypass upper airway obstruction and provide a reliable interface for mechanical ventilation, it does not prevent aspiration. In fact, a tracheostomy can interfere with normal swallowing function and may increase the risk of aspiration,[191,192] perhaps by fixing tracheal position and preventing closure of the airway by the epiglottis.

For a patient with or at risk of swallowing dysfunction, it is important to minimize the volume of secretions around the glottis. Upper airway secretions from rhinitis or sinus drainage can be treated effectively with decongestant and antihistamine therapy. Hypersalivation can be treated effectively on a temporary basis with anticholinergic therapy using glycopyrollate or scopolamine,[193,194] and botulinum toxin injections of specific salivary glands.[195,196] Salivary gland duct ligation and denervation can be used for patients in whom pharmacotherapy has been ineffective,[197,198] but these procedures are irreversible. The risk of any of these interventions is overdrying secretions, which can put patients with tracheostomy tubes at higher risk of airway occlusion.

For reasons incompletely understood, the prevalence of gastroesophageal reflux (GER) is higher in patients with neuromuscular disease than in the general population. In patients with cortical dysfunction, some have proposed a link between spasticity and increased intra-abdominal pressure exacerbating GER, while esophageal dysmotility and decreased upper esophageal sphincter tone can also contribute. GER is treated with motility agents such as metoclopramide or bethanechol and antacids including both H_2-receptor antagonists and proton pump inhibitors. If medical management fails, fundoplication may be performed, although the success can be compromised in patients with seizure activity or tonic-clonic activity with intermittent increases in abdominal pressure. Fundoplication may also exacerbate swallowing dysfunction if the lower esophageal sphincter is wrapped too tightly.

RESPIRATORY FAILURE

Chronic respiratory failure is the hallmark and a unifying factor among the progressive neuromuscular disorders. The level of respiratory muscle fatigue in patients with neuromuscular disease is the balance between respiratory muscle strength and the resistive and elastic load on the respiratory system. Fatigue occurs in patients with normal respiratory muscle strength when increased elastic or resistive respiratory loads are great. In patients with neuromuscular disease, modestly increased elastic loads from scoliosis and chronic pulmonary fibrosis secondary to chronic aspiration, recurrent pneumonias, and other conditions may produce fatigue.

Nocturnal ventilatory support can enhance the quality of life in many patients with nighttime hypoxemia and hypercarbia. Supplemental oxygen by nasal cannula may suffice in patients with hypoxemia caused by chronic lung disease without hypercarbia. The physiology of chronic respiratory muscle fatigue and its treatment with respiratory muscle rest are discussed earlier in this chapter.

Noninvasive ventilation has been used for over 60 years to treat chronic respiratory form neuromuscular disease. Although modern versions of the Drinker and Emerson tank ventilator "iron lung" are available today to provide negative pressure ventilation, negative pressure cannot be used in patients with upper airway obstruction. The vast majority of patients using noninvasive ventilation use positive pressure ventilation via nasal, oral, or oronasal interfaces. Although the available bilevel positive airway pressure units were originally developed for adult use, there are a number of interfaces that can be used effectively in pediatric patients.

Once the need for noninvasive ventilation extends well into the daytime hours, chronic invasive ventilation via tracheostomy tube can be useful. This is a decision that is predicated on a number of issues. The first issue is how well the ventilator and interface is working for the patient. If the ventilator can adequately augment ventilation for a substantial portion of the day, and the skin underneath the interface remains intact, then there is no need to transition to invasive ventilation. However, with progression of the neuromuscular disease and/or decreased chest wall compliance, the noninvasive ventilator may not be able to assist ventilation with a high enough pressure to inflate the lungs adequately. The final, and perhaps most important, issue is the patient's and family's wishes. For many patients and family, invasive ventilation is an intervention that exceeds their own sense of propriety. Although for some families it is a value judgment, for others there may be a lack of understanding of what life with a tracheostomy means. With a properly sized tracheos-

tomy tube, patients can still vocalize, and this can be improved substantially by using a speaking valve, which allows air in through the tracheostomy tube, but exhalation around the tracheostomy tube and between the vocal cords.

In chronic respiratory failure there is often a compensatory metabolic alkalosis. When the P_{CO_2} is reduced by mechanical ventilation, chloride supplementation is often required in order to promote excretion of the retained HCO_3^-.

Acute respiratory failure usually occurs in the setting of acute pneumonia or increased mucus plugging and atelectasis, causing hypoxic respiratory failure with ventilation perfusion mismatch. Because of this, it is critical to aggressively treat these episodes with increased airway clearance therapy, antibiotics, and ventilatory support if indicated. Patients with marginally compensated respiratory muscle strength caused by underlying neuromuscular disease are also more likely to develop respiratory pump failure during an acute infection. Patients with general muscle weakness caused by myopathies often decompensate during intercurrent systemic illness, such as viral infections. The respiratory muscles are no exception, and even nonpulmonary infections can lead to respiratory failure in this setting.

COR PULMONALE

Cor pulmonale is a common end-stage complication of neuromuscular disease, and the genesis is multifactoral. An early sign of respiratory failure is nocturnal hypoxemia, which can cause pulmonary vasoconstriction and increased right heart strain. The severe scoliosis that can develop can cause restrictive disease and a decreased FRC. The decreased FRC may decrease further during REM sleep, when intercostal muscle tone decreases. Prolonged periods of breathing at low FRC can cause airway closure and atelectasis, both of which result in hypoxemia from low $\dot{V}/\dot{Q}$ ratios due to airway closure and a decreased surface area for diffusion. In addition, hypoventilation is common in neuromuscular disease. Furthermore, the abnormal upper airway muscle control of patients with neuromuscular disease can lead to upper airway obstruction during sleep.

NUTRITIONAL STATUS

Because of swallowing inefficiency, maintaining an adequate daily intake of calories for growth can be difficult. The actual caloric need in patients with progressive neuromuscular disease is controversial, with some suggesting a basal metabolic need less than that of an age- and weight-matched child due to the relative lack of muscle mass and inactivity. The clear risk in not providing enough calories is weakening the muscles further by not meeting the basic metabolic needs, and running the risk of decreasing muscle mass further. Conversely, an overweight child has the added burden of moving a heavier chest wall and fatiguing the respiratory muscles.

OTHER CONSIDERATIONS

Many of the general principles of the care of patients with neuromuscular disease have been outlined in a recent American Thoracic Society statement.[56] General supportive measures should be stressed. Influenza vaccine should be given annually, and patients should receive all routine immunizations, including *Haemophilus influenzae* vaccine, as well as pneumococcal vaccine. Giving the palivizumab vaccine for RSV prophylaxis remains controversial. Although there are not the same published data demonstrating efficacy in reducing the morbidity of RSV infection as with patients with bronchopulmonary dysplasia and congenital lung disease, many clinicians will use it in patients under 2 years of age with more severe conditions, such as SMA type 1 and nemaline rod myopathy. The enormous financial and psychological burdens of patients with chronic progressive neuromuscular disorders and their families are best addressed by a multidisciplinary approach, with collaboration among the treating primary and subspecialty physicians, nurses, physical therapists, nutritionists, and social workers.

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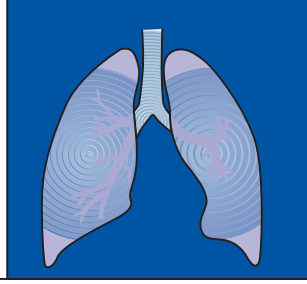

CHAPTER 67 Respiratory Ciliary Dysfunction

Jonathan Rutland, Lucy Morgan, and Robbert de Iongh

TEACHING POINTS

- Cilia line the respiratory tract (upper and lower) and form the basis for effective mucociliary clearance, a major component of the respiratory tract host defense system. Some other organs also have ciliated epithelium—some only in embryonic life.
- Ciliary structure and/or function may be defective, resulting in recurrent and chronic respiratory tract disease.
- Patients with defective cilia may develop a variety of clinical features—which correlate with the anatomical distribution of cilia throughout the body, including bronchitis, bronchiectasis, sinusitis, organ malrotation, and infertility.
- Primary ciliary dyskinesia is a rare cause of respiratory tract disease caused by a heterogeneous group of genetic disorders that are usually autosomal recessive.
- The diagnosis of primary ciliary dyskinesia may be suspected on the basis of clinical features and the results of measurements of mucociliary clearance and/or nasal nitric oxide, but ciliary ultrastructure and function studies are required for confirmation.
- There is no accepted specific therapy available for primary ciliary dyskinesia. Management is aimed at the treatment of respiratory tract infection and minimization of end organ damage based on the principles of treatment of other chronic respiratory tract diseases.

A relationship between abnormal ciliary function and respiratory disease was first suggested in the mid-1970s.[1,2] An association between bronchiectasis and situs inversus was first noted by Siewert[3] in 1904, but it was not until the 1930s that Kartagener reported a series of patients with sinusitis, situs inversus, and bronchiectasis.[4] In time this became known as Kartagener syndrome. The underlying pathogenesis was not known. In 1975, sperm immotility and absence of dynein arms in the axonemes of sperm from patients with Kartagener syndrome were reported,[5,6] thus linking male infertility with this syndrome. Subsequent studies of respiratory tract cilia (which have the same axonemal structure as sperm) revealed defective ciliary motility and deficient dynein arms.[1,2] Initially it was thought that these patients had immotile cilia and the term *immotile-cilia syndrome* was suggested.[7] Subsequent studies demonstrated a wide range of ciliary motility, ranging from complete absence to almost normal motility.[8,9] The ciliary motility in these patients was often noted to be uncoordinated or dyskinetic. The term *primary ciliary dyskinesia* (PCD) is now in wide use.[10]

A range of ultrastructural abnormalities of the ciliary axoneme has been found in patients with PCD. These cause defective ciliary function with resultant impairment of mucociliary clearance. Chronic and recurrent upper and lower respiratory tract disease result.

CILIARY STRUCTURE AND FUNCTION

Distribution of Human Cilia

Cilia are widely distributed throughout the animal kingdom. Throughout the phylogenetic tree, there is little variation in the ultrastructural features of motile cilia involved in the propulsion of mucus and water. These types of cilia have the characteristic 9 + 2 microtubular structure (see later) and are distributed in various organs, including the respiratory tract, oviduct, epididymis, and the ependymal lining of the brain ventricles (Fig. 67-1). There are also cilia with a 9 + 0 microtubular structure that occur transiently during development (embryonic nodal cilia) or on many cell types (e.g., corneal endothelium, thyroid epithelium, glia, neurons, chondrocytes, fibroblasts, and kidney cells) as rudimentary, primary, or monocilia cilia.[11,12] In photoreceptors, 9 + 0 cilia connect the outer and inner segments and, although not motile, they function in the transport of cellular materials (intraflagellar transport) between these parts of the cell. Cilia can also be specialized to act as receptors, as occurs in the olfactory epithelium. Whereas many of these cilia have poorly defined functions, there is increasing evidence that defects of these primary cilia are associated with a range of human diseases, such as polycystic kidney disease, hydrocephalus, forms of retinal degeneration, and Bardet-Biedl syndrome.[11-14] Moreover, the cilia that are present in the node during early embryonic development have a vortical beat pattern and have been implicated in regulating the orientation of the viscera and assignment of laterality (left-right symmetry) during development.[15,16]

Flagella, including sperm tails, have a similar internal structure (axoneme) to the 9 + 2 motile cilia.

Structure of Respiratory Cilia

When ciliated epithelium is adapted for mucus transport, as in the human respiratory tract, cilia are shorter and more numerous and beat mainly within a low-viscosity, periciliary fluid layer, moving a more viscous overlying mucus layer (see Fig. 67-1). The tips of the cilia enter the mucus layer only during the effective stroke and retract beneath the mucus

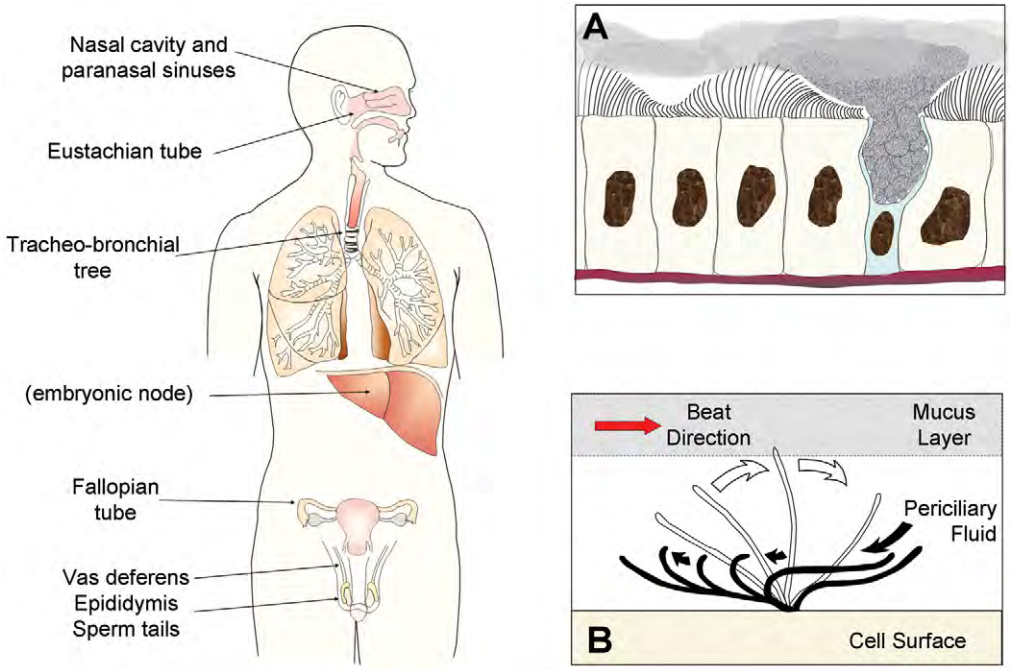

Figure 67-1 Distribution of ciliated organs. The tracheobronchial tree, nasal cavity, and paranasal sinuses are lined by pseudostratified ciliated epithelium, which functions in the clearance of inhaled particles, secretions, cellular debris, and bacterial products from the upper and lower respiratory tract. Ciliated cells are also present in the middle ear, eustachian tube, ependyma, male genital tract, and female genital tract. Other cells can express cilia transiently during embryogenesis. Cilia in the embryonic node are thought to regulate the situs of organs such as the heart and other viscera. **A,** Diagram of a portion of ciliated epithelium. Cilia on the surface of the epithelial cells beat rhythmically in a wavelike motion that moves the overlying mucus produced by the goblet cells within the epithelium and the subepithelial mucus glands. **B,** The beat cycle of a single cilium. The mucus is moved in the same direction as the effective stroke *(open arrows)*. The recovery stroke is shown by the *solid arrows*.

layer during the recovery stroke so that the mucus is moved in one direction only (see Fig. 67-1).

The human tracheobronchial tree is lined by pseudostratified, ciliated epithelium from the larynx down to the level of the terminal bronchiole (see Fig. 67-1). The nasal cavity (apart from its most anterior portion) and the paranasal sinuses are also lined by ciliated epithelium, the predominant direction of clearance being toward the oropharynx. Respiratory epithelium undergoes a continual turnover, with cells being replaced approximately once every 4 to 8 weeks.

Human respiratory tract ciliated cells bear 200 to 300 cilia on their surface. Cilia are elongated motile cylindrical projections from the apical cell membrane, approximately 0.25 μm in diameter, that contain microtubules and cytoplasm in continuity with that of the cell. Human tracheal cilia are 5 to 8 μm long, becoming shorter in more distal airways. Ultrastructural examination of a transverse section of a respiratory tract cilium (Fig. 67-2*B*,C) reveals that the axoneme consists of a characteristic 9 + 2 structure of nine pairs of microtubules (composed of the proteins, α- and β-tubulin) arranged around two single central microtubules that are surrounded and held together by the central sheath. The peripheral doublets are linked to neighboring doublets by fine filaments (nexin links) composed of a protein called nexin. Radial spokes are thicker filaments that project centrally from the "A" microtubule and end in a terminal knob, a short distance from the central sheath and central microtubules. Projecting at regular intervals from the "A" microtubule toward the "B" microtubule of the adjacent outer doublet are the inner and outer dynein arms, which are curved or hooklike filamentous structures. The dynein arms contain proteins with adenosine triphosphatase (ATPase) activity and, according to the sliding microtubule hypothesis of ciliary bending,[17] attach intermittently to the adjacent "B" microtubule, and change shape, with resultant sliding of doublets in relation to each other. Such a cyclical movement of different microtubule pairs in relation to each other causes ciliary bending, first in one direction and then in the other. The microtubules, radial spokes, and nexin links are considered to form a "skeletal" structure for the cilium. This confers properties of elasticity and rigidity on the cilium and may transfer bending forces through the cilium and help the cilium to resume its initial shape after each beat.

The peripheral doublets extend along the length of the cilium and, at the base, continue into the cell in a modified form, becoming triplets and, in association with several accessory structures, form a basal body. Striated or ciliary rootlets extend from the basal extremity of the basal body into the apical cytoplasm. Together with the basal body, they anchor the cilium and maintain the orientation of its direction of beating (see Fig. 67-2*A*). Projecting laterally from the basal body in the direction of the active stroke of the cilium is a structure called the basal foot (see Fig. 67-2*A*). All basal feet in a cell and in the whole epithelium are normally oriented in approximately the same direction,[18,19] so that the effective strokes of all cilia move in the same direction.

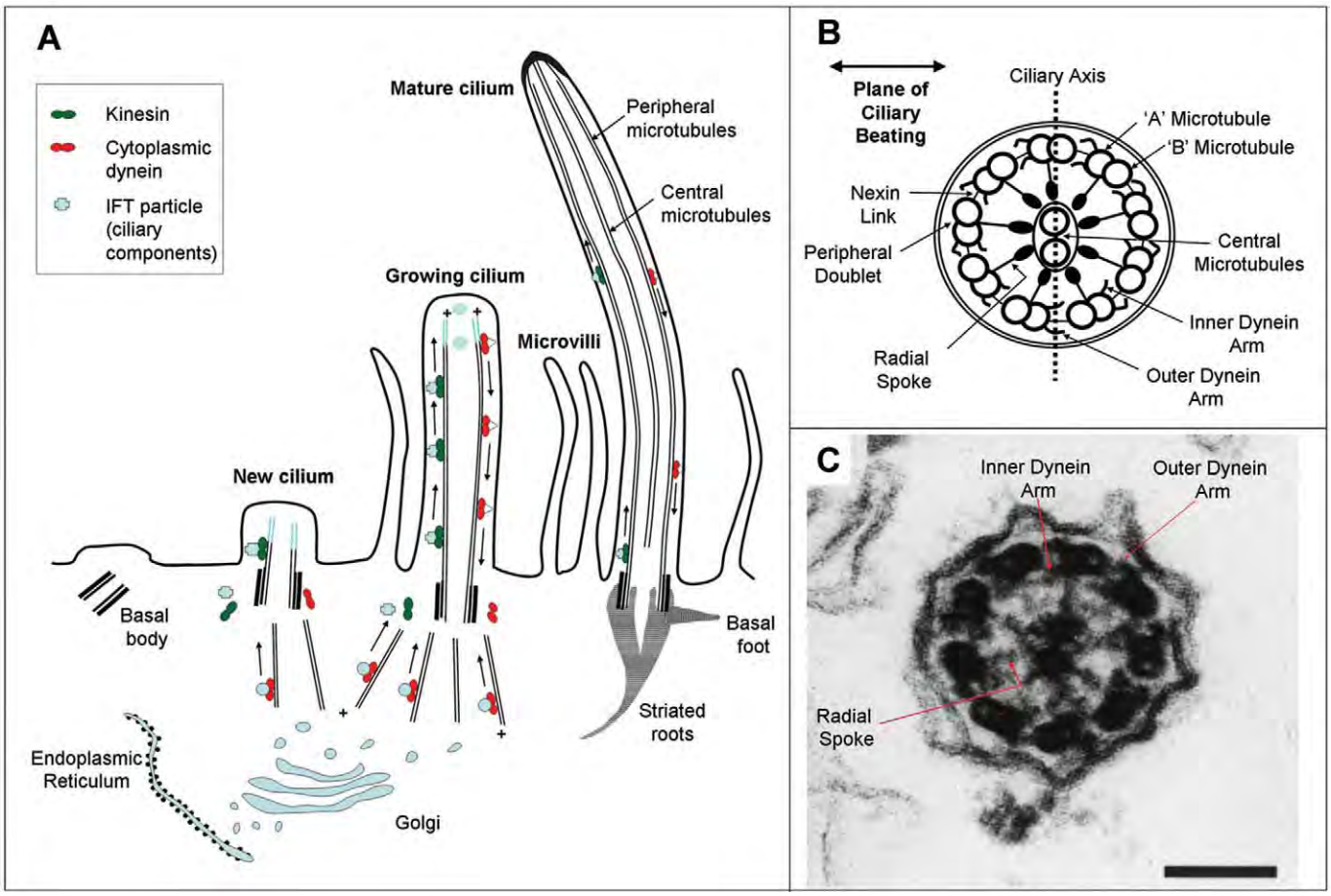

Figure 67-2 **A,** Ciliogenesis and model of intraflagellar transport (IFT). During ciliogenesis, a basal body is formed from centrioles and moves to the apical cytoplasm of the cell. Elongation of the cilium occurs by intraflagellar transport. Ciliary proteins, synthesized in the endoplasmic reticulum and processed by the Golgi complex, are transported in vesicles to the base of the cilium via cytoplasmic dynein complexes operating on microtubules. At the base of the cilium, proteins are processed and concentrated in IFT particles that are transported by kinesin II, interacting with the B tubule, to the tip of the flagellum. Kinesins move toward the plus end of the microtubules. At the tip kinesin II is inactivated and components of the axoneme are added to the growing tip. Cytoplasmic dynein, moving toward the minus end of the microtubules, carries particles back to the base of the cilium. These processes continue to maintain the mature cilium. The final stages of ciliogenesis involve the addition of the ancillary structures that anchor the cilium in the apical cytoplasm (basal foot and striated roots). **B,** Diagram of cilia in transverse section showing the organization of the axoneme. **C,** Electromicrograph of a cilium in transverse section showing normal axonemal structure. Inner and outer dynein arms and radial spokes are indicated. (Scale bar, 0.1 μm. Adapted from References 14, 18, 19, and 46.)

Much of the molecular regulation of ciliary beating has been elucidated from studies of the unicellular, diflagellate green alga *Chlamydomonas reinhardtii*, for which the flagella have been characterized biochemically, and there are numerous genetic mutants that have assisted in identifying genes involved in flagellar motility. From such studies, it is known that the axoneme consists of approximately 250 proteins,[20] and considerable information is available on the composition of the dynein arms and how mutations of the genes encoding these proteins affect flagellar motility.[21-23] Dynein arms, which generate ciliary motility, are large polypeptide assemblies, variably composed of different dynein chains, including 14 heavy (400-500 kDa), 7 intermediate (45-110 kDa), and 15 light (8-55 kDa) chains. Moreover, the outer and inner dynein arms have different compositions: the outer arms are composed consistently of three heavy, two intermediate, and eight light chains, whereas the inner dynein arms have a much more diverse composition of one or two heavy, two or three intermediate, and two or three light chains.[24]

The most recent findings indicate that each component of the axoneme plays a key role in regulating ciliary or flagellar motility. For instance, inner dynein arms are sufficient for generating bending, and together with the central microtubule apparatus and radial spokes determine the size and shape of the waveform, but outer dynein arms provide the power and increase the beat frequency.[22] Increasingly, studies are focussed at studying the roles of individual dynein isoforms in outer and inner dynein arms in regulating the beat cycle.[22,25] Many of the genes identified in *Chlamydomonas* have human homologs, and this has permitted translation of findings to human cilia and provided a basis for identifying mutations that cause ciliary dysfunction in humans (see later).

Physiology of Respiratory Cilia

Human nasal and tracheal cilia beat at a rate of approximately 10 to 15 Hz (600 to 900 beats/min). Each beat consists of two phases: an effective and a recovery stroke.[17] During the

effective stroke, the cilium is extended and moves rapidly around its point of attachment to the cell, extending into and engaging the overlying mucus, thus moving it forward. This is followed by a slower recovery stroke, when the cilium bends on itself and in a different plane to that of the effective stroke, retracting below the mucus layer, within the periciliary fluid, to resume its original position for a short resting phase before the next effective stroke (see Fig. 67-1*B*).

Ciliary beating is coordinated so that each cilium beats slightly later in the beat cycle than the one in front. This results in waves of coordinated beating (metachronal waves) that progress across a field of ciliated cells (see Fig. 67-1*A*). Control of the initiation of ciliary beating is thought to be regulated by calcium ion fluxes within the ciliated cell.[26-29] Two other factors that play a part in ciliary coordination are mechanical stimulation of ciliary activity (as may occur from foreign material) and hydrodynamic forces (which may influence nearby cilia).[17,30] Electric coupling of the cells via gap junctions allows for transmission of calcium fluxes throughout the epithelium.[26,31]

If ciliary beating is impaired or discoordinated, mucus transport is slowed. Effective clearance of mucus requires coordinated ciliary beating, the optimal physicochemical properties of mucus, and efficient interaction of the cilia with the overlying mucus layer. The direction of ciliary beating must be consistent, and the beat patterns must be coordinated and normal.

Ciliogenesis and Intraflagellar Transport

As cilia lack ribosomes, they do not have the machinery required for protein biosynthesis. Thus, all the components of the cilium need to be synthesized and often assembled in the cytoplasm before being transported into the cilium by a process called intraflagellar transport (IFT). The ciliary microtubules not only function in generating ciliary bending but also act as "highways" along which molecular motors, such as kinesin and dynein proteins, transport proteins and particles (see Fig. 67-2*A*). Kinesins and dyneins travel in different directions along the microtubules: kinesins travel toward the plus end of the microtubule and thus move cellular components towards the tip of the cilium (anterograde transport), whereas cytoplasmic dyneins travel toward the minus end of the microtubules and thus move cellular components toward the base of the cilium (retrograde transport).[32,33]

Ciliogenesis involves four stages: (1) formation of new centrioles in the cytoplasm, (2) migration of centrioles to the apical cytoplasm, (3) elongation of cilia, and (4) formation of basal body–associated structures (striated roots, transitional fibers, and the basal foot).[18] Cilium elongation is thought to be initiated at the basal body and involves IFT due to microtubular motors assembling on the outer microtubules of the basal body. The cycling transport (anterograde and retrograde) of particles along the microtubules allows for ciliary components to be added to and removed from the microtubule tips.[34] During ciliogenesis, the basal feet are randomly oriented, but as the ciliary beat cycle becomes established, the basal feet become oriented in the direction of the active stroke. It is thought that this reorientation is achieved by basal body rotation and involves the cytoskeleton in the apical cytoplasm.[35]

The importance of IFT for ciliary function in various cell types has been highlighted by the increasing number of diseases that have been associated with disruptions of IFT genes as well as studies showing that mutations of IFT genes result in phenotypes that model disease processes.[12,13,34,36,37] Thus far, the mutations detected, which have been associated with polycystic kidney, retinal degeneration, and Bardet-Biedl syndrome, appear to affect these processes in primary cilia, which are specialized for sensory function, rather than the motile cilia of the respiratory tract. However, mutations of several IFT genes, particularly kinesin genes (*Kif3a* and *Kif3b*), have also resulted in abnormalities of left-right symmetry (random situs of organs). It remains to be determined whether mutations of IFT genes have a role in PCD or Kartagener syndrome, particularly in patients with abnormal situs and normal ciliary motility or ciliary aplasia.

RECOGNIZED DEFECTS OF RESPIRATORY CILIA

Most patients with PCD have deficient dynein arms (inner, outer, or both). There is a wide spectrum of dynein arm defects, ranging from partial to complete absence (Fig. 67-3). Consistent with findings in *Chlamydomonas*, there are distinct correlations between defects of inner and outer dynein arms and ciliary motility in humans. There is a positive correlation of ciliary motility with the numbers of outer dynein arm numbers seen on electron microscopy but not with numbers of inner dynein arms, indicating that the outer dynein arms are essential for ciliary motility.[38] In patients in whom inner dynein arms are defective, in vitro measures of ciliary beat frequency can be normal but mucociliary clearance (MCC) is still abnormal, suggesting that, while outer dynein arms are sufficient to produce motility in an aqueous in vitro environment, they are ineffective under a mucus load.[38]

A number of other defects have been identified, such as radial spoke defects[39] (see Fig. 67-3*D*), absence of nexin links,[40] and microtubule translocation defects,[41] in which a peripheral doublet passes to the center of the axoneme to substitute for absent central tubules. Abnormal ciliary orientation has been identified in patients with PCD.[19,38,42-48] In some PCD patients, axonemal ultrastructure is normal, but ciliary orientation and/or ciliary function are not.[43,46,49-51]

Abnormally long[52] and short[53] cilia, complete ciliary aplasia,[54-56] abnormal basal bodies,[57] and axonemal cysts[58] have also been reported (Table 67-1). These ciliary structural abnormalities are suggestive of defects of IFT. However, to date, there are no studies reporting mutations of IFT genes in PCD patients with such defects.

CLINICAL FEATURES

Several excellent reviews have been written about the clinical features of PCD and their significance.[59-63]

Patients with PCD usually present with respiratory tract disease. The clinical features range widely in severity, extent, and time of onset (Fig. 67-4). Children may present with neonatal respiratory distress[64] or recurrent lower respiratory

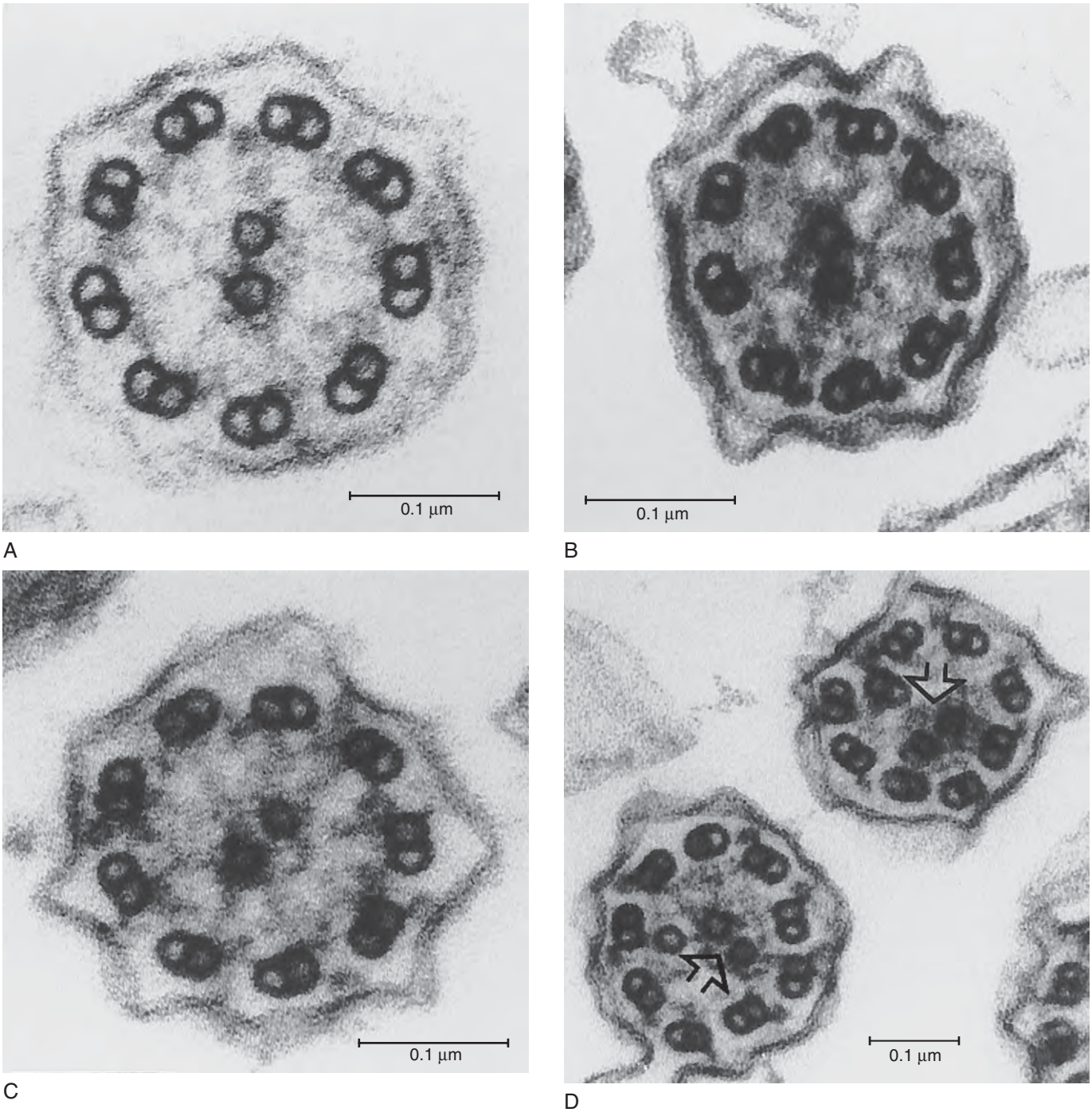

Figure 67-3 Electronmicrographs of ciliary profiles from four patients with primary ciliary dyskinesia, showing a range of dynein arm defects. **A,** Absence of inner and outer dynein arms; cilia from this patient had no motility. **B,** Absence of inner dynein arms; cilia from this patient had beat frequencies within the normal range. **C,** Absence of outer dynein arms; cilia from this patient had very low motility. **D,** Absence of inner dynein arms and radial spoke defects; cilia from this patient had grossly abnormal beat patterns and reduced beat frequencies. *Arrows* indicate eccentrically located central tubules, a feature of the radial spoke defect. (Adapted from de Iongh RU, Rutland J: Ciliary defects in healthy subjects, bronchiectasis, and primary ciliary dyskinesia. Am J Respir Crit Care Med 151:1559-1567, 1995.)

tract infections. These patients almost always have a chronic cough (often productive) as a result of recurrent and, later, chronic bronchitis. In many, this progresses over years to bronchiectasis. The symptoms and clinical findings in these patients are not different from those found in patients with bronchiectasis not caused by defective cilia and may include digital clubbing.

Upper respiratory tract infections are usual, with most patients having chronic sinusitis and recurrent otitis media.[65] Mucopurulent secretions are usually present in the nasal cavity, and nasal obstruction, rhinorrhea, postnasal drip, anosmia, and nasal polyps are common.

Males are almost always infertile; spermatozoa are present in normal numbers but usually have defective motility.

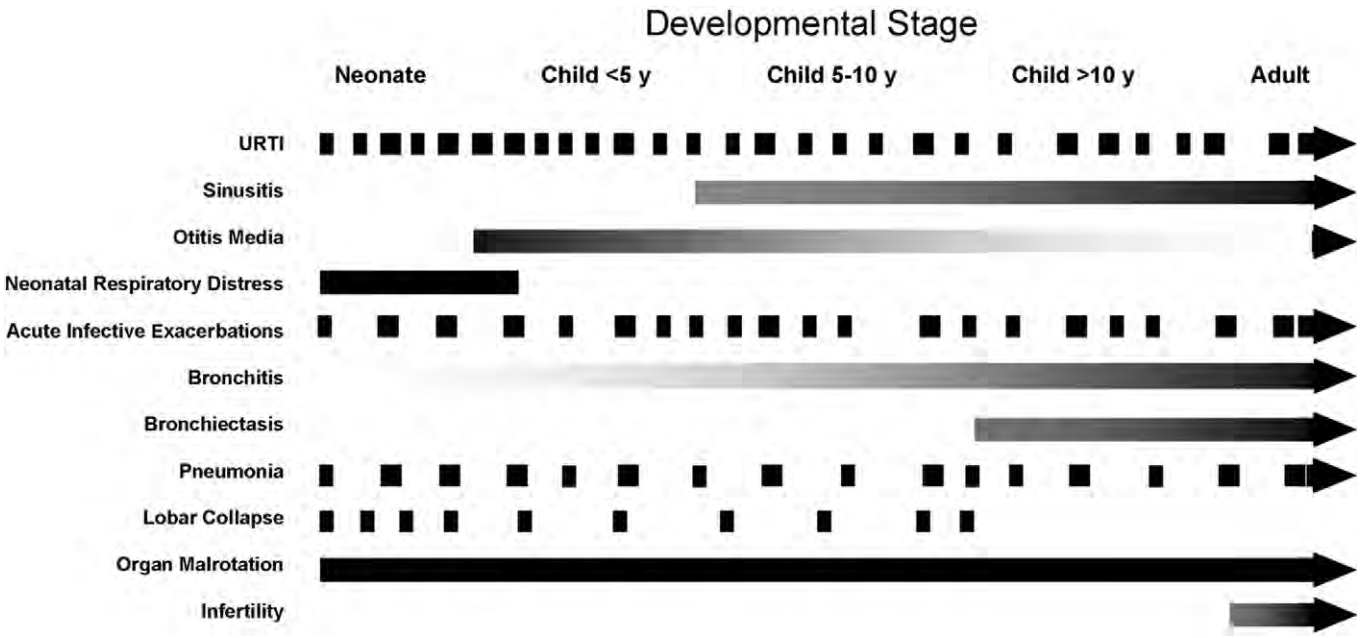

Figure 67-4 Schematic diagram of major clinical features seen in patients with PCD at varying ages. Some (e.g., acute infective exacerbations) occur intermittently, whereas some (e.g., bronchitis, bronchiectasis) develop with time. The presence of neonatal respiratory distress, lobar collapse, and/or organ malrotation should raise suspicion of possible PCD.

Females are usually fertile, despite possible impaired fallopian tube ciliary function.

Malrotation of internal viscera is common. Patients may have dextrocardia, abdominal situs inversus, or situs inversus totalis. Hydrocephalus[66,67] and biliary atresia[68,69] have been reported, but a causal link with PCD has not yet been clearly established.[63,70]

Radiographs of the paranasal sinuses often reveal mucosal thickening, opacification, or fluid levels. Chest radiographs may reveal changes consistent with bronchiectasis that can be imaged by high-resolution computed tomography scanning. When indicated, both rhinoscopy and bronchoscopy reveal excessive and often purulent secretions.

When measurements of MCC are available, this is always reduced. Other investigations of respiratory function reveal abnormalities of variable severity. These may include airway obstruction, gas trapping, and arterial hypoxemia.

Kartagener's original description[4] was of a triad consisting of chronic sinusitis, bronchiectasis, and situs inversus totalis (now commonly interpreted as the presence of any organ malrotation: dextrocardia or situs inversus viscerum). A study[59] of the clinical features of patients with recurrent respiratory tract disease caused by PCD compared with patients without PCD showed that although patients who manifested the triad were likely to have PCD (86%), the use of these criteria alone was an insufficient basis for suspecting PCD; of the patients with PCD, only 29% presented in this way. It is often not appreciated that most patients with PCD do not present with Kartagener syndrome. The diagnosis of PCD may be delayed despite the presence of sentinel symptoms,[71] and many patients are not diagnosed until adulthood. Delay in diagnosis may lead to poor outcomes such as learning and behavioral difficulties caused by deafness and inappropriate upper and lower respiratory tract surgery. In most patients, the respiratory disease progresses slowly. Prognosis is good and, for most affected subjects, life expectancy is normal.[62]

Table 67-1
Types of Ciliary Ultrastructural Defects Identified in PCD

	Ciliary Defect	Reference(s)
I	Dynein arm defects Inner dynein arms Outer dynein arms Inner and outer dynein arms	1, 2, 5-7
II	Radial spoke defect	39
III	Microtubule translocation defect	41
IV	Normal ultrastructure but impaired function	49-51
V	Random ciliary orientation	19, 23, 43-48
VI	Ciliary aplasia	33, 54, 56, 66
VII	Abnormally long cilia	52
VIII	Abnormally short cilia	53
IX	Abnormal basal bodies	57
X	Axonemal cysts	58

GENETICS

The estimated prevalence of PCD varies from 1 : 12,500 to 1 : 60,000, based on the assumption that PCD is at least twice as common as Kartagener syndrome.[72,73] It affects both sexes and has been found in all racial groups. Although the incidence appears to increase with consanguineous parentage, it is not affected by increased parental age. Cytogenetic studies generally show normal karyotypes.[73] Inheritance is predominantly autosomal recessive, although there are reports of autosomal dominant and X-linked modes of inheritance.[72,74]

PCD is a congenital defect, and the structural and functional abnormalities have been shown to be present in motile cilia from different tissues (nasal, tracheal, sinus, oviduct) and also to be similar in affected siblings. Although clinical findings are homogeneous, PCD appears to be caused by a group of heterogeneous genetic disorders, based on the observation of the various ultrastructural defects. Indeed, genome-wide scans and linkage analyses indicate that even within groups of patients with similar ultrastructural findings, there is significant heterogeneity of linked loci.[75] Proteomic analysis of human cilia[76] indicates that there are approximately 240 distinct polypeptides in the axoneme; thus, the potential for mutations to affect axonemal structure and function is large.

Two main approaches have been used to identify genes that cause PCD: (1) the candidate gene approach uses the known function of genes in animal models of ciliary function or laterality disorders, whereas (2) linkage studies investigate the association of numerous specific chromosomal markers with disease in PCD families. Despite the large number of genes involved in the axoneme and the numerous candidate genes and loci that appear to be associated with ciliary dysfunction or laterality defects in animals, mutations in only three genes—*DNAI1* (Online Mendelian Inheritance in Man [OMIM] 604366),[77] *DNAH5* (OMIM 603335),[78] and *DNAH11* (OMIM 603339)[79]—have thus far been shown to be responsible for ultrastructural defects of respiratory cilia in patients with PCD. Mutations in these genes, encoding intermediate and heavy chain dyneins, have been implicated in outer dynein arm deficiencies (including shortened and absent outer dynein arms) as well as situs inversus.[80-87] Linkage studies have identified numerous potential PCD loci at various chromosomal regions (4q, 5p, 6p, 8q, 10p, 11q, 13q, 15q, 16p, 17q, and 19q), but gene mutations causing PCD at these loci have not yet been identified.[72,88]

LEFT-RIGHT AXIS ASYMMETRY

Approximately 50% of patients with PCD have abnormal situs of the viscera and/or dextrocardia (Kartagener syndrome). In his original paper, Afzelius[2] proposed that motile cilia, present on cells of developing organs in the embryo, were responsible for positioning the organs during development and that the loss of motility of these cilia led to random organ positioning. Several studies have since shown that in the early mouse embryo (E7.5) cells in the node of the primitive streak, which is located in the posterior tip of the gastrulating embryo and is the major organizing center of the embryo, have single cilia[89,90] that project ventrally into the extracellular fluid. These nodal cilia have a vortical beat pattern and have been shown to generate an asymmetric leftward flow of extracellular fluid across the embryo.[15,89,91-93] The fluid is hypothesized to contain morphogens, which initiate the differential patterns of gene expression in the left and right sides of the embryo[94] that specify the left-right axis. This nodal flow model of left-right determination has recently been modified to incorporate cilia that act as mechanosensors of the nodal flow. It is proposed that these mechanosensory cilia transduce the flow generated by the nodal cilia and elicit cellular signals that contribute to the asymmetric signaling and gene expression between the left and right sides of the embryo.[95] While several genes have been identified in mouse models as having key roles in regulating nodal cilia and laterality, very few have been implicated in PCD/Kartagener syndrome.

DIAGNOSIS

The presence of PCD should be considered in all patients with recurrent or chronic lower and upper respiratory tract infections when no other cause, such as cystic fibrosis or immunodeficiency, has been demonstrated. A number of specialized investigations assist in establishing the diagnosis of PCD (Fig. 67-5).

Nitric Oxide

Studies of nitric oxide (NO) concentration in exhaled air have demonstrated a marked reduction in patients with PCD.[96-100] Reduced airway NO concentrations have also been demonstrated in cystic fibrosis[99-103] and in systemic sclerosis with pulmonary hypertension.[104] The use of nasal NO measurements (nNO) has proved far more discriminatory than exhaled NO. Nasal NO measurements (available in some specialized units) have been shown to be a reliable and noninvasive screening tool in PCD in children who are old enough to cooperate with the breath-hold required.[97-100] A nNO concentration greater than 250 ppb excludes the presence of PCD.[97,99] However, it should be noted that a low nNO concentration does not confirm the diagnosis of PCD. This must be done by studies of ciliary function and structure.

Mucociliary Clearance

Mucociliary clearance is abnormal in PCD and can be measured by the rate of clearance of an inhaled radiolabeled aerosol from the lung, or mucus transport rate of a marker can be measured directly in the respiratory tract. These specialized investigations are not widely available and have limited application in pediatric practice. Nasal MCC may be gauged with the saccharin technique[105-107] in older children. This involves placement of a small particle of saccharin (approximately 1 mm^3) on the inferior turbinate. The time taken for the particles to be carried posteriorly to the oropharynx, where they stimulate taste receptors, is measured as the nasal clearance time. This is normally less than 30 minutes.[106,107] Many factors affect the reliability of this technique and its usefulness is limited to that of a screening test. Mucociliary clearance is impaired in many respiratory diseases (such as cystic fibrosis, sinusitis, and postviral infections) and a finding of impaired MCC alone does not necessarily indicate the presence of a ciliary defect.

Ciliary Function

Suitable samples of ciliated epithelium may be obtained by mucosal brushing at bronchoscopy or rhinoscopy.[108] Ciliary beat frequency can be measured in vitro and has been shown to be correlated between the nasal cavity and lower respiratory tract.[109] The use of nasal mucosal brushings avoids the morbidity often associated with the use of nasal biopsy forceps and the requirement for local anesthesia. Ciliary

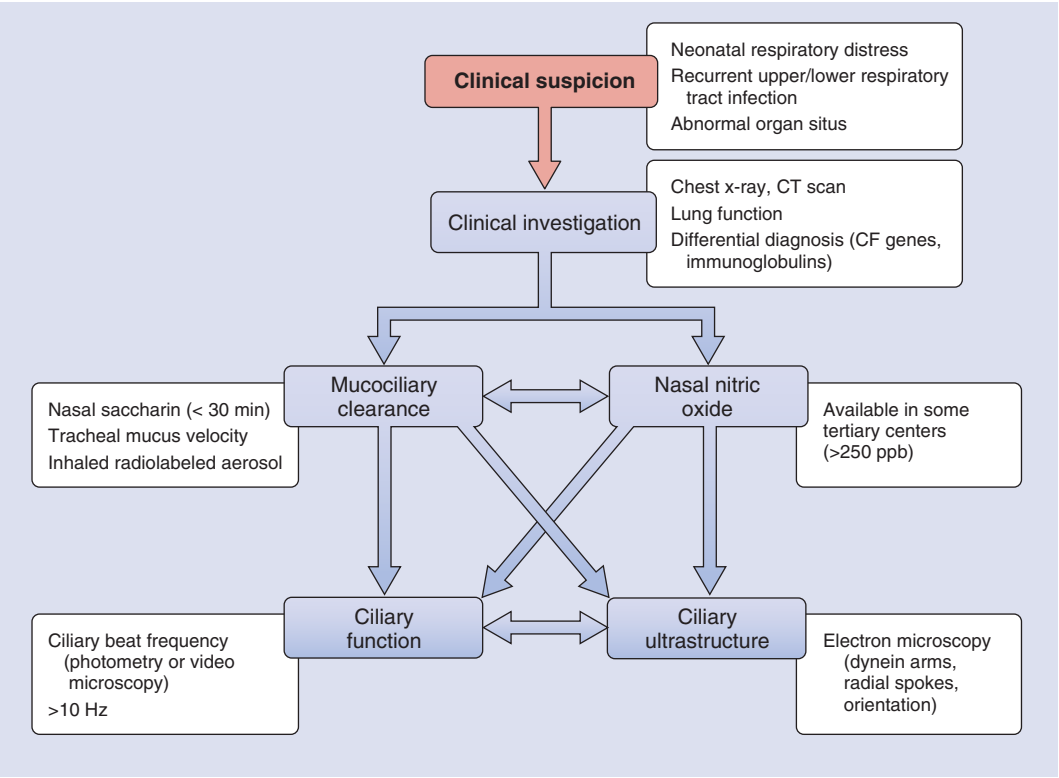

Figure 67-5 Algorithm of investigations in suspected PCD; different tests are available in various institutions.

beating may be observed in mucosal brushings suspended in nutrient medium by light microscopy and can be measured by microscope photometry[108,110] and other techniques such as high-speed cinematography and video.[111,112] Ciliary beat pattern and coordination can be observed and filmed but not readily quantified.

Ciliary Ultrastructure

Mucosal brushings can also be placed into fixative for examination by high-magnification (×100,000 to ×200,000) electron microscopy[113,114] (see Figs. 67-2 and 67-3). There is concordance between the nasal cavity and lower respiratory tract in ciliary ultrastructure.[115] If possible, abnormalities of structure and function should be studied in more than one body site or on more than one occasion, particularly if the diagnosis is in doubt. In postpubertal male patients, sperm motility and ultrastructure can be determined. However, because spermatozoan and ciliary axonemes may be regulated by different genes,[120] ultrastructural defects in spermatozoa and cilia may not be concordant in some patients. Ciliary ultrastructure has been quantified by many investigators,[38,42,114,116,117] and several distinct types of ciliary ultrastructural defects that lead to respiratory disease have been identified (see Table 67-1). The orientation of cilia can also be studied and quantified.[19,118,119] In various studies, up to 10% of cilia in normal subjects may have ultrastructural defects. These are usually microtubular defects or compound cilia.[38,42,116,117] Transitory ciliary defects have been reported in cilia from patients with respiratory tract infection,[121,122] and these reflect a secondary ciliary dysfunction. Ideally, patients should not be studied at times of acute infection and ultrastructural studies should be complemented by measurements of ciliary function.

TREATMENT

No specific therapy is yet available for the management of PCD. This is a chronic condition and the main directions of management are aimed at the treatment of lower respiratory tract infections and minimization of end organ (particularly lung) damage. Immunization against respiratory pathogens is essential. For patients who have progressed to bronchiectasis, physical removal of secretions by postural drainage and other forms of physiotherapy is helpful and may limit progression of disease. In acute infective exacerbations, antibiotics and physiotherapy are appropriate. A number of drugs such as β-adrenergic agonists and xanthines have been shown to stimulate ciliary beating in vitro and to increase mucociliary clearance in patients,[123] but their efficacy in clinical practice in patients with defective cilia has not been documented. In one study[124] bronchodilation was enhanced more by exercise than by inhaled β_2-agonists. In another, aerosolized uridine triphosphate improved MCC in patients with defective cilia.[125] Mucolytics have not been shown to be effective in patients who have PCD. Antitussives are to be avoided because, in patients with impaired MCC, cough may be the only remaining mechanism for removing respiratory tract secretions. Early diagnosis and treatment of respiratory tract infections may slow progress to bronchiectasis. Surgical resection of affected lung is rarely necessary and should be avoided because the basic defect is not confined to one part of the lung. Insertion of myringotomy tubes should be undertaken with caution, because of concern that chronic purulent otor-

rhea may result.[61] In rare instances, lung disease may progress sufficiently for lung transplantation to be considered (normal ciliary function has been shown to continue in the transplanted lung).[126-129] Patients with PCD are best managed in a multidisciplinary environment.

Future directions for research include the use of nebulized mannitol, which has been shown to increase MCC in bronchiectasis,[130,131] and more specific therapies such as inhaled purines and possibly L-arginine.[131-133]

SECONDARY CILIARY DYSFUNCTION

Delayed MCC often occurs secondary to respiratory tract diseases, particularly those in which purulent secretions are common, such as bronchiectasis, cystic fibrosis, and sinusitis. During viral and bacterial infections, the rheologic properties of mucus may change, becoming less elastic during viral infection[134] or more viscous in bacterial infections.[135] Similarly, viral or bacterial infections may cause changes in the ciliated epithelium, both structural and functional, and thus cause impairment of MCC.[136-138] Purulent infection has been shown to cause reduced ciliary beat frequency and abnormal ciliary beat patterns (ciliary dyskinesia).[139] Disruption of ciliary function and structure can also be caused by cell products such as elastases and proteinases liberated by leukocytes in inflammatory lung disease.[140]

Secondary ciliary dyskinesia may result from factors produced by bacteria. Organisms that are known to affect ciliary activity or integrity of the ciliated epithelium and thus affect mucociliary clearance include *Pseudomonas aeruginosa*, *Haemophilus influenzae*, *Staphylococcus aureus*, *Mycoplasma pneumoniae*, *Bordetella pertussis*, and *Streptococcus pneumoniae*.[140]

CONCLUSION

Impairment of MCC may occur as the result of a congenital defect (PCD) or a secondary ciliary dysfunction. Situs inversus can be due to defects of embryonic nodal cilia, which share many genes with respiratory cilia. Secondary ciliary dysfunction can be caused by a variety of microorganisms. In PCD, impaired mucociliary clearance, affecting particularly the upper and lower respiratory tracts, leads to sinusitis, bronchitis, and bronchiectasis. Mutations in three dynein genes have been identified in patients with PCD. Measurement of MCC and nasal NO are useful for screening patients with a clinical suspicion of PCD. However, a definite diagnosis is still usually made by studies of ciliary function and structure. No specific effective treatment is currently available for PCD.

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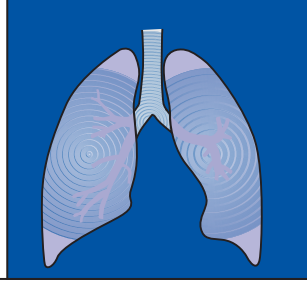


CHAPTER 68 Abnormalities of the Pleural Space

Danna Tauber and Daniel V. Schidlow

TEACHING POINTS

- The pleura allows for mechanical coupling of the lung and chest wall throughout the respiratory cycle.
- Pleural fluid accumulates in the pleural space either by an increase in fluid production or by obstructed fluid drainage.
- Pleural effusions can present with dyspnea, cough, pain, tachypnea, and diminished breath sounds.
- Treatment of purulent effusions includes antibiotics, antibiotics plus chest tube drainage, chest tube drainage plus fibrinolytic therapy, and early debridement by video-assisted thoracoscopic surgery (VATS).
- Pneumothorax presents with the sudden onset of chest pain, tachypnea, and dyspnea.
- Treatment of pneumothorax depends on the size, cause, extent of respiratory distress, and presence of underlying lung disease.

The pleural space is a cavity surrounded by two membranes. The visceral pleura covers the entire surface of the lung, and the parietal pleura covers the inner surface of the chest wall, mediastinum, and diaphragm. The two membranes meet at the hilar root of the lung. The normal pleural space is approximately 18 μm wide at its least dependent point and widens to about 20 μm in the dependent regions.[1] Under normal conditions, the pleural space contains 0.1 to 0.2 mL/kg of fluid with a protein concentration of less than 1.5 g/dL that flows down gravity-dependent gradients.[2,3] The pleural membranes and the space they define play an integral function in respiration. The pleura allows for mechanical coupling of the lung and chest wall throughout the respiratory cycle, providing support to the lung tissue while allowing the lung to move extensively in relation to the chest wall. The anatomy and structure of the pleural space are essential to an understanding of its function and abnormalities.

EMBRYOLOGY AND ANATOMY

By the third week of gestation, the pleural, pericardial, and peritoneal spaces begin to develop. All of these cavities are lined by visceral and parietal membranes made up of mesothelial cells. As the lung develops, the lung buds invaginate into the visceral pleura and become invested in this layer. The mesothelial cells can be flat, cuboidal, or columnar in shape. They have microvilli projections on their free surface. Mesothelial cells are capable of multiple functions, including active transport of small particles,[4] secretion and organization of components of the extracellular matrix such as collagen, elastin, and connective tissue glycoproteins,[5] secretion of neutrophil and monocyte chemotactic factors,[6] phagocytosis of particles,[7] and production of fibrinolytic and procoagulant factors.[8]

Stomata are 2- to 12-μm openings between mesothelial cells of the parietal pleura.[2] These stomata communicate the pleural space and lymphatics, allowing for clearance of large particles and blood cells.[9] The fluid flows into lacunae, spider-like submesothelial collecting lymphatics, which drain into intercostal lymphatics. From there, fluid drains into mediastinal, parasternal, and periaortic nodes, subsequently into the thoracic duct, and ultimately into the systemic venous system[2] (Fig. 68-1).

The parietal pleural is fed by the intercostal arteries. The visceral pleura is supplied by the bronchial circulation and is drained by the pulmonary veins.[10,11] Because the pulmonary venous system is a low-pressure system, the perfusion pressure is lower in the visceral pleura.[10] The parietal pleura has sensory nerve fibers supplied by intercostal and phrenic nerves, whereas the visceral pleura has no sensory nerve innervation.

PHYSIOLOGY OF THE PLEURAL SPACE

Pressure in the pleural space is subatmospheric. Gases do not accumulate in the pleural space because the sum of all partial pressures of gases in venous blood and tissue is lower than that of atmospheric or alveolar gas. There is a 60-mm Hg pressure gradient that maintains dissolved gases in the venous blood and promotes absorption of gases from the pleural space.

The small amount of fluid contained within the pleural space is the result of a dynamic balance between fluid filtered from subpleural capillaries into the intrapleural space and removal of fluid from the space via lymphatics. Sufficient fluid must remain in the pleural space to provide lubrication for the lungs to move but not so much as to uncouple the mechanical forces of the chest wall and the lung.[12]

Starling forces across both the parietal and visceral membranes favor filtration of fluid out of the capillaries and into the interstitial spaces.[4] Fluid then filters from the interstitial spaces into the pleural space because the pleural liquid pressure is subatmospheric and therefore lower than interstitial pressure.[4,12,13] Fluid, cells, and protein are then removed

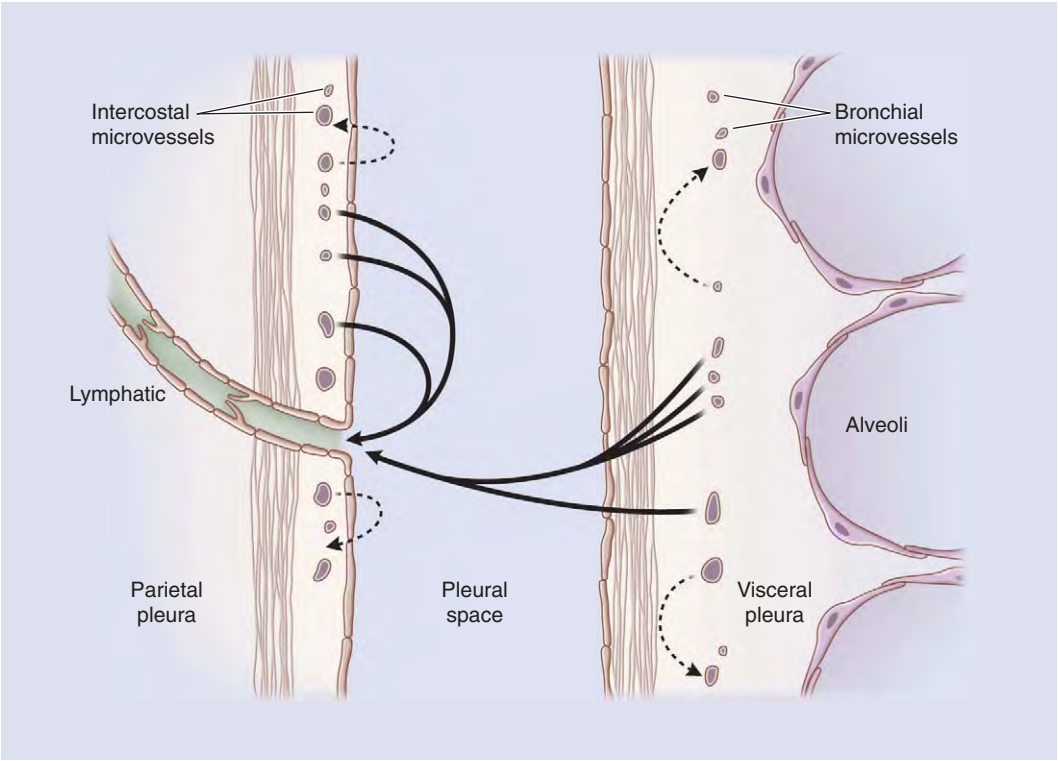


Figure 68-1 Schema showing normal pleural liquid turnover. The initial microvascular filtrate in the parietal and visceral pleura is partly reabsorbed (*dashed arrows*). The remaining low-protein interstitial liquid flows across the leaky pleural mesothelial layers into the pleural space. The pleural liquid exits the pleural space via the parietal pleural lymphatic stomata. (Redrawn from Staub NC, Wiener-Kronish JP, Albertine KH:Transport through the pleura: Physiology of normal liquid and solute exchange in the pleural space. In Chretien J, Bignon J, Hirsch A [eds]: The Pleura in Health and Disease [Lung Biology in Health and Disease, Vol. 30]. New York: Marcel Dekker, 1985, p. 182.)

from the pleural space by the lymphatics of the parietal pleura via bulk flow and not by diffusion or active transport.[4,13] There are two essential mechanisms for fluid accumulation in the pleural space: (1) changes in the balance between hydrostatic and oncotic pressures result in increased fluid production as can changes in the permeability of the capillary membrane or (2) fluid removal is disturbed by obstruction of the lymphatic drainage (Table 68-1).

CLINICAL MANIFESTATIONS

The severity of presenting signs and symptoms of pleural effusion directly correlates to its size and nature. Small effusions rarely cause symptoms. Larger effusions cause dyspnea, dry cough, and orthopnea due to lung compression. Pain results from stretching of the sensory nerve fibers of the parietal pleura, which worsens with inspiration and can radiate to the chest or shoulder. Breath sounds are diminished over the affected area, as are tactile and voice fremitus. There is increased resonance of the voice (egophony) and dullness to percussion. Larger effusions can cause tachypnea, decreased rib excursion, ipsilateral bulging of the intercostal spaces, and contralateral displacement of the heart and trachea.

A chest radiograph is the first laboratory examination that should be done when considering a diagnosis of pleural effusion. With larger effusions, a meniscus is present at the costophrenic angle when the patient is in the upright position.[14] Lateral decubitus films are useful in cases where a "white-out" is seen to differentiate solid underlying lung collapse or consolidation from pleural effusion. The fluid "layers out," allowing abnormalities such as mediastinal masses or lung consolidation to be visualized. Ultrasound and computed tomography (CT) are helpful in differentiating empyema from simple effusions. An ultrasound examination can estimate the size of an effusion and can differentiate free from loculated fluid and can also identify septations in pleural fluid collections.[15,16] CT scans assist in delineating loculated pleural fluid and parenchymal lung abnormalities such as a lung abscess, as well as defining possible mediastinal pathology or mediastinal tumors.[17,18]

DIAGNOSIS

The best method of determining the cause of an effusion is sampling of the fluid accumulation. Thoracocentesis is impractical if the effusion is small or if the cause is known (i.e., congestive heart failure, nephrotic syndrome, ascites, or peritoneal dialysis). Thoracocentesis may be safely performed when a layer of at least 1 cm of fluid is present on decubitus films. If no fluid shift is seen, ultrasound may reveal loculated fluid and guide thoracocentesis or chest tube insertion. Complications of thoracocentesis are pneumothorax, pain, and bleeding due to improper insertion of the needle into the nerve, blood vessel, or lung parenchyma. Intercostal nerve damage, puncture of the liver or spleen, and secondary empyema have been reported.[19-21]

Table 68-1
Pathophysiology of Pleural Fluid Accumulation

Effusion Type	Mechanism	Clinical Diagnosis
Transudate	Increased capillary hydrostatic pressure	Overhydration, congestive heart failure, venous hypertension, pericarditis
	Decreased hydrostatic pressure of the interstitial space	Trapped lung with chronic pleural space, post-thoracentesis
	Decreased plasma oncotic pressure	Hypoalbuminemia, nephrotic syndrome, hepatic cirrhosis
Exudate	Increased permeability of the capillary membrane	Infection—pleural or parenchymal, circulating toxins
		Connective tissue disease: systemic lupus erythmatosus, rheumatoid arthritis, sarcoidosis
	Impaired/obstructed flow	Malignancy: lymphoma, leukemia, neuroblastoma, chest wall sarcoma, Wilms tumor, hepatoma
		Pancreatitis
		Subphrenic abscess
		Superior vena caval syndrome
	Increased oncotic pressure of the interstitial space	Pulmonary infarction
Chyle	Leakage from lymphatic vessels	Thoracic duct injury post cardiac surgery
	Obstruction of lymphatic vessels or vena cava	Tumors (i.e., lymphoma)
		Tuberculosis
		Sarcoidosis
	Congenital abnormalities (thoracic duct atresia or abnormal connections)	Trisomy 21, Noonan syndrome, extralobar sequestration, lymphangiomatosis, or lymphangiectasia
Blood	Vascular leak	Trauma, spontaneous rupture, vascular erosion by neoplasm, hemorrhagic disease

Table 68-2
Pleural Fluid Appearance

Fluid Appearance	Cause
Grossly purulent fluid	Empyema; rarely pancreatitis, ruptured esophagus
Thick, tan-brown	*Staphylococcus aureus*
Putrid	Anaerobes
Also bloody	Group A *Streptococcus*
Milky fluid	Chylothorax
Bloody fluid	Hemothorax, traumatic thoracocentesis, malignancy, tuberculosis, uremia, or empyema due to group A *Streptococcus*
Yellow-green fluid, debris	Rheumatoid arthritis
Black fluid	*Aspergillus niger*
"Anchovy" brown fluid	*Entamoeba histolytica*

Table 68-3
Laboratory Studies to Be Obtained in All Cases of Pleural Fluid Accumulation

Specimen	Laboratory Study
Pleural fluid	Protein
	Lactic dehydrogenase (LDH)
	Glucose
	pH
	Cholesterol
	Bacterial culture and Gram stain
	Differential cell count
	Staining and culture for acid-fast bacilli
	Amylase
Serum	Complete blood cell count
	Complete metabolic panel including:
	LDH
	Total protein
	Glucose
	Albumin
	BUN/creatinine

Pleural fluid appearance varies with the cause (Table 68-2). Transudates are serous or straw colored, whereas chylous effusions are milky. There are a number of laboratory studies that should always be performed on the sampled fluid (Table 68-3). Analysis of the fluid should first determine if the effusion is transudative or exudative[22] (Table 68-4). Exudative effusions arise from inflammation of the pleural membranes or lymphatics resulting in leaky capillary membranes that allow passage of large particles such as proteins.[23] Therefore, exudates have elevated protein, lactic dehydrogenase (LDH), and cholesterol. LDH levels rise as a result of tissue breakdown from inflammation and thus serves as a marker for inflammation. Transudates are not associated with inflammation, so their protein and LDH levels are low. Additional studies should be performed in cases when certain characteristics of the pleural fluid are seen (Table 68-5).

TRANSUDATES

A transudate develops from an imbalance of hydrostatic or oncotic pressure. Inflammation is not present; therefore, transudates have a low cellular count and low protein concentration. Correction of the forces governing pleural fluid homeostasis will lead to resolution of the transudate; drainage is required only for immediate symptomatic relief. Disorders associated with transudative effusions in children include atelectasis, nephrotic syndrome, left ventricular failure, free peritoneal fluid, and hypothyroidism.

Table 68-4
Distinguishing Exudate from Transudate

Exudate	Fulfill at least one of the following criteria:
	Pleural fluid/serum lactic dehydrogenase (LDH) > 0.6
	Pleural fluid/serum protein >0.5
	Pleural fluid LDH > $^2/_3$ upper limit of normal serum values
	Pleural fluid cholesterol >55 mg/dL
Transudate	Fulfill none of the above criteria

Table 68-5
Additional Studies to Be Obtained in Specific Cases

Effusions	Studies
Purulent	Blood culture Sputum culture Serum C-reactive protein
Lymphocytic	Fluid cytospin/cytology Fluid triglyceride level Tuberculin skin test Effusion and serum antinuclear antibody, rheumatoid factor, and complement Fungal titers and skin tests
Bloody	Fluid hematocrit Fluid triglyceride level Fluid hemosiderin-laden macrophages

Atelectasis, trapped lung, and upper airway obstruction can cause effusions by generating excessive negative pleural pressure.[13] Parietal pleural pressure becomes more negative when lung separates from parietal pleura or when inspiratory effort against an obstruction increases.

In nephrotic syndrome, a decrease in oncotic pressure from hypoalbuminemia coupled with an increase in hydrostatic pressure from fluid overload favors movement of fluid into the pleural space.[13] The resulting effusions are generally small and bilateral and resolve with correction of the hypervolemia and protein concentration. Thoracocentesis is indicated with chest or abdominal pain, unilateral or large effusions, fever, or pulmonary infiltrates. If effusion persists after correction of renal function, thoracocentesis should be performed to evaluate for infection, thromboembolism, or collagen vascular disease. Therapeutic thoracocentesis should be performed with caution because removal of a large amount of fluid can result in hypotension.

Patients with cardiac disease develop effusions when left atrial or pulmonary capillary wedge pressure is elevated.[23,24] Effusions are usually bilateral; if unilateral, they are typically right sided.[25] Fluid collections that persist for several months can become exudative due to reabsorption of water over protein.[26] In some cases, repeated thoracocentesis or pleurodesis is necessary to control symptomatic effusions that result from refractory heart failure.[27]

Free fluid in the peritoneal cavity can traverse small openings in the diaphragm and enter the pleural space. Effusions caused by ascites usually occur on the right side,[28] whereas effusions secondary to dialysis are usually bilateral and small.[13,29] Hypothyroidism has been reported to cause effusions as a result of significantly lowered metabolic state. These are often associated with heart failure, pericardial effusions, or ascites and respond to thyroid replacement.[30]

EXUDATES

Exudative effusions result from inflammation of the pleura or obstruction of lymphatic flow. Inflammation leads to leakage of fluid and protein from pleural capillaries and blocks reabsorption of the fluid by the lymphatic lacunae of the parietal pleura. Diffuse destruction or obstruction of lymphatic vessels, which occurs in malignancy or granulomatous disease, also can result in pleural fluid accumulation. The cause of an exudative effusion is not often evident from the clinical presentation. The diagnosis can be narrowed by the appearance of the fluid and the principal cell type found in the fluid (Table 68-6).

NEUTROPHILIC PREDOMINANCE (PURULENT EFFUSION)

Purulent or parapneumonic effusions are a rare but recognized complication of bacterial pneumonia. Studies have cited an incidence of 0.4 to 6 cases per 1000 pediatric hospital admissions.[31] Empyema is defined as the presence of pus in the pleural space. There are three distinct phases of development of an empyema[32] (Table 68-7). Early in the process, in the *exudative phase*, the fluid that accumulates is thin and free flowing, with normal values of glucose, pH, LDH, and a low white blood cell count. In the *fibrinopurulent phase*, there is a deposition of fibrin in the pleural space leading to septation (fibrous strands) and loculation (parietal-visceral pleural adhesion) of infected fluid. The white blood cell count increases as the fluid thickens. The pH and glucose fall as the LDH level rises secondary to the bacterial consumption of glucose and release of lactic acid. In the final, *organizing phase*, fibroblasts invade the cavity, forming a dense peel on both pleural surfaces while the fluid becomes a thick, gelatinous mass. This visceral pleural peel contracts, leading to compression and trapping of the lung. The pH and glucose levels are extremely low, whereas the LDH is very elevated. This stage has also been referred to as complicated empyema. Further complications are uncommon in children but include bronchopleural fistula, lung abscess, or even perforation through the chest wall (empyema necessitatis).

Identification of a causative organism from the pleural fluid or blood is made difficult by the use of antibiotics before the diagnosis of parapneumonic effusion is made. The most frequently recovered pathogens include *Streptococcus pneumoniae*, *Streptococcus pyogenes*, and *Staphylococcus aureus*.[33] Of these, *S. pneumoniae* has emerged as the predominant pathogen in childhood empyema. Polymerase chain reaction (PCR) can be used in culture-negative cases and has identified a pathogen in 75% of those cases.[34] *S. aureus* causes a more severe pneumonia and empyema than other pathogens. The increasing incidence of methicillin-resistant *S. aureus* in the community poses a new challenge to successful treatment. Other pathogens include *Klebsiella* spp, *Pseudomonas* spp., anaerobic organisms, and viruses.[35]

Clinical manifestations of parapneumonic effusions are very similar to those of classic pneumonia—fever, cough, lethargy, malaise, poor appetite, and lower exercise tolerance. However, in the presence of a purulent effusion, the child will appear sicker with pleuritic chest pain and splinting of the affected side. Suspicion for a parapneumonic effusion should be raised in the case of pneumonia that does not respond to traditional treatment within 48 hours.[36]

Diagnosis of a parapneumonic effusion is made on chest radiograph. Staging of the effusion can be made with either computed tomography or ultrasound (Fig. 68-2). Recent studies point to the advantages of early ultrasound in diagnosing effusions in the fibrinopurulent or organizing phase. Ultrasound is able to differentiate loculated, septated fluid from free-flowing effusions as well as identify a pleural peel.[16] CT

Table 68-6
Categories of Exudative Pleural Effusion

Type	Cell Characteristics	Cause
Purulent	>5000 leukocytes/mm^3	Parapneumonic effusions Pancreatitis Perforation of the esophagus Pulmonary infarction Pericardial or myocardial injury
Lymphocytic	>50% lymphocytes, usually 1000-1500 cells/mm^3	Tuberculosis Malignancy: lymphoma (predominantly), leukemia, neuroblastoma, chest wall sarcoma, Wilms tumor, hepatoma Uremia Connective tissue disorder: rheumatoid arthritis, systemic lupus erythematosus Fungal infections
Monocytic	>20% monocytes, usually <5000 cells/mm^3	Viruses: adenovirus, influenza, herpes, varicella, measles, and cytomegalovirus *Mycoplasma* pneumomia
Eosinophilic	>10% eosinophils	Recent pneumothorax or blood in pleural space Drugs: dantrolene, nitrofurantoin Uremia Fungal infections Parasitic infections: histoplasmosis, coccidiodomycosis, ascariasis, paragonimiasis, echinococcosis, amebiasis
Chylothorax	Pleural fluid triglyceride >110 mg/dL	Injury to thoracic duct Tumors: lymphoma Tuberculosis Sarcoidosis Neonatal: Trisomy 21, Noonan syndrome, extralobar sequestration, lymphangiomatosis, lymphangiectasia
Hemothorax	Fluid hematocrit >50% blood hematocrit	Trauma Erosion of vessels by central venous catheters Pulmonary infarction Malignancy Thrombocytopenia Hemophilia Rupture of bronchopulmonary sequestration Rupture of arteriovenous malformation Rupture of intrathoracic vessel

provides detailed images of the pleural cavity as well as differentiating empyema from abscess.[17] However, CT may miss multiloculations or septations within fluid collections. Ultrasound has the additional advantage over CT in that it is portable, involves no radiation, and does not usually require sedation.

Treatment of parapneumonic effusions has been an ongoing focus of debate. Early surgical intervention in the form of video-assisted thoracoscopic surgery (VATS) for debridement of the empyema has become more prevalent. Most authors agree that the goals of treatment include elimination of the empyema, reexpansion of the lung, decreased duration of symptoms, and a shortened length of stay.[37] In all cases, treatment with antibiotics is essential. Most uncomplicated cases will respond to a single agent, such as a second- or third-generation cephalosporin or a beta-lactam antibiotic or a beta-lactamase inhibitor such as ampicillin-sulbactam or ticarcillin-clavulanate at high dose[33] (Table 68-8). Small effusions in association with pneumonia can be treated with antibiotics alone. Larger effusions in the early, exudative phase can be treated with intravenous antibiotics plus chest tube drainage.[38,39]

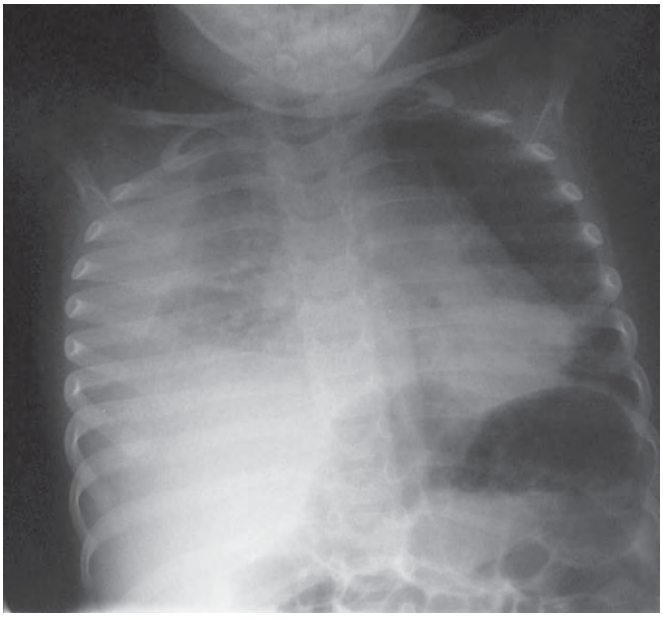
Treatment with simple chest tube drainage is insufficient for effusions in the later stages, once septations, loculations,

Table 68-7
Stages of Purulent Effusion

Phase	Characteristics
Exudative	Thin, free-flowing fluid Normal glucose, pH, LDH Low WBC count
Fibrinopurulent	Deposition of fibrin leading to septations and loculations High WBC count Low pH and glucose High LDH
Organizing	Fibroblasts invade, fluid thickens, dense peel forms Extremely low pH and glucose Extremely elevated LDH

Table 68-8
Antibiotic Treatment for Purulent Effusion

Bacteria	Antibiotic
Streptonomis pneumoniae	Second-generation cephalosporin Third-generation cephalosporin Ampicillin-sulbactam Ticarcillin-clavulanate
Staphylococcus aureus	Oxacillin
Methicillin-resistant *S. aureus*	Vancomycin Linezolid
Mycoplasma/Chlamydia	Erythromycin Azithromycin



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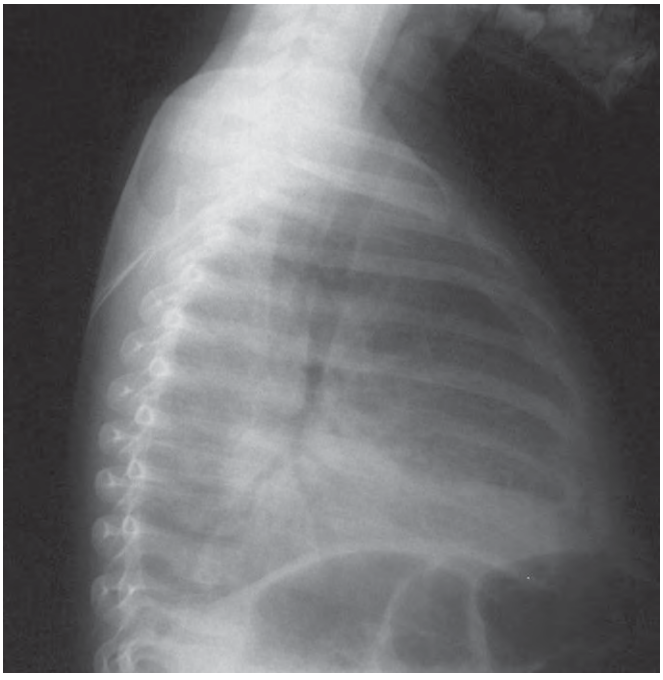

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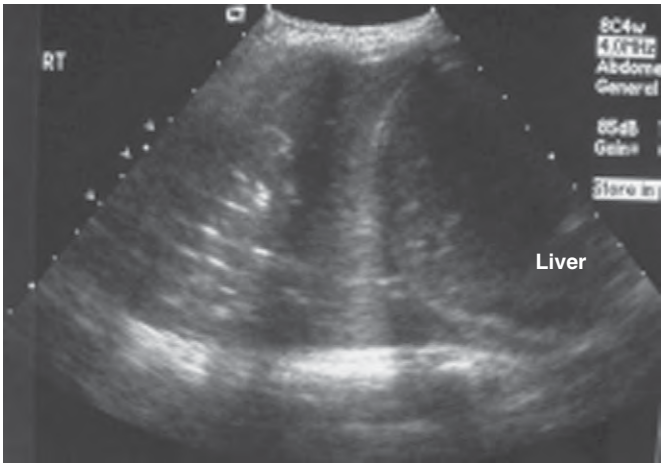

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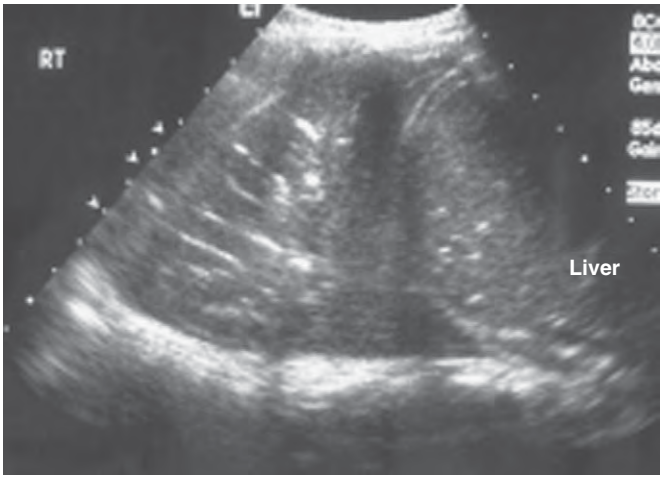

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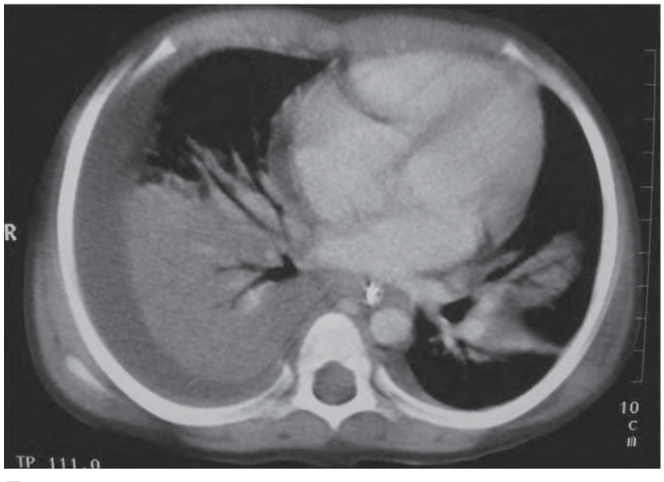

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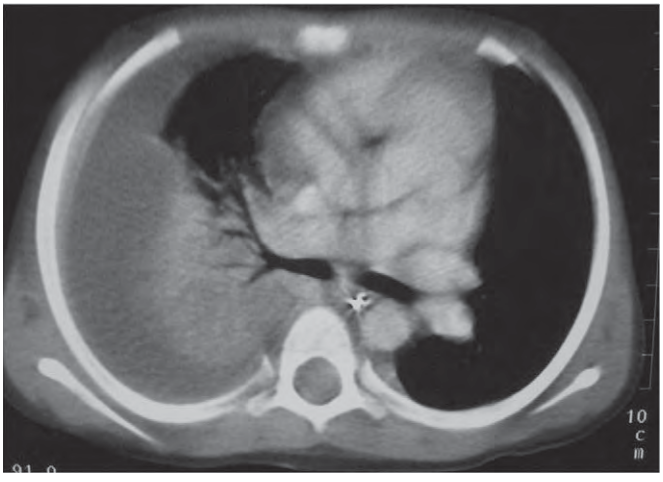
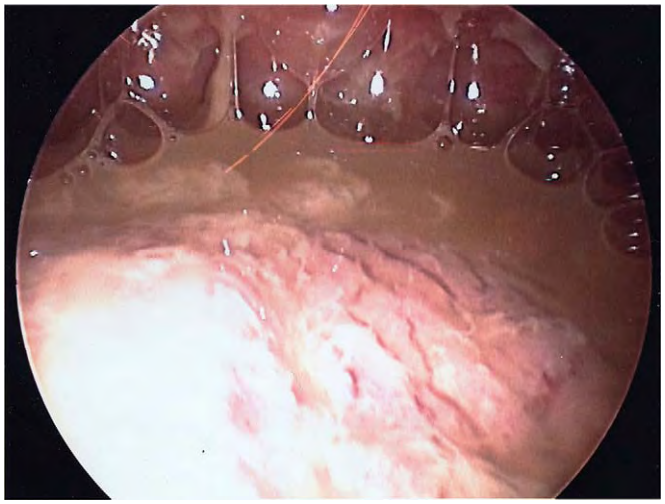


F

Figure 68-2 Images of a 4-year-old girl with a cough, fever, and abdominal pain. **A and B**, Anteroposterior and lateral chest radiographs demonstrating a large pleural effusion on the right with bilateral lower lobe infiltrates. **C and D,** Ultrasound images of the same patient demonstrating an inhomogeneous area of consolidation on the right, which is predominantly hypoechoic with scattered mildly echogenic foci. **E and F,** CT images of the chest, again demonstrating the large consolidation with pleural effusion.



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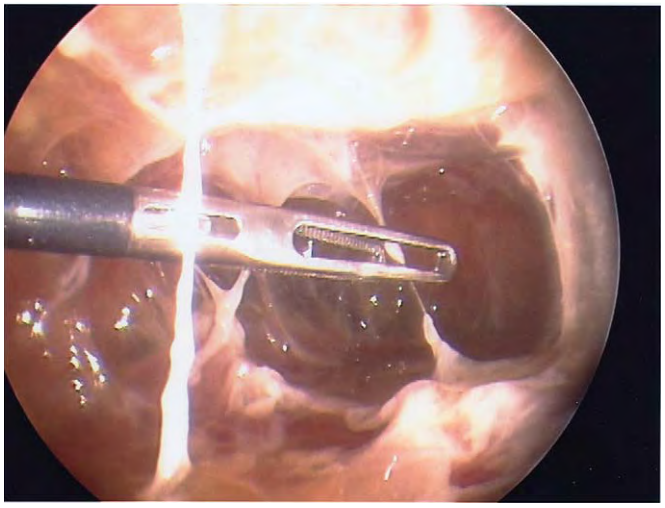

H

Figure 68-2, cont'd **G and H,** Images from VATS demonstrating a thick, visceral peel with septations.

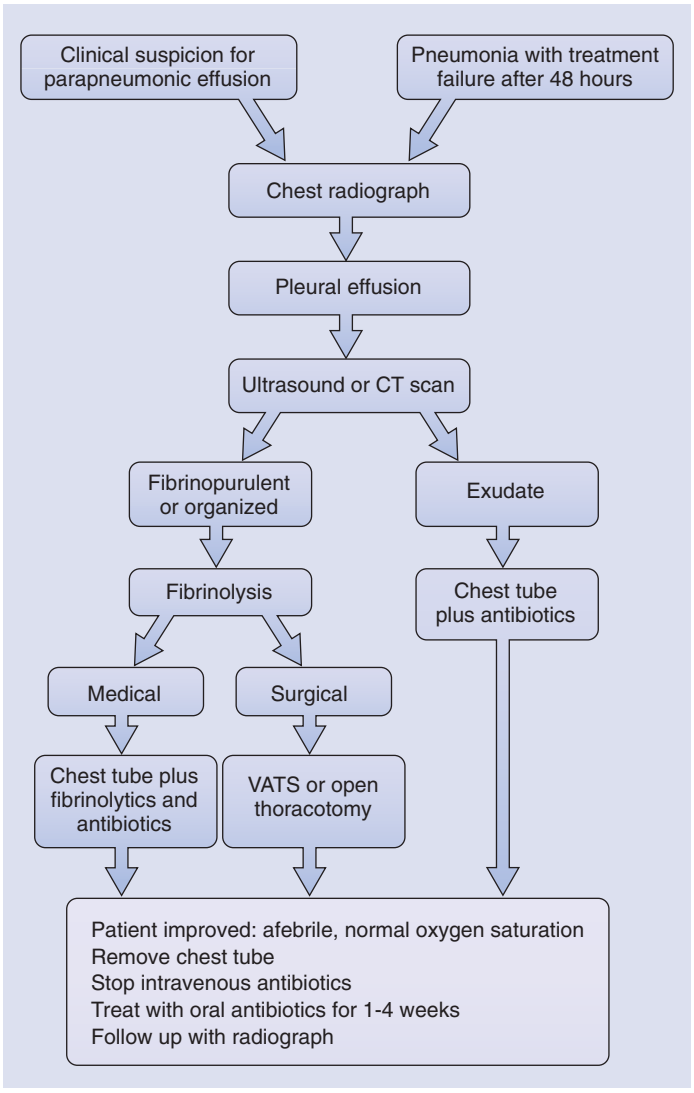

Figure 68-3 Treatment algorithm for parapneumonic effusion. VATS, video assisted thorascopic surgery.

or pleural peels have been identified. Other options include the instillation of fibrinolytics into the pleural cavity or surgical decortications through VATS or open thoracotomy. Fibrinolytics degrade fibrin and allow better drainage of the pleural space with the chest tube and antibiotics. Urokinase and streptokinase seem to be effective, with success rates of 60% to 90%.[40-45]

Early surgical debridement of the pleural cavity via VATS has been used with increasing frequency and success. Two trocars (one for the video equipment, the other for surgical tools) are inserted through two small incisions in the chest wall. Under direct visualization, loculations are broken down and pus is drained from the pleural cavity. This method of treatment is associated with a shorter length of stay, shorter duration of fever, fewer days with a chest tube, lower failure rates, and lower complication rates.[46-50] Open thoracotomy has been the definitive treatment for empyema over the past century.[51,52] Pus is evacuated from the cavity, and the pleural peel is resected or stripped of all fibrous tissue. The incision is larger, and issues with postoperative pain and cosmesis are significant. Published studies comparing the different treatment options are retrospective reviews, and therefore difficult to interpret and lack sufficient data regarding the stage of effusion before treatment. There is no consensus, and the decision to proceed to VATS versus treatment with fibrinolytics is left to the practitioner. A treatment algorithm has been proposed by some authors[33,36] (Fig. 68-3).

In addition to purulent effusions there are other categories of exudative effusions. For a complete list and their causes, please refer to Table 68-6.

PNEUMOTHORAX

Pneumothorax is defined as the abnormal collection of air in the pleural space outside of the lung. Air can enter the pleural space by a leak in either the visceral or parietal pleura. Pneumothorax can be categorized as spontaneous or traumatic. Traumatic pneumothorax occurs as the result of blunt or penetrating trauma to the chest wall or an injury from a diagnostic or therapeutic procedure. Spontaneous pneumothorax occurs without identified trauma and can be further subdivided into primary and secondary. In primary pneumo-

thorax, there is no identifiable lung disease that would lead to air leak. Many patients with primary pneumothorax have apical blebs of unknown etiology that are often diagnosed at the time of surgery or on CT examination.[53] Secondary pneumothorax occurs as a complication of underlying lung disease such as cystic fibrosis. The incidence of primary spontaneous pneumothorax is highest between 15 and 34 years of age.[54] The incidence of secondary spontaneous pneumothorax is highest later in life due to its association with chronic obstructive lung disease. Primary spontaneous pneumothorax typically occurs in tall, asthenic patients and more commonly in males in both the adult and pediatric populations.[55,56] Smoking increases the risk of pneumothorax.[57] A complete list of causes of pneumothorax is listed in Table 68-9.

Two causative mechanisms for pneumothorax have been proposed. The first mechanism suggests that large increases in transpulmonary pressure cause alveolar distention and high-pressure gradients cause the alveolus to rupture. Superficial alveoli can form subpleural blebs that rupture directly into the pleural space. In the second mechanism, direct injury to the visceral pleura secondary to underlying lung disease leads to pneumothorax. A tension pneumothorax develops when air enters the pleural space during inspiration but cannot exit during exhalation. This will lead to collapse of the affected lung and shift of the mediastium away from the affected side.

The cardinal manifestation of pneumothorax is the sudden onset of chest pain. Other common clinical manifestations include tachypnea, dyspnea, tachycardia, and cyanosis. The severity of symptoms depends on the volume of air in the pleural space, rapidity of onset, and the degree of respiratory compromise before the occurrence of the pneumothorax, which is influenced by the presence of underlying lung disease. Pain can range from localized acute retrosternal pain to overwhelming pleuritic pain as well as ipsilateral shoulder pain. Physical examination findings include decreased breath sounds, decreased thoracic excursion, and hyperresonant percussion on the affected side. In cases of tension pneumothorax with shift of the mediastinum, the trachea will be displaced, as will the point of maximal cardiac impulse. Subcutaneous emphysema results from air moving to areas of lower resistance and can reach the neck, upper extremities, abdominal wall, and peritoneum. In cases where the pneumothorax is small, the patient will frequently be asymptomatic and it is usually an incidental finding on radiograph.

Table 68-9
Causes of Pneumothorax

Type of Pneumothrax	Cause
Traumatic	Penetrating or blunt chest trauma
Iatrogenic	Mechanical ventilation (barotrauma)
	Central vein catheterization
	Procedures on airways: intubation, endoscopy, transbronchial biopsy
	Laparoscopic procedures
	Percutaneous biopsies
Primary spontaneous	Aesthenic body habitus
	Idiopathic
	Cocaine or marijuana inhalation
Secondary spontaneous	Airway disease: asthma, cystic fibrosis
	Postinfection: measles, *Pneumocystis carinii,* tuberculosis, necrotizing pneumonia or abscess, parasitic (ecchinococcal)
	Interstitial lung disease: sarcoidosis
	Langerhans cell granulomatosis
	Connective tissue disease: Marfan, Ehlers-Danlos, rheumatoid arthritis, systemic lupus erythematosus, polymyositis, dermatomyositis
	Malignancy: lymphoma, metastasis
	Aspiration: foreign body, other
	Catamenial pneumothorax
	Congenital malformations

Diagnosis of a pneumothorax is accomplished with a chest radiograph. Anteroposterior and lateral views reveal the characteristic findings of air in the pleural space outlining the visceral pleura (pleural line) and hyperlucency and attenuation of vascular and lung markings on the affected side. CT of the chest is helpful to detect bullae and blebs in patients with recurrent pneumothorax and in cases where the radiograph is inconclusive.[58,59] Arterial blood gas measurements should be obtained in cases of respiratory distress. Hypoxemia occurs due to collapse and poor ventilation. Hypercapnia is not usually seen in cases of pneumothorax without underlying chronic lung disease.[53] In cases of severe tension pneumothorax with mediastinal shift and cardiac displacement and rotation, an electrocardiogram can reveal changes in the amplitude of the QRS complex and the cardiac axis.

Treatment depends on the size and cause of the pneumothorax, the extent of respiratory distress, and the presence of underlying lung disease. The goals of treatment are removal of air from the pleural space and prevention of recurrence.[53,60] Treatment can range from observation and supplemental oxygen to simple needle aspiration or chest tube to pleurodesis and, in some cases, more invasive surgery. Information on pediatric spontaneous pneumothorax is limited and management guidelines are based on published adult data.

Observation. In the case of a small pneumothorax (<15% of the involved hemithorax) when the patient is asymptomatic, simple observation can be instituted.[61,62] In a younger child, hospitalization is recommended. In the older child, observation may be done on an outpatient basis.

Supplemental oxygen. The rate of resorption of air from the pleural space is increased with the use of supplemental oxygen.[63] The increased alveolar oxygen tension creates a large gradient between capillary and pleural gas partial pressure of nitrogen, resulting in faster reabsorption of intrapleural air. Use of 100% oxygen via a nonrebreathing facemask has been suggested with a minimal flow rate of 15 L/min.

Needle aspiration. Evacuation of air is required for symptomatic patients where the pneumothorax has been identified to occupy more than 15% of the involved hemithorax. Simple aspiration is done via a large-bore intravenous catheter connected to a large syringe with a three-way stopcock. Air is withdrawn manually until no more can be aspirated. If air continues to be aspirated, this indicates a persistent air leak and a tube thoracostomy should be performed. If no further air can be aspirated, the stopcock is closed and the catheter is secured to the chest wall. A chest radiograph should be performed after 4 hours of observation and if adequate lung reexpansion is seen, the catheter can be removed and the patient observed. Published success rates vary and depend on

whether the pneumothorax is primary or secondary.[60] The recent ACCP guidelines did not support simple needle aspiration in any clinical circumstance.[64]

Thoracostomy tube. This is indicated for patients who have large pneumothoraces, are clinically stable or unstable or who have recurrent spontaneous pneumothorax.[64] This involves the use of a one-way Heimlich valve or water seal device to prevent reaccumulation of air. In the ACCP guidelines, half of the group recommended clamping of the tube 4 hours after the last evidence of an air leak. A repeat chest radiograph should be taken 5 to 12 hours after the last evidence of an air leak in preparation for removal of the tube.

Pleurodesis. This involves injection of a sclerosis agent such as talc, tetracycline, doxycycline, autologous blood patches, or fibrin glue at the time of thoracostomy tube placement. This method is less favorable than surgical intervention for persistent air leak.[65] Mechanical pleurodesis by direct abrasion with gauze, or laser or chemical pleurodesis with talc or doxycycline at the time of surgery has support in the literature to prevent recurrence.[64]

Surgical intervention. This involves stapling or oversewing ruptured blebs (bullectomy) or tears in the visceral pleura and resection of abnormal lung tissue. Mechanical and chemical pleurodesis can also be done with bullectomy. This can be done via VATS, minithoracotomy, or open thoracotomy, although many physicians prefer VATS. Surgery is indicated to treat persistent air leaks and to prevent recurrence. Surgery is recommended at the time of the first occurrence of a secondary spontaneous pneumothorax[65] and at the second occurrence of a primary spontaneous pneumothorax.[66]

Data regarding prognosis after spontaneous pneumothorax in children are limited. One reported series showed a 37% incidence of recurrent spontaneous pneumothorax.[67] In pediatric patients undergoing surgical management, the reported risk of recurrence was 6% to 9%.[68,69] A recent study[70] evaluated primary versus delayed surgery for pediatric patients with primary spontaneous pneumothorax. The authors found that patients who had VATS-directed bullectomy and pleurodesis at the first presentation of spontaneous pneumothorax had a 29% recurrence rate compared with 0% in the group of patients undergoing VATS on the second occurrence.

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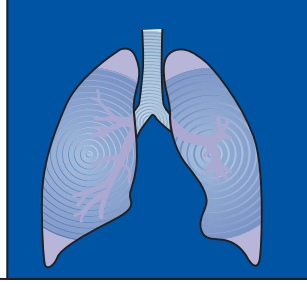

CHAPTER 69 Bronchiectasis

Marcus Herbert Jones and Paulo José Cauduro Marostica

TEACHING POINTS

- Bronchiectasis should be suspected in children with chronic respiratory symptoms.
- A chest radiograph may not detect bronchiectasis.
- High-resolution computed tomography is the gold standard for the diagnosis of bronchiectasis.
- Cystic fibrosis should be considered in children with bronchiectasis.
- Postinfectious bronchiectasis is still frequent in developing countries.
- Antibiotics and chest physiotherapy are recommended by most experts.
- Patients with localized disease may benefit from surgery.

Bronchiectasis is a structural abnormality characterized by dilatation of the medium-sized bronchi. The usual clinical presentation is chronic productive cough and may lead to significant social and physical problems. Although bronchiectasis is observed in some congenital conditions, it usually occurs as a sequel to severe or repeated insults of respiratory infections or chronic aspiration.

Bronchiectasis has been considered an irreversible abnormality. However, since high-resolution computed tomography (HRCT) has become available, some radiologically diagnosed cases in children were found to be reversible.[1] This is a challenge to the paradigm of a permanent finding suggesting that either different HRCT criteria for bronchiectasis in children should be used or this condition should be deemed as actually reversible in childhood. Most children with idiopathic bronchiectasis and those with nonprogressive causes have a good prognosis, with an almost normal life span, whereas those with background diseases like cystic fibrosis (CF) have a much worse prognosis, related to the progressive nature of the underlying illness.

EPIDEMIOLOGY

Estimates of the prevalence of bronchiectasis are scarce. There are few reports of prevalence and incidence available, and further epidemiologic studies should be carried out to better assess the impact of this condition. The scarcity of prevalence studies reflects the lack of a noninvasive, simple, and accurate test that can be used in population investigations, so most diagnosed cases represent the more severe ones.[2-4]

Although the prevalence of bronchiectasis is unknown, it seems to be higher in developing countries, where tuberculosis and childhood preventable diseases like pertussis and measles are still common.[3,5]

In developed countries, the introduction of widespread immunization, improvement of social conditions, breastfeeding encouragement policies, and the access to antimicrobial therapy for tuberculosis and pneumonia have caused a decline in the incidence of bronchiectasis. However, bronchiectasis is still prevalent among indigenous peoples such as the Australian Aboriginal,[6] Alaskan,[7] Pacific and Maori children from New Zealand.[8,9] The prevalences reflect the socioeconomic conditions of a particular population.[4,10]

At present, there has been a rise in tuberculosis rates directly related to the AIDS epidemic. This will cause an increase in the incidence of bronchiectasis, which will probably be diagnosed later during adulthood.

PATHOPHYSIOLOGY

Usually a chronic or an intense insult, such as a severe viral infection, causes the initial lung damage, eventually leading to the emergence of bronchiectasis. Damage to the mucociliary clearance system evolves, leading to stasis of pulmonary secretions and further lung injury. There is a change in the epithelium from ciliated to cuboidal and squamous, reserve cell hyperplasia, and mucosal thickening. With progression, there is damage to the muscular and elastic layers. Inflammatory mediators and release of elastase from leukocytes lead to additional damage and eventual bronchial wall destruction with erosion of bronchial cartilage, especially in advanced saccular bronchiectasis. Elastase and cathepsin G are found in elevated concentrations in bronchoalveolar lavage fluid (BALF) from patients with bronchiectasis compared with normal controls, suggesting a decrease in downregulation of such enzymes by antiproteinases. Interleukin-8, a proinflammatory cytokine, is also overly expressed in BALF from patients with this disorder.[3] Once secondary infection is present, a cycle of infection and inflammation predisposes to further mucosal and bronchial wall injury[3,11,12] (Figs. 69-1 and 69-2).

Localized bronchiectasis is usually related to a single bronchial obstruction, such as in foreign body aspiration or congenital malformations.

In chronic cases, there may be vascular proliferation of the adjacent bronchial arteries that anastomose with pulmonary arteries and predispose the child to hemoptysis.[3]

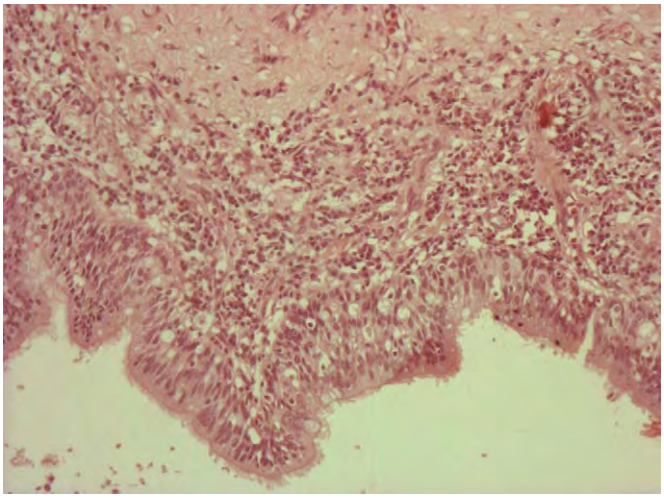

Figure 69-1 Reserve cell hyperplasia, a dense mononuclear inflammatory infiltrate, and fibrosis. (Hematoxylin and eosin stain, original magnification ×100.)

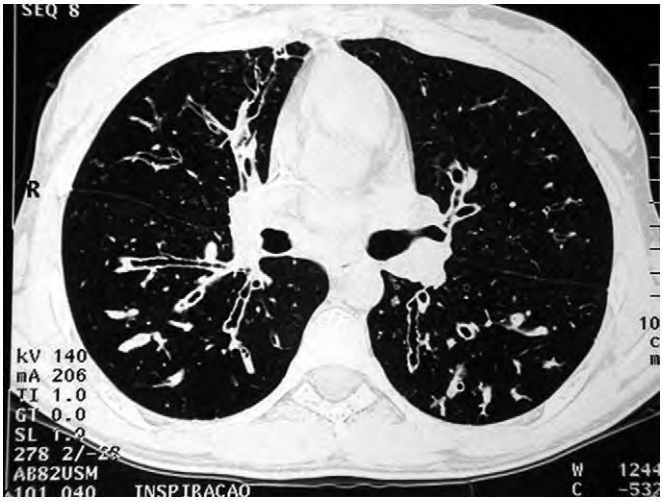

Figure 69-3 HRCT scan of a 14-year-old cystic fibrosis patient showing cylindrical bronchiectasis in lower lobes.

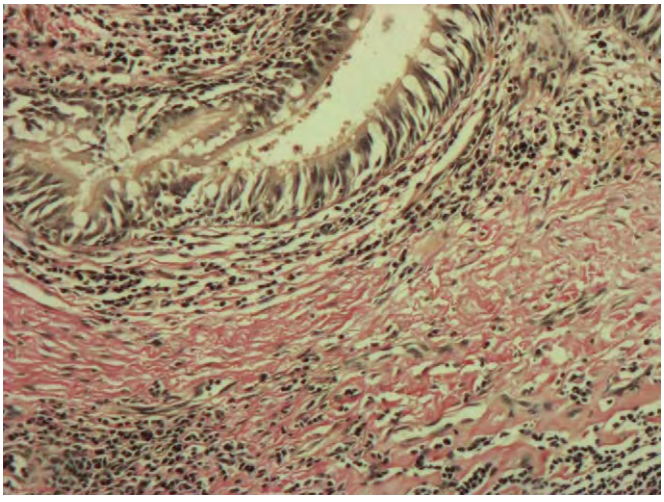

Figure 69-2 The fibrotic area is stained in red, surrounding a bronchus with mononuclear infiltrate. (Verhoeff stain, original magnification ×100.)

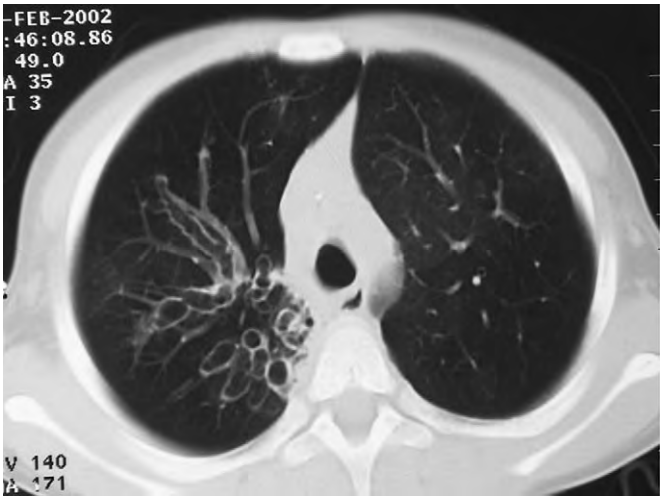

Figure 69-4 HRCT scan of a 4-year-old patient with postinfectious bronchiolitis obliterans and localized cystic bronchiectasis in the right lower lobe.

The shape of the bronchiectasis is variable. The classic Reid classification[13] divides bronchiectasis into three different patterns: (1) cylindrical, where a uniform dilatation is found, (2) varicose, with constrictions superimposed on cylindrical bronchiectasis, and (3) cystic or saccular, where progressive dilation occurs, usually associated with more advanced disruption of the lung architecture, although such correlation is not always evident.[4] Figures 69-3 and 69-4 show the typical pattern of bronchiectasis on HRCT.

CAUSES

In many situations, bronchiectasis is secondary to a specific disease, but often no cause will be identified, despite a comprehensive etiologic investigation. In recently published series, 25% to 38% of pediatric patients did not have an identifiable underlying etiology for bronchiectasis. The most common causes in children include CF, severe respiratory infection, immunodeficiency, congenital malformations, and aspiration syndromes.[11,14,15] Box 69-1 presents a list of known causes of bronchiectasis in children.

In developing countries, infectious cases secondary to tuberculosis and pneumonia are still prevalent. In South America, postviral (especially adenovirus) bronchiolitis obliterans is a relatively common cause of bronchiectasis.[16,17] In a case-control study with Australian Aboriginal children, a strong and significant association was noted between hospitalized pneumonia and bronchiectasis, especially for recurrent and more severe pneumonia episodes with requirement for oxygen and longer hospital stays.[12]

After the development of new antiviral drugs for the treatment of AIDS, vertically infected children are surviving longer and bronchiectasis is becoming a more frequent finding among such patients. Tuberculosis, lymphocytic interstitial pneumonia, and bacterial or *Pneumocystis carinii* pneumonia are frequently associated conditions with HIV-infected children.[18-20]

BOX 69-1 Causes of Bronchiectasis in Children

Infectious

Bacterial pneumonia
Pertussis
Measles
Adenovirus
Influenza
Tuberculosis

Immunodeficiency

Hypogammaglobulinemias
Neutrophil deficiencies
Complement deficiency
AIDS

Other

Cystic fibrosis
Primary ciliary dyskinesia
Allergic bronchopulmonary aspergillosis
Foreign body aspiration
Aspiration syndromes
Autoimmune diseases
Young syndrome
Mounier-Kuhn syndrome
Ehlers-Danlos syndrome
Marfan syndrome
Yellow nail syndrome
Alpha-1 anti-trypsin syndrome

Asthma itself is rarely, if ever, associated with bronchiectasis. In this situation, physicians should consider a different diagnosis or associated allergic bronchopulmonary aspergillosis or infection.[5,7,21]

When localized disease is the case, one should consider an obstruction such as a foreign body or a congenital malformation. In cases of more diffuse disease, a systemic cause like CF, immunodeficiency, or primary ciliary dyskinesia is usually implicated.[5]

CLINICAL FINDINGS

Chronic respiratory complaints are the usual clinical findings. A productive cough is frequently present, and the association with wheezing or dyspnea often misleads physicians to the diagnosis of difficult asthma. As normal children often have respiratory tract infections, the presence of abundant sputum production may remain undetected, leading to diagnostic delay. Fetid sputum may also be present, although in the authors' experience, it is only found, as is hemoptysis, in the more severely affected. Crackles and rhonchi are the usual auscultatory findings, more often detected during disease exacerbations. Digital clubbing is a variable finding, being reported in up to half of the patients, and does not necessarily correlate with severity of the disease.[9] There may be chest deformities. Malnutrition is frequently present in patients.[3,5,12,21-23]

DIAGNOSTIC METHODS

Bronchiectasis should be considered in all children with chronic respiratory symptoms, particularly if associated with a history of a severe respiratory infection in the past, digital clubbing, and malnutrition.

HRCT of the chest has largely replaced bronchography for the diagnosis of bronchiectasis. It can accurately localize lesions, identify mucus plugging and bronchiolar abnormalities to the level of sixth-order bronchi and also identify focal areas of air trapping secondary to small airway disease.[11,21] Occasionally, bronchography is performed as a presurgical evaluation and when the diagnosis is uncertain.[24] Bronchography is associated with a risk of allergic reactions to the contrast media and with the possibility of ventilatory failure in patients who already have some degree of respiratory insufficiency. Most surgical series currently published do not mention bronchography as a mandatory preoperative test.[25]

Ventilation-perfusion scintigraphy can be used to evaluate vascular perfusion and the extent of gas exchange in different areas.[26]

Chest radiographs can be indicative of bronchiectasis, but they are not very sensitive. In the series by Eastham and coworkers,[22] 66% of the HRCT diagnosed cases would have been missed by chest radiography alone; HRCT should be performed when the clinical picture is compatible, despite a normal chest radiograph. Usual radiographic findings are increased linear markings, the so-called tram lines, crowding of bronchi, cystic spaces, air-fluid levels, and honeycombing.[4,27]

The standard HRCT technique is a thin section (1.0- to 1.5-mm collimation), at 10-mm intervals, with a high-frequency reconstruction algorithm. Usual window levels are –600 to –700 HU, and window width is 1000 to 1500 HU.[27,28]

One of the classic signs of bronchiectasis in HRCT is a bronchial/adjacent pulmonary artery ratio greater than 1, which corresponds to bronchial dilatation; this is also known as the "signet ring" sign. It has been suggested that a 1.5 ratio should be used instead, because healthy people can have ratios as great as 1.5. Other classic signs include parallel bronchial walls that do not taper, the tram line appearance, or demonstration of bronchi in the peripheral third of the lung, mainly within 1 cm of the pleura.[4,11,28,29] In the retrospective series of bronchiectasis by Kang and coworkers,[28] 87% of 47 resected lobes from adolescents and adults were correctly identified by the presurgical HRCT scans. Because all the patients had clinical indication for surgery, they probably represent the more symptomatic children.

Areas of decreased attenuation can often be seen in HRCTs of patients with bronchiectasis. Pifferi and coworkers were able to identify attenuations in 37% of pulmonary lobes from 16 patients with bronchiectasis.[29] These areas correlated well with ventilatory and perfusional scintigraphy findings but did not necessarily correspond to the same areas where bronchiectatic changes could be observed. These changes could represent hemodynamic changes surrounding bronchiectasis.

Pathologically, bronchiectasis consists of dilated bronchi, with inflammation and fibrous distortion of the bronchial wall, but biopsy specimens are not usually required, because image studies usually suffice for the diagnosis.[28]

Interestingly, many cases of HRCT-diagnosed bronchiectasis have been demonstrated to be reversible. Either more strict criteria should be used to interpret HRCT in childhood, or some mild cases may actually be reversible. Gaillard and coworkers suggest that the persistence of clinical and CT findings for a period of 2 years is required to confirm the presence of true bronchiectasis.[1,22,30]

Although some diseases can show a more frequent pattern of distribution of bronchiectatic lesions, none of the HRCT findings should be considered diagnostic, because there is great overlap.[4,11] In CF, upper lobe involvement is frequent, in contrast with other diseases where bronchiectasis tends to be more evident at other sites, especially in the lower lobes.[7,11,25] Aspiration typically causes more lower lobe bronchiectasis. In the series of Li and coworkers,[11] 80% of such patients had bronchiectasis in the lower lobes. According to Hansel,[4] the middle lobe was more commonly involved in hypogammaglobulinemia. Li and coworkers[11] found a preponderance of lower and right middle lobe involvement in children with various types of immunodeficiency. Typical cases with an underlying cause such as CF, primary ciliary dyskinesia, or immunodeficiency usually show a multilobar involvement, in contrast to localized disease caused by infection.[5]

MICROBIOLOGY

Haemophilus influenzae, *Streptococcus pneumoniae*, *Moraxella catarrhalis*, *Haemophilus parainfluenzae*, *Staphylococcus aureus*, and *Pseudomonas* spp. are the usual pathogens in children with bronchiectasis.[11,21-23] In CF, the most frequent bacteria are *S. aureus*, *Pseudomonas aeruginosa*, *H. influenzae*, and *Burkholderia cepacia*.[31]

LUNG FUNCTION TESTS

In non-CF patients, the correlation between bronchiectasis, assessed by an HRCT score, and lung function is weak.[32,33] Patients with bronchiectasis limited to a segment or lobe probably would have minimal abnormalities on spirometry. In CF patients, there is a mismatch between HRCT scores and spirometry, with a faster worsening of the bronchiectasis compared with lung function parameters.[34,35] However, some authors detected a moderate correlation between forced vital capacity (FVC) and forced expiratory volume is 1 second (FEV_1) and HRCT scores in CF patients.[25,29,36] Children with bronchiectasis may have abnormal exercise with increased oxygen consumption and heart rates compared with controls, although exercise abnormalities have a poor correlation with HRCT scores or spirometry.[33]

MANAGEMENT

The management of bronchiectasis should focus on the care of the underlying condition, when this is the case, and the management of the suppurative lung injury itself. The former is beyond the scope of this chapter.

Physiotherapy, one of the main treatments for CF patients, has not been appropriately evaluated for the care of non-CF bronchiectasis, but most experts recommend this therapy.

No antibiotic strategies have been adequately evaluated with well-designed randomized controlled trials, mainly because bronchiectasis patients are not a homogeneous group and the studies that have been done are difficult to compare because of diverse study designs.[37]

Infectious exacerbations should be treated with antibiotics. Some patients will need frequent courses of antibiotics for infection control. Some authors have suggested long-term antibiotic courses, aiming to reduce the bacterial population in order to avoid further inflammation and tissue destruction.[37]

Inhaled tobramycin has been tried in adults with bronchiectasis infected with *P. aeruginosa*, and improvement in clinical outcomes was noted.[38] Although a safety study has already been conducted with inhaled gentamicin, the issue of its efficacy in children still needs to be addressed.[39] Macrolides have both an antimicrobial as well as anti-inflammatory and mucoregulatory effects. Different studies have shown the benefits of this class of drugs in patients with CF. Macrolides decrease interleukin-8 and neutrophil elastase in BALFs, improve spirometry parameters, and decrease the number of exacerbations and hospital admissions in most of the studies.[40] They are usually recommended in most centers for CF patients with moderate pulmonary involvement and especially for those chronically colonized by *P. aeruginosa*. In an uncontrolled study in adults, a decrease in pulmonary exacerbations and improvement in lung function in patients with non-CF bronchiectasis receiving azithromycin for a median period of 20 months was demonstrated.[41] Similar studies in children are needed to define the role of macrolides in non-CF bronchiectasis

DNase, a mucolytic agent that causes lysis of DNA originating from bacteria and defense line cells, has been useful in the management of CF patients with bronchiectasis. However, it was found to be ineffective and potentially harmful in two studies of adults in stable condition with idiopathic bronchiectasis.[42,43]

Surgery is usually indicated when adequate control is not achieved with clinical management. In adults, persistent symptoms following a 2-year treatment program is considered an indication for surgery, as is major hemoptysis. In children, social and general well-being issues, such as a failure to comply with a chest physiotherapy program, poverty, or failure to thrive, should be considered as possible indications for a surgical approach.[23,25,26]

Good outcomes are obtained in children with localized disease, especially when there is no underlying disease that predisposes to new bronchiectasis formation and when all diseased segments can be resected. In one series, 44% of children eventually underwent surgery for localized disease.[15] Postoperative mortality is very low in most centers.[23,26]

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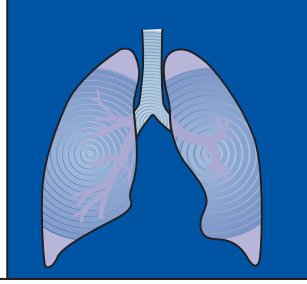


CHAPTER 70 Atelectasis

Kai-Håkon Carlsen and Bjarne Smevik

TEACHING POINTS

- Atelectasis may be caused by obstruction in the bronchial lumen or by compression of lung tissue from outside.
- The most common causes of atelectasis are obstructed airways by inflammatory processes such as in asthma or lower respiratory tract infections, or foreign bodies in the bronchial tree.
- During anesthesia, atelectasis may be a frequent, insignificant finding.
- Early intervention may reduce long-term morbidity.

Atelectasis was first described by Laennec in 1819[1] on observation at autopsy. The term *atelectasis* means "imperfect expansion" and comes from the Greek words *atelez (ateles)* for "imperfect" and *ektasiz (ektasis)* for "expansion." Atelectasis of the lung (or parts of the lungs) is an incomplete expansion of pulmonary tissue. This may be due to a congenital defect (congenital or primary atelectasis) but is mostly used to describe the collapse of lung tissue (acquired or secondary atelectasis). Atelectasis is defined as "1. incomplete expansion of a lung or portion of a lung, occurring congenitally as a primary or secondary condition, or as an acquired condition; 2. airlessness of a lung that had once been expanded; 3. collapse of a lung."[2]

ETIOLOGY AND PATHOGENESIS

Etiology

Atelectasis may be caused by several different conditions: (1) obstruction of the bronchial lumen, (2) compression of lung tissue from outside the lung, (3) muscle weakness of respiratory muscles such as the diaphragm and intercostal muscles (neuromuscular disease), and/or (4) reduction in surface tension of the the periciliary fluid lining the respiratory tract. The different causes for atelectasis are dealt with in the chapters describing other respiratory disorders, and a short list of the causes is given in Box 70-1.

The most common causes of atelectasis are airways obstructed by inflammatory processes as occur in asthma or lower respiratory tract infections or foreign bodies in the bronchial tree.

Disease Mechanisms

In congenital malformations, parts of the lung tissue may be without communication with the main bronchial tree, without the normal aerification of lung tissue developing at birth. The affected parts of the lung have never been inflated and have not undergone the normal pulmonary adaptation.[3] This is a primary atelectasis, but secondary atelectasis may develop shortly after birth, due to a congenital malformation occluding or narrowing the bronchial lumen.[4]

In secondary atelectasis, normal lung tissue may collapse due to an occluded bronchial lumen or compression. This is the most usual form of atelectasis. More than 100 years ago, Kohn[5] described collateral communications between neighboring alveoli, and at the preductal level, collateral communication between the peripheral bronchioles and adjacent alveoli has been described.[6] These collateral communications help to ensure an even ventilation/perfusion ratio in the lung. At the more proximal bronchial levels, no such collateral communications exist, and occlusion of the bronchial lumen therefore leads to trapping of the air in the lung tissue peripheral to the occlusion. The trapped air is then gradually absorbed by the blood perfusing the occluded lung tissue, and the occluded part of the lung collapses accordingly. The rate of absorption into the bloodstream depends on the solubility of the trapped gases. Atmospheric air will be absorbed within a few hours, whereas oxygen is absorbed much more rapidly, within minutes.[7] During ventilation with 100% oxygen, atelectasis may therefore develop more rapidly than during normal air breathing. This may partly explain the increased risk of atelectasis during anesthesia,[8] which is even more pronounced in the presence of respiratory tract symptoms such as cough.[8]

Secondary to the occlusion of the bronchial lumen, vasoconstriction of the pulmonary vessels perfusing the affected lung tissue will occur due to hypoxia.[9] Hypoxic pulmonary vasoconstriction appears to be the major cause of increased vascular resistance in the atelectatic lung tissue, thereby regulating the ventilation/perfusion ratio. Nevertheless, the magnitude of shunting has been found to be related to the atelectatic area seen during anesthesia.[10] In experimental studies, the dynamic compliance of atelectatic dog lung lobes increased during inflation with air, and this was found to be mainly due to increased static vascular compliance, suggesting that atelectasis results in a stiffer pulmonary capillary bed.[11]

All processes or procedures occluding the bronchial lumen may cause atelectasis or pulmonary collapse. This includes misplaced tracheal intubation, which may cause total collapse of one lung, when the distal part of the tracheal tube is located in a main bronchus (usually the right one).

BOX 70-1 Causes of Pulmonary Atelectasis

Intraluminal Bronchial Obstruction

Foreign body
- Nuts
- Plastics
- Misplaced tracheal tube
- Others

Bronchial Inflammation with Mucus Plug

Bronchial asthma
Infection
- Bronchiolitis
- Pneumonia

Cystic fibrosis
Ciliar dyskinesia
Immunodeficiency
Chronic lung disease of the newborn
After operation for atresia of the esophagus or tracheoesophageal fistula

Bronchial Wall Involvement

Airways stenosis
- After intubation
- Aspiration or inhalation injury

Tracheobronchomalacia
Bronchiectasias
Bronchial tumor
Other

Compression of Bronchi

Vascular ring
Lobar emphysema
Involvement of lymph nodes

Surfactant Dysfunction

Respiratory distress syndrome of the newborn
Adult respiratory distress syndrome
Other

Compression of Lung Tissue

Pneumothorax
Cardiac enlargement
Hemothorax
Chylothorax
Lung tumor

Primary Atelectasis

Congenital malformation

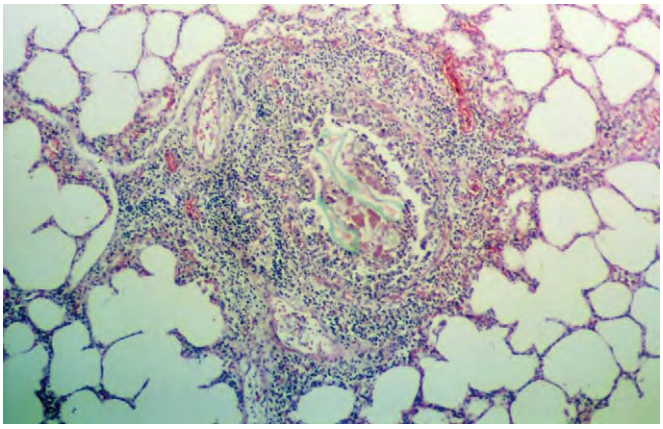


Figure 70-1 Section of lung tissue from a 20-month-old boy with bronchiolitis. The section shows mucosal and peribronchial inflammation with epithelial destruction and increased intraluminal mucosal secretions and mucus plugging. (Hematoxylin-eosin stain.) (Courtesy of Aud D. Svindland.)

Foreign bodies of the airways may result in complete or partial occlusion of a bronchus. In cases of complete occlusion, atelectasis will occur. However, even when the bronchial lumen initially is not totally occluded, total occlusion may gradually develop. Some foreign bodies will swell when exposed to the humid respiratory mucous membranes, and thereby cause complete obstruction. Impaction of a foreign body into the bronchial lumen may initiate inflammatory processes of the respiratory mucous membranes. Swelling of the mucosa may occur together with increased bronchial secretions and possibly bronchial smooth muscle contraction, resulting in total obstruction of the bronchial lumen and atelectasis.[12]

Among the most common causes of obstruction of the bronchial lumen, leading to atelectasis, are inflammatory processes within the bronchial tree, including eosinophilic inflammation due to asthma,[13-15] infections such as bronchiolitis due to respiratory syncytial virus,[16] or bacterial pneumonias. In asthma and bronchiolitis, the right middle lobe and the lingula segment are the most common areas of atelectasis, so common that this has been given the name of *middle lobe syndrome*.[17,18] Enlargement of hilar lymph nodes compressing the middle lobe bronchus has been denoted as the probable cause of this preferential localization.[18] The compression enhances the obstruction caused by inflammatory mucus, mucosal edema, and bronchial constriction. Positive bacterial culture findings in bronchoalveolar lavage fluid and in sputum from a majority of children with middle lobe atelectasis in asthma[16] or respiratory syncytial virus infections[13] have led to a suggested role of bacterial infection in longstanding atelectasis of asthma and bronchiolitis.

A number of cytokines and mediators are involved in the airways inflammation in asthma, bronchiolitis, and other respiratory tract illnesses. They have a number of effects upon the bronchial mucosa. In addition to increased mucus secretions, the following occur: edema of the mucous membranes, bronchial smooth muscle constriction, destruction of bronchial epithelium, and cessation of ciliar function with stagnating sticky mucus within the bronchial lumen (Fig. 70-1). In the atelectatic lung, altered cellular immune function has been described.[19] Airway inflammation may lead to destruction of airway epithelium, as occurs in asthma,[20] and this may alter the periciliary fluid lining the airways epithelium, reducing the effect of surfactant proteins and thereby further enhancing the tendency to bronchial collapse. Illnesses affecting the surfactant function of the airways are known to be complicated by the formation of atelectasis. This is the case for both the respiratory distress syndrome of the newborn (chronic lung disease of the newborn) and the adult respiratory distress syndrome.[18] Also, aspiration of irritating fluids

such as acids, alkali, amniotic fluid,[17] and meconium have this effect. In atelectasis of lobes or major lung segments, totally obstructed lobar or segmental bronchi may be found on bronchoscopy. All diseases that increase the susceptibility to respiratory tract infections and to stagnation of mucus are at risk for the occurrence of atelectasis. This includes several types of immunodeficiencies, congenital or acquired ciliar dysfunction,[21] and cystic fibrosis.

Processes affecting the bronchial wall causing narrowing of the bronchial lumen predispose to atelectasis. This includes airway stenosis complicating longstanding intubation, tracheobronchomalacia, vascular rings, and tumors such as polyps, papillomas, and bronchial carcinoid.[22,23] Bronchiolitis obliterans will gradually cause fibrotic obliteration of bronchi, leading to atelectasis.[24] Bronchiectasis is often caused by longstanding airways inflammation, which also may be complicated by atelectasis. Bronchiectasis may also contribute to atelectasis formation due to stagnation of bronchial secretions.

Normal lung tissue may be compressed due to extrapulmonary processes without bronchi being affected. This is seen in patients with congenital heart defects and cardiomegaly[25] but may also be due to pneumothorax (Fig. 70-2) or hemothorax.

Rounded atelectasis is a special form of atelectasis seen more often in adults than in children. It is most often asymptomatic and is thought to be associated with chronic pleural disease, lung fibrosis, or pleural effusions. It consists of infolding of atelectatic lung tissue intermingled with blood vessels, pleura, and, sometimes, bronchi.[26]

Atelectasis of lung tissue is a common manifestation in neuromuscular diseases of various types. Several mechanisms contribute in the atelectasis formation in these children. Muscular hypotonia, with reduced movement of the diaphragm, reduces ventilation and contributes to collapse of lung tissue, in addition to causing difficulties in the clearing of bronchial secretions with increased susceptibility to respiratory tract infections. The same pattern is seen in acute spinal cord injuries.[27] Hypoventilation may also be the cause of the pulmonary collapse not infrequently seen during anaesthesia in children.[8]

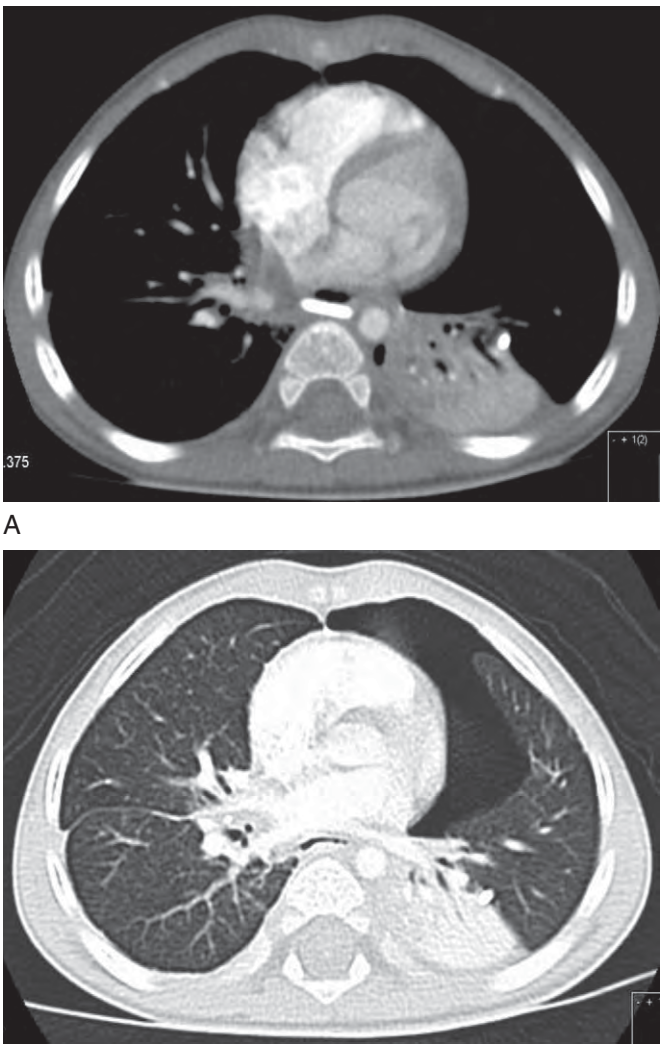


Figure 70-2 Seventeen-month-old boy with atelectasis of left lower lobe. **A,** CT scan with mediastinal window setting shows a paravertebral atelectasis on the left side. **B,** CT scan with lung parenchyma window shows a pneumothorax clearly.

CLINICAL FEATURES

The symptoms and signs of atelectasis depend on the extent of atelectasis and on the rate of formation, in addition to the age of the patient and the causative illness. In infants with bronchiolitis, atelectasis of a lung lobe, occurring suddenly, may cause a severe exacerbation in an infant who is already critically ill. Acute respiratory disturbance may also occur from the aspiration of a foreign body in a previously healthy child. On the other hand, even extensive atelectasis may pass totally unnoticed clinically. In the case of total obstruction of a bronchus, the hypoxia of the bronchial and pulmonary tissues peripheral to the obstruction will cause pulmonary vasoconstriction in the affected lung segment, thereby regulating the ventilation/perfusion ratio.[9] The net result of the atelectasis will thereby be minimized. However, in the case of atelectasis occurring during anaesthesia or in the postoperative period, significant reductions in PaO_2, FEV_1, and FVC will be seen, correlating to the size of the atelectatic area.[23]

Symptoms of pulmonary infections may occur due to atelectasis, as stagnation of secretions predisposes to secondary bacterial infections originating in the atelectatic area.

The findings during clinical examination will also depend on the size and localization of the atelectatic area. When an entire lung lobe is affected, diminished respiratory sounds may be evident on auscultation, as well as reduced resonance on percussion. With careful examination, an asymmetric expansion of the thorax may be observed with restrained expansion over the atelectatic area. In atelectasis of large areas, such as an entire lung, displacement of the heart and the mediastinum may take place.

When smaller areas of lung tissue are atelectatic, the clinical signs are scarce and difficult to observe. The diagnosis may depend entirely on chest radiography results.

DIAGNOSIS

The diagnosis of atelectasis in children must recognize the atelectasis as such, and if possible, the underlying cause of

the collapsed lung must be found. The diagnosis of atelectasis must be based on an understanding of the etiology, pathophysiology, and anatomy relevant to its development.

Usually the first imaging modality is chest radiography. Depending on the patient's age and clinical condition and the complexity of the process, the study may include frontal, lateral, and oblique views. When lung tissue collapses and atelectasis occurs, the volume of the lung tissue is reduced, and the typical radiographic changes will include elevation of the diaphragm, shift of the mediastinum, and narrowing of the rib spaces on the affected side. These signs may be missing when both lungs are affected or when compensatory emphysema develops in parts of the ipsilateral lung. In most cases, biplane chest radiographs will give adequate information about the extent of the collapsed lung parenchyma. In the majority of children, repeat chest radiographs will suffice to ascertain that the therapy is effective and that the atelectasis has finally cleared. The atelectasis will frequently be seen as an area of increased density that may vary with the location and size of the collapsed area. An atelectatic lung will present itself as a radiopaque homogeneous hemithorax (Fig. 70-3). A lobar atelectasis will often be more dense centrally than in the periphery of the lesion. When volume reduction is pronounced, it will often lead to herniation of parts of the contralateral lung across the midline (Fig. 70-4). The lower lobes are most frequently affected by atelectasis.

Different characteristic signs are associated with different locations and types of atelectasis:

- Right upper lobe atelectasis is often encountered in children after surgery. The lobe increases somewhat in density, and the interlobar fissure may be elevated (Fig. 70-5).
- Left upper lobe atelectasis may produce a density in the upper hilar region on the left side, and the mediastinal structures may be shifted to the left, together with an elevation of the left hemidiaphragm.
- Middle lobe atelectasisis is also often referred to as *right middle lobe syndrome* because of its frequent involvement with malignancies or infection causing hilar node enlargement. It is also the most commonly involved lobe in asthma patients.[15,22] The right cardiac contour is indistinct, and the atelectasis is usually better recognized on lateral films where the triangular density points to the hilus with its apex (Fig. 70-6). Compensatory emphysema may produce concave borders.
- Right and left lower lobe atelectases will produce a dense triangle medially, with the base at the diaphragm and the apex near the hilus (Fig. 70-7). The shadow of the heart may obscure this feature unless the radiograph is well exposed. In the lateral projection, the fissure is shifted posteriorly and downward.
- Segmental atelectasis affects parts of a lobe and may be more difficult to delineate (Fig. 70-8). Oblique views are more often necessary to determine the exact location.
- Focal atelectasis occurs when a subsegmental bronchus is affected, and the density is usually located in the basal lung fields and presents as a thin horizontal or plate-like line, often disappearing or "moving" between studies.
- Rounded atelectasis may be confused with a tumor on plain chest films. The computed tomography findings are quite characteristic: a rounded mass adjacent to a thickened pleural surface in the periphery of the lung with blurring of the margin closest to the hilus caused by the entering vessels and bronchi.
- Alveolar atelectasis is commonly encountered in premature babies suffering from the respiratory distress syndrome (Fig. 70-9).

Fluoroscopy may be necessary to determine the exact location of a density and may be helpful in the differential diagnosis (Fig. 70-10). It is also used when a foreign body is suspected to be the cause of the lung density.

Computed tomography (CT) often reveals atelectasis that is not recognized on chest radiographs.[23] The axial projection

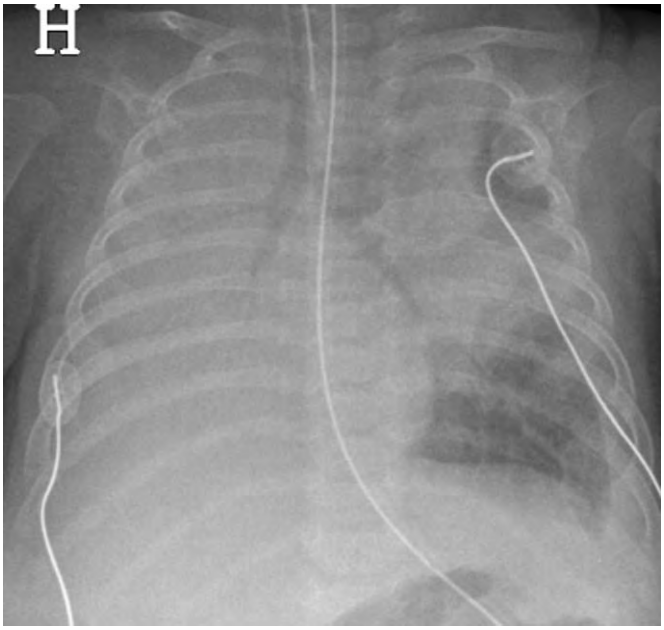


Figure 70-3 Six-month-old boy with total atelectasis of the right lung after heart surgery.

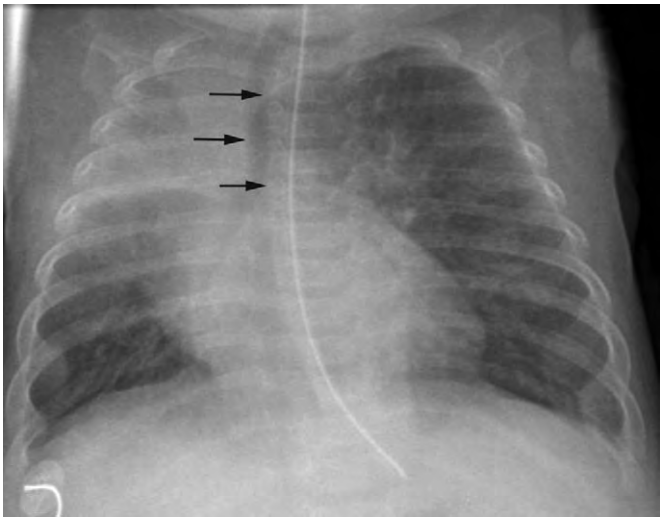
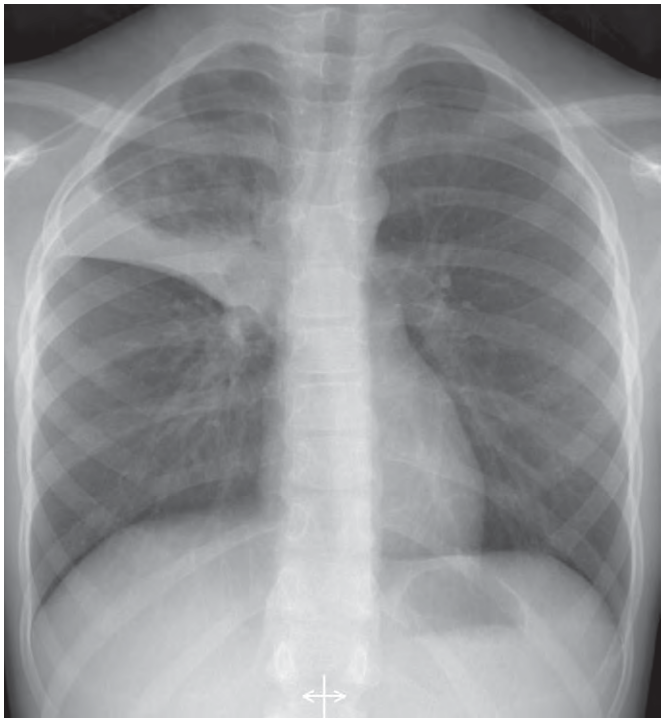


Figure 70-4 Five-month-old girl with atelectasis of the right upper lobe and herniation of the anterior portion of the left upper lobe across the midline *(arrows)*.



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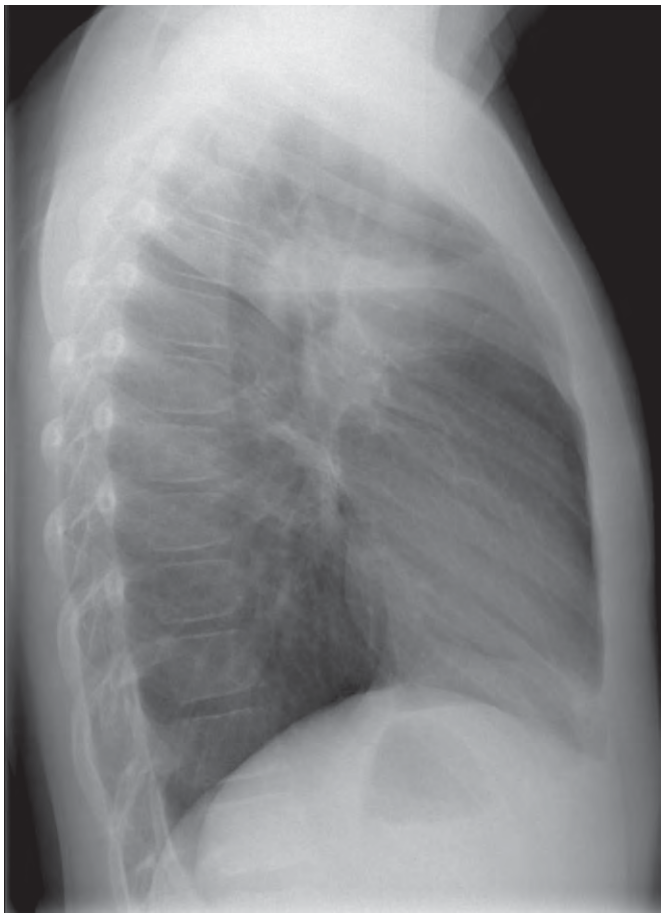
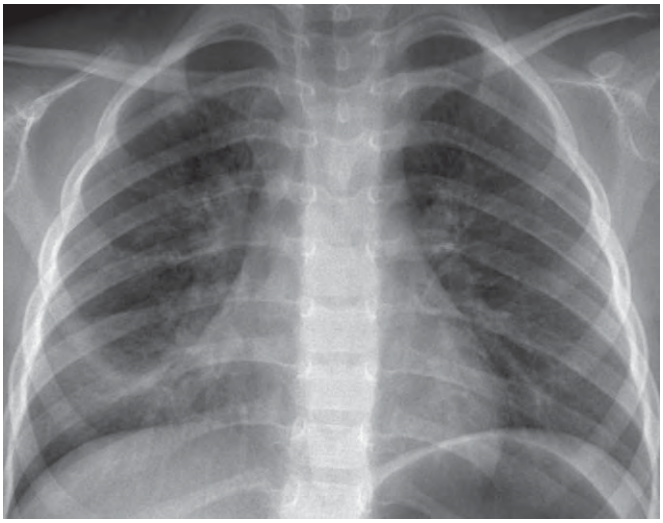


B

Figure 70-5 Eleven-year-old girl with partial atelectasis of the right upper lobe. **A,** The interlobar fissure is slightly elevated. **B,** Lateral view shows the atelectasis superior to the central lung vessels.



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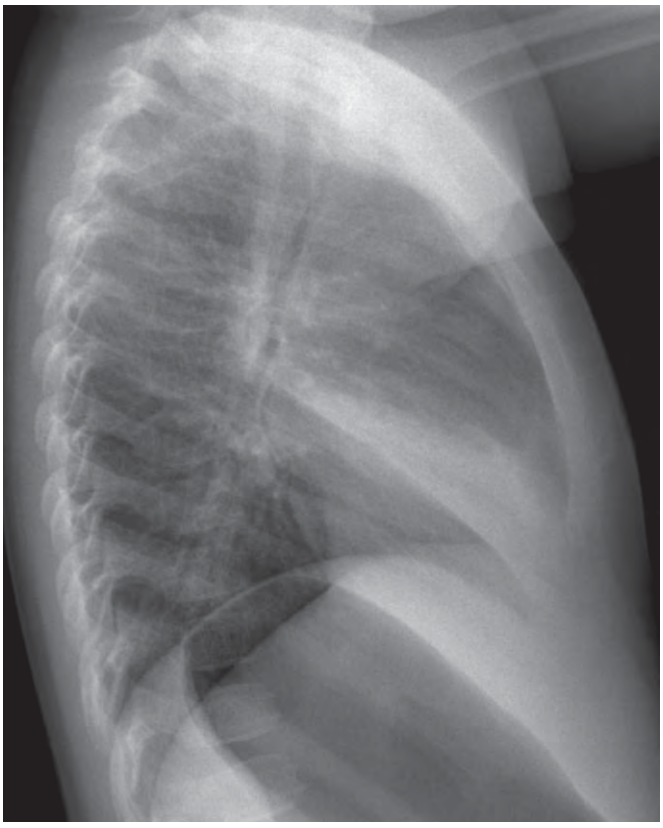

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Figure 70-6 Three-year-old girl with atelectasis of the middle lobe. **A,** Frontal projection shows blurred right heart contour. **B,** Lateral radiograph better outlines atelectasis of the right middle lobe.

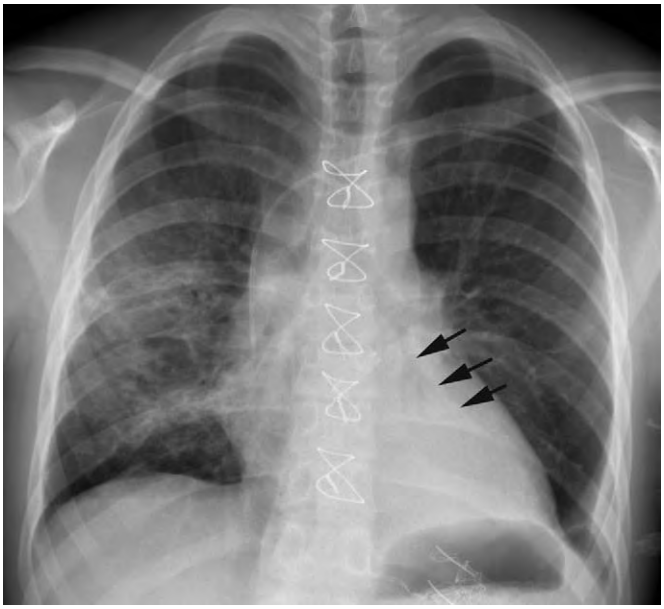


Figure 70-7 Eleven-year-old girl with atelectasis of the left lower lobe, partly obscured by the heart.

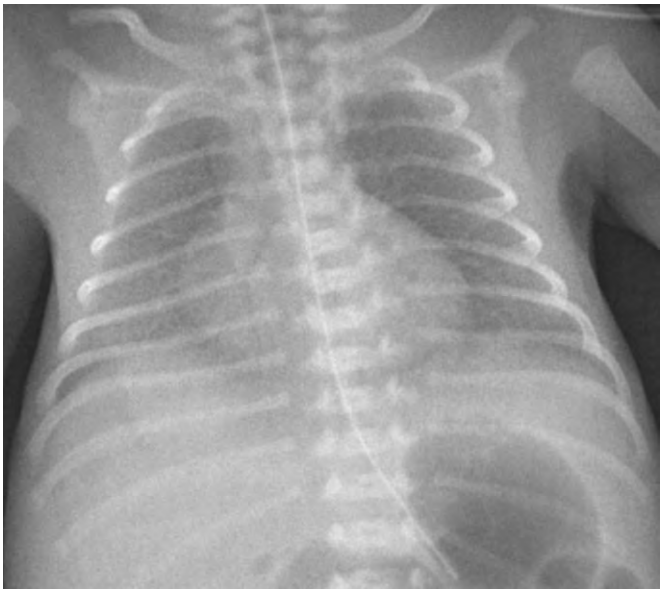


Figure 70-9 One-day-old premature boy with respiratory distress syndrome. The lungs are hypoinflated and appear gray—a result of typical microatelectases of the alveoli.

has advantages when the lesion is located in the periphery of the lungs close to the chest wall (Fig. 70-11), near the heart and great vessels, close to the diaphragm, or in the apical regions. This advantage is utilized in children with malignancies in the search for lung metastases. However, CT of the chest often necessitates general anesthesia in children, and the well-known tendency of general anesthesia to produce dependent atelectases[28] is of major concern to the pediatric radiologist (Fig. 70-12). In our experience, general anesthesia produces atelectasis in more than 90% of children, as opposed to less than 10% when light sedation is used. Multislice CT with reconstructions in two and three dimensions may help to complete the diagnostic picture in complex congenital malformations of the heart and lungs leading to atelectasis (Fig. 70-13). Magnetic resonance imaging (MRI) may also clearly depict atelectasis in the axial plane. This modality is superior when the process is located in the apical regions or near the diaphragm, because of the ability of MRI to produce pictures of equally good quality in any plane. Modern multislice CT with short examination time, thin slices, and coronal or sagittal reconstructions may offer the same diagnostic advantage, but the patient is of course exposed to ionizing radiation. The MRI signal patterns of atelectasis have been described, and obstructive and nonobstructive atelectasis may be differentiated to some extent on the basis of T2-weighted images.[29] Consolidation and atelectasis will produce different patterns both on CT and MRI.

Ultrasonography of the collapsed lung may be of some use when the density is large enough to provide an acoustic window. An underlying tumor as cause of the atelectasis may then be recognized.[30,31]

Bronchography is well suited for the diagnosis of several conditions leading to atelectasis. Bronchomalacia, short peripheral stenosis, and extrinsic compression may be revealed by this technique.

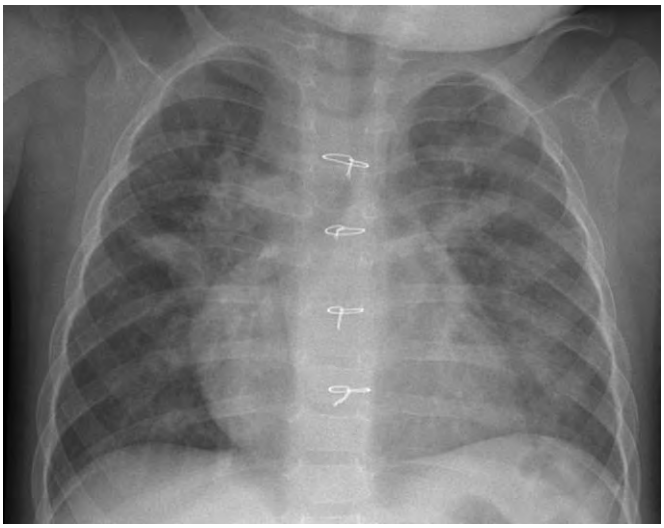


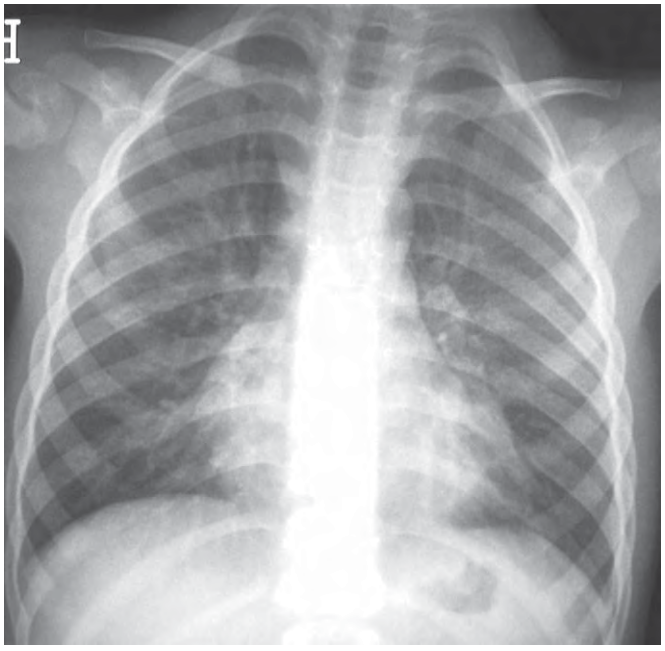
Figure 70-8 One-year-old girl with segmental atelectasis in the postoperative period after heart surgery.

Diagnosis of Atelectasis in Neonates

Alveolar atelectasis is an important aspect of the respiratory distress syndrome. Neonates (usually premature infants) often need mechanical ventilation, and during intubation, the tracheal tube may inadvertently be situated too low. This may give rise to atelectasis in the contralateral or ipsilateral lung (Fig. 70-14). Atelectasis may also be encountered in meconium aspiration and in advanced cases of chronic lung disease of the newborn.[18]

Other Diagnostic Procedures

In order to diagnose the cause of atelectasis, bronchoscopy with flexible fiberoptic bronchoscopes or rigid bronchoscopes is an important procedure. Foreign bodies in the airways



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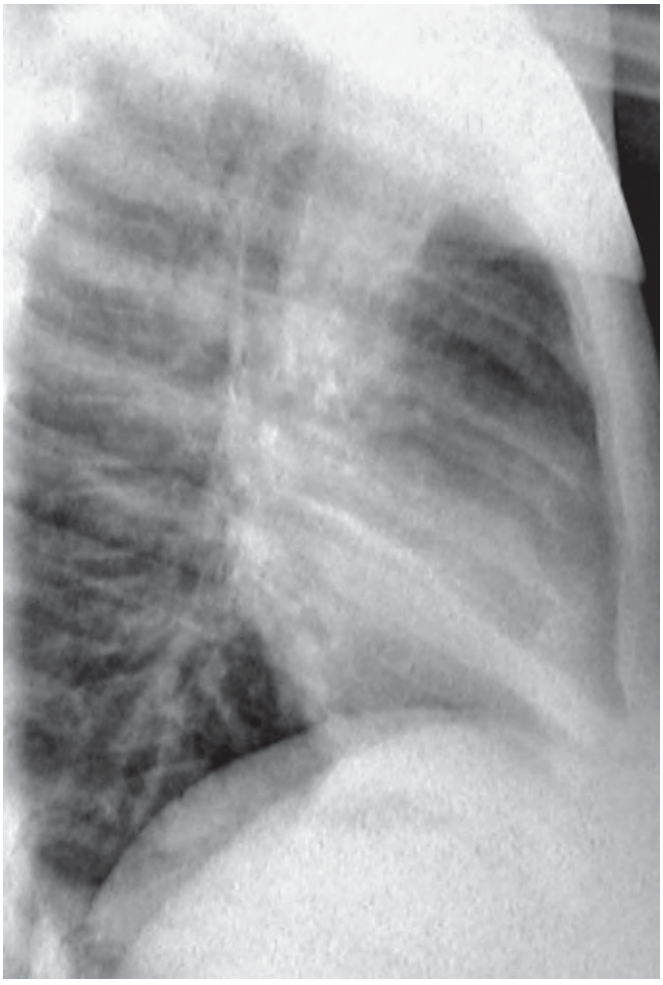

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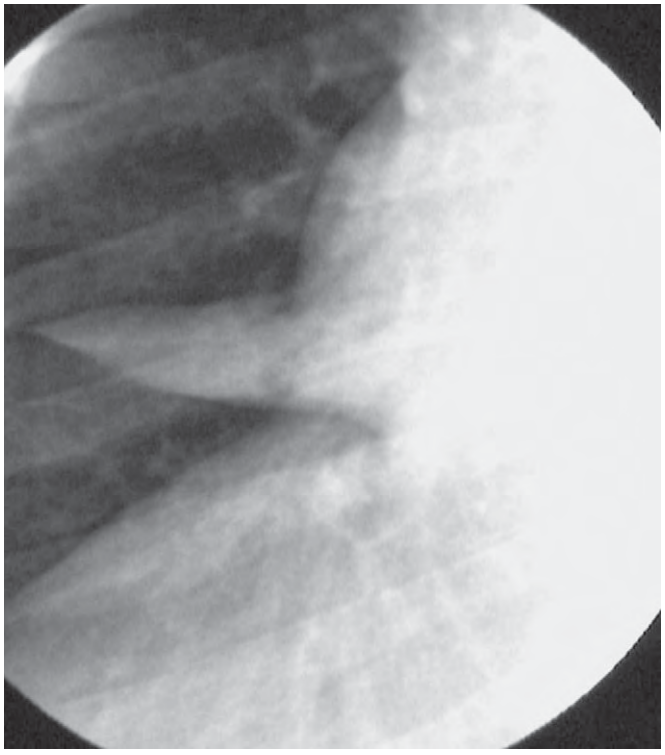


C

Figure 70-10 This 5-year-old boy had a history of unproductive cough during the past 2 weeks. **A,** Frontal chest radiograph shows only slightly blurred heart contours on both sides. **B,** Lateral chest radiograph shows an anterior density projected over the heart. **C,** Fluoroscopy angled 35 degrees caudally reveals an atelectasis in the middle lobe.

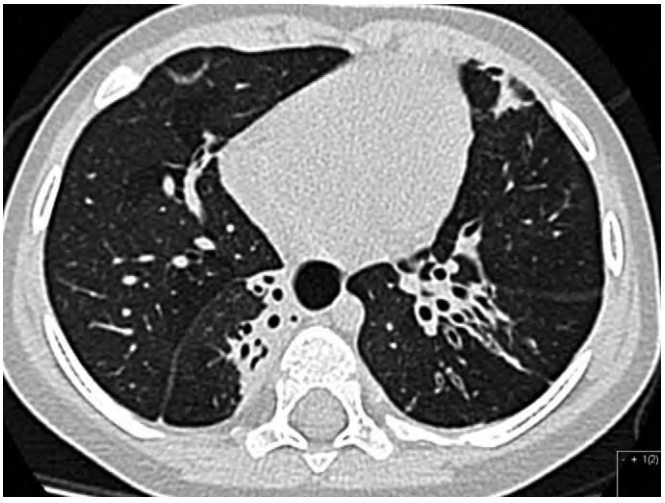


Figure 70-11 Fifteen-month-old boy with bronchiectasis and a paravertebral atelectasis, easily depicted on CT scan.

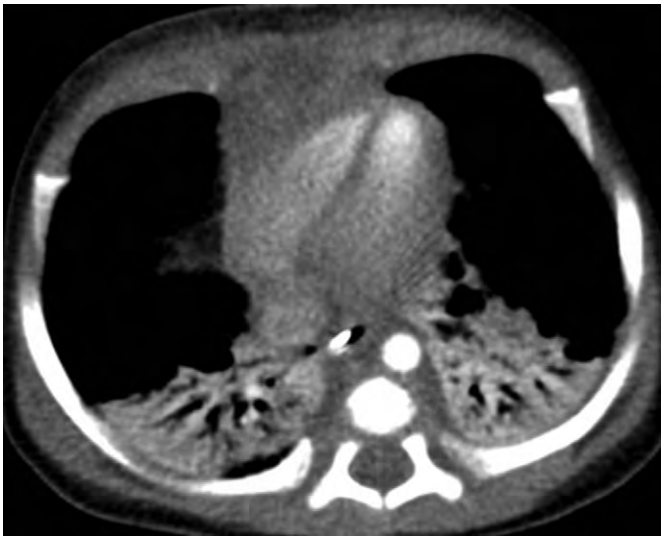


Figure 70-12 Eighteen-day-old boy with typical dependent atelectasis bilaterally, induced by general anesthesia.

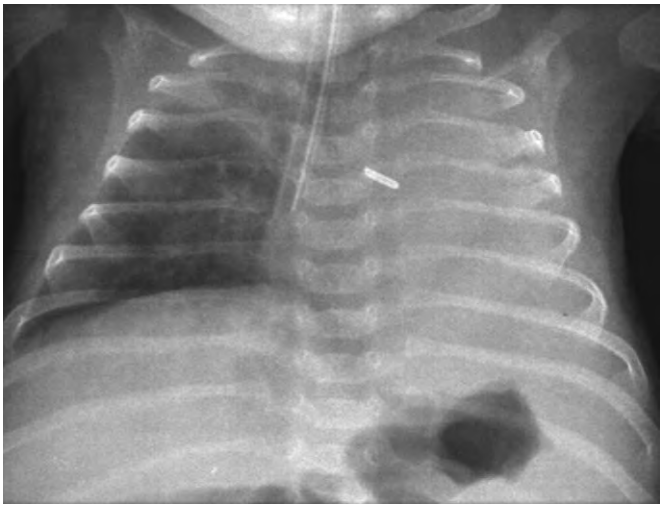
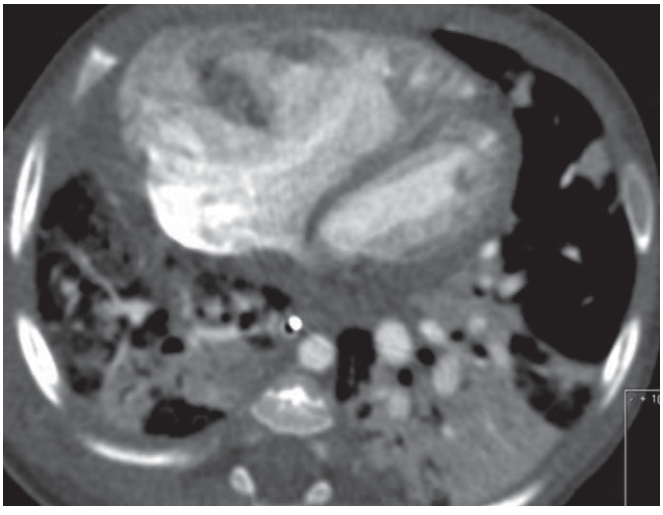


Figure 70-14 Three-month-old boy with the tracheal tube in the right main bronchus, resulting in atelectasis of the left lung and partial atelectasis of the right upper lobe.



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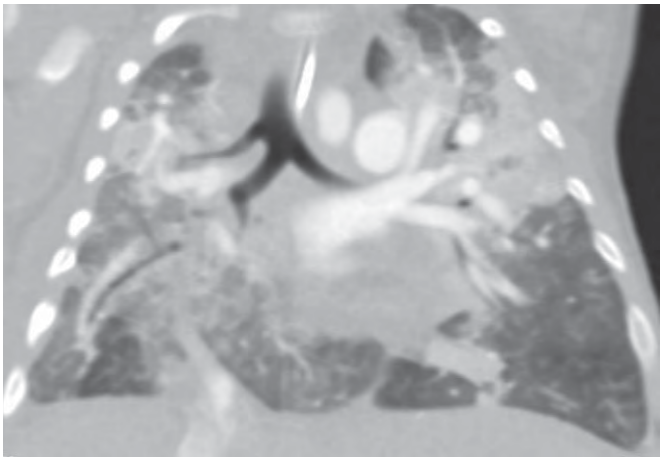

B

Figure 70-13 Four-month-old girl with anomalies in the respiratory and cardiovascular system, including an atrial septal defect, underdeveloped right pulmonary artery, an aberrant right bronchus, and tracheobronchomalacia. **A,** Axial CT scan shows posterior atelectases, partly caused by the enlarged heart. **B,** Coronal two-dimensional reconstruction shows a tracheal bronchus.

may be diagnosed, localized, and removed via the bronchoscope. Thus, bronchoscopy in such cases is the diagnostic and the therapeutic tool of choice.[32] Vascular rings and other narrow areas in the bronchi that predispose to atelectasis may be seen through the bronchoscope. Furthermore, mucus plugs (Fig. 70-15) may be visualized and removed by suctioning or bronchoalveolar lavage, followed by suctioning. Biopsy samples taken through the bronchoscope may occasionally reveal the causal diagnosis of atelectasis, such as ciliar dyskinesia.[21]

TREATMENT AND MANAGEMENT

It is important to observe that atelectasis is not a disease by itself but rather a sign of disease. Atelectasis may have several different causes, and the treatment depends on the underlying illness. Primary atelectasis seen with a congenital malformation may require surgical intervention. Atelectasis is also a frequent complication with bronchial and pulmonary tumors, even if these occur less frequently in childhood than among adults. In such cases, it is especially important to diagnose and treat the underlying cause.

When atelectasis occurs due to airways inflammation such as bronchiolitis caused by respiratory syncytial virus or acute attacks of bronchial asthma or pneumonias, the atelectasis often resolves spontaneously in a few weeks. Inhalation therapy with nebulized bronchodilators such as racemic epinephrine or β_2-agonists and saline may help in the resolution by loosening mucus plugs and dilating the airways. Such measures are often combined with chest physiotherapy, consisting of positioning, vibrations of the thorax, and suctioning.[33] The use of nebulized DNase has also been demonstrated to rapidly improve or dissolve acute atelectases caused by infections.[34] Measures such as continuous positive airways pressure breathing and positive end-expiratory pressure ventilation have also been used.[35-37] However, experience shows that physical activity of different kinds may be the most effective physiotherapeutic regimen in mobilizing mucus plugs and resolving atelectasis in children.

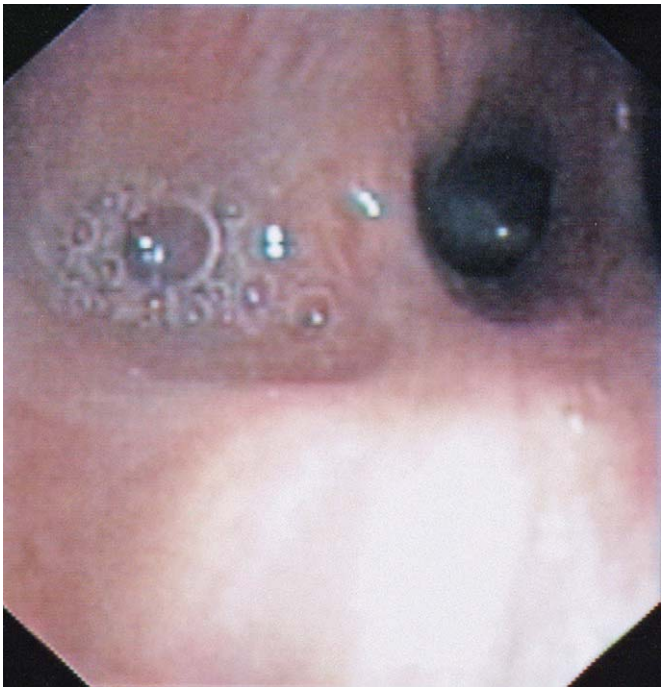

Figure 70-15 Bronchoscopy demonstrating mucus plugging of the lower lobe apical segmental bronchus on the right side. (Courtesy of Gunnar Hansen.)

Because positive bacterial culture findings from bronchoalveolar lavage or sputum often are present in atelectasis,[13,15] antibiotic treatment may be useful.

Although atelectases occurring secondary to pulmonary infections and bronchial asthma usually resolve spontaneously, this is not always the case. Diagnostic or therapeutic procedures such as bronchoscopy may then be needed.

Bronchoscopy is increasingly used in the treatment of atelectasis and is the treatment of choice for removing foreign bodies; rigid bronchoscopy is usually used.[32] When the atelectasis has been present for longer than 6 weeks, bronchoscopy is used for both diagnostic and therapeutic measures. Early intervention, after 1 month of persistent atelectasis in the right middle lobe syndrome, through diagnostic and therapeutic measures including flexible bronchoscopy and broncho-alveolar lavage, was shown to be effective in resolving the atelectasis in more than 60% of cases.[38] In many cases, mucous plugs are removed by suctioning and lavage, and the atelectasis resolves.[39] Selective bronchial suctioning in the absence of bronchoscopy has been used.[40] Instillation of surfactant through a bronchoscope has also been demonstrated to be effective in clearing lobar atelectasis in children of different ages.[41] Attempts at insufflating atelectatic lung segments have been made using a balloon-tipped catheter introduced through the nostrils or an endotracheal tube[42] or a fiberoptic bronchoscope.[43] Insufflation has mostly been used in adults. During such procedures, it is important to realize that nonatelectatic portions of the lung have higher compliance than the atelectatic portions[11] and that insufflation may result in overexpansion of the normal parts of the lung.

In neonates, the standard regimen for the resolving of atelectases consists of postural drainage with suctioning and, in some cases, also selective intubation with suctioning of a major bronchus.[44] Recently, an approach by bronchoscopy under direct vision without interrupting the mechanical ventilation has been used with success in 10 cases.[45]

When longstanding atelectasis is a sign of underlying severe lung pathology with formation of bronchiectasis, standard therapeutic measures may be inadequate. Chronic atelectatic portions of the lung are susceptible to recurrent bacterial infections. If there is no other lung pathology, lung resection may be useful, and it has been used for several different causes of atelectasis such as bronchial malformations and stenosis, sequestrations, cysts, lobar emphysema, bronchiectasis, and chronic pneumonia.[46]

As atelectasis most often is caused by airways inflammation, optimal treatment of the causative disease may be an effective prophylactic measure against atelectasis. This is the case in bronchial asthma with prophylactic anti-inflammatory therapy, in immunodeficiencies with immunosubstitution, as well as in cystic fibrosis. In patients with chronic pulmonary symptoms, it is important to use inhalation therapy with nebulized drugs in order to make the mobilization of bronchial secretions easier and to prevent mucus stagnation and plugging.

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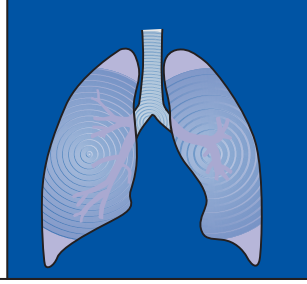

CHAPTER 71 α_1-Antitrypsin Deficiency

Robert A. Sandhaus

TEACHING POINTS

- α_1-Antitrypsin deficiency is one of the most common genetic causes of liver and lung disease.
- Although labeled as a protein deficiency, liver injury is related to excess protein accumulation.
- Screening of immediate family members of an affected individual may help identify those at risk of associated diseases.
- Reduction of environmental and infectious risk factors is key.
- Augmentation therapy is available to slow progression in those with lung disease.

The hereditary deficiency of the body's major circulating antiprotease has gone by many names since its first description in 1963: α_1-antitrypsin deficiency, α_1-proteinase inhibitor deficiency, or, more simply, alpha-1. This confusing lexicon seems even more perplexing as our understanding of the diseases associated with this condition has led to the conclusion that the major pediatric manifestation, liver injury, is due to an *overabundance* of abnormal α_1-antitrypsin protein (AAT) within the hepatocyte rather than a deficiency. Because of this, the condition will be referred to in this chapter as AATD and one is free to interpret the "D" as *deficiency* or *dysfunction*.

AATD was first described in Sweden by Eriksson and Laurell,[1] a young hepatologist and his mentor, respectively. They were studying unusual serum protein electrophoretic patterns and their initial manuscript described the association between a serum deficiency of AAT and familial, precocious emphysema in young adults. The association between liver disease and AATD was still 6 years away. Often forgotten in references to this publication is that several of the individuals described were adults without clinical sequelae associated with their AATD. It is important to remember that this condition does not invariably lead to disease. All indications are that, in the absence of environmental, infectious, or additional genetic risk factors, many individuals with AATD will lead normal healthy lives, unaffected by significant related disease.

After Sharp described the association between AATD and fulminant liver failure in newborns in 1969,[2] the stereotypical presentations of this condition became embedded in the training and experience of physicians: AATD leads to liver failure in the first months of life or emphysema in young adults. In retrospect, this understanding has hampered identification of the many affected individuals who do not fit these stereotypes, including more elderly individuals with chronic obstructive pulmonary disease (COPD), adults with liver disease, and adolescents with abnormal liver function, all due to AATD.

AATD is most commonly associated with panlobular or panacinar emphysema often predominantly affecting the lower lung fields. The National Institutes of Health Registry of Individuals With Alpha-1 Antitrypsin Deficiency documented that this lower zone predominance is not universal, with a significant proportion of affected individuals presenting with upper zone and sometimes centrilobular disease.[3]

In addition to pulmonary emphysema and liver disease, a number of other conditions have been associated with AATD, including bronchiectasis, Wegener granulomatosis, and necrotizing panniculitis.[4] This last condition is associated with a vasculitic inflammation of the vessels nourishing the subcutaneous fat, leading to necrotic, painful skin lesions. Augmentation therapy, usually reserved for the treatment of pulmonary emphysema due to AATD (see later), has been effective at reducing or eliminating panniculitis.[5] A number of other diseases have been statistically associated with abnormal AAT phenotypes, including chronic active hepatitis, nontuberculous mycobacterial infections, and a variety of other inflammatory conditions. These secondary associations often rely on demonstrating an unexpectedly high prevalence of AAT mutations in individuals already identified as having these conditions. Unfortunately, because large population-based studies identifying the exact prevalence of these abnormal AAT variants are currently lacking, conclusions about a particular prevalence being "unexpectedly high" may be subject to error. A recent summary of existing literature has suggested that over 20 million Americans carry at least one abnormal gene for AAT.[6]

There is an increased risk of hepatocellular carcinoma in individuals with AATD.[7] This increased risk was initially attributed to the increase in hepatic scarring associated with the liver disease of AATD and the known association of scarring with carcinoma risk. However, subsequent studies have found no relationship between the presence of scarring and the risk of hepatocellular carcinoma in AATD.[8]

Testing for AATD has become confusing in recent years as a proliferation of testing methodologies and reporting conventions has led to occasional misinterpretations. The simplest test, a serum level of AAT protein, is reported using

three different units of measurement depending on which laboratory is performing the test (see Diagnosis, later). A level that is severely low using the milligrams per deciliter (mg/dL) scale can appear to be within the normal range if misinterpreted as the micromolar (μmol/L) scale. The limitations of more specific testing, looking at AAT protein phenotype or directly at the genotype, must be understood to accurately assess the results.

Finally, the use of specific therapy for the lung disease of AATD has been controversial since its marketing approval in the United States in late 1987, followed by approvals in several European countries.

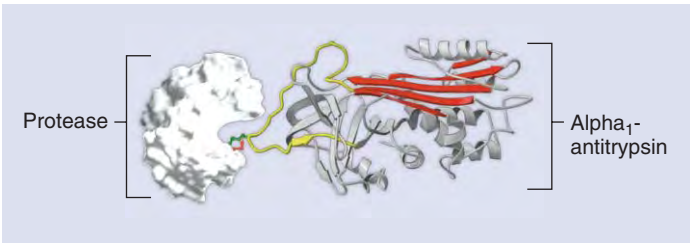

Figure 71-1 Interaction of the AAT molecule *(right)* and a representative serine protease *(left)*. The cleavage of the *(yellow)* bait loop of the AAT molecule leads to a dramatic conformational change in the complex, translocating the protease to the opposite side of the AAT molecule while inactivating its proteolytic activity. (From Carrell RW, Lomas DA: Alpha$_1$-antitrypsin deficiency—a model for conformational disease. N Engl J Med 346:47, 2002.)

EPIDEMIOLOGY, RISK FACTORS, AND PATHOGENESIS

Prevalence

The prevalence of homozygous AATD in the general U.S. population has been calculated to be between 60,000 and 100,000 individuals. This is based on a classic study by Silverman from 1983,[9] in which all St. Louis blood donors during one donation cycle (7 weeks) were tested for AATD. Recently, however, several programs have begun testing individuals with the diagnosis of COPD for AATD. These programs have reported finding between 1% and 2% of those diagnosed with COPD have undetected AATD. With a known prevalence of about 15 million individuals in the United States with diagnosed COPD, this suggests a much higher number of individuals with AATD in the general population, perhaps approaching 500,000 when individuals with AATD who have liver disease and individuals who are healthy are added to the COPD population. One explanation for the underestimate of the original study is that individuals with liver or lung disease are unlikely to be blood donors.

Structure and Function

The gene for AAT resides toward the end of the long arm of chromosome 14 (14q32.1) within the PI (protease inhibitor) locus and codes for a 394–amino acid protein with a 52,000 Da molecular weight.[10,11] The PI locus includes a number of related genes coding for a variety of protease inhibitors, many of them inhibitors of proteases with a serine in their active site. These inhibitors form the superclass of serine protease inhibitors, or serpins, and AAT has been among the most important members of the serpin family. AAT has activity against a broad range of serine proteases but is known primarily for its unique ability to effectively block the activity of the serine elastases, especially the elastase contained within the azurophilic granules of the human neutrophilic leukocyte (human neutrophil elastase [HNE])[12] (Fig. 71-1). AAT also appears to have anti-inflammatory properties that are independent of its antiprotease function.[13]

Individuals with AATD have approximately 10% to 15% of the normal circulating levels of this protein. Initially, the slight biochemical differences between "normal" AAT protein and the abnormal variant were identified using starch gel electrophoresis. Using this technique, it was soon discovered that there were individuals with aberrant gene products that did not migrate in the position of either the normal or the deficient protein. Some of these individuals had levels below normal and some had normal levels. A naming convention was devised called the PI system,[14] which assigned letters of the alphabet to these various AAT proteins (and thus their genes) according to their migration in these starch gels. The electrophoretic technique was designed to cause the normal protein to migrate to the center of the gel. The normal protein was given the letter M (PI M), the initially described deficient protein migrated much more slowly in this system and was labeled Z (PI Z), and others were added as they were identified. Isoelectric focusing (IEF) in the pH 4 to 5 range has proved to be more consistent and reproducible than the original electrophoretic techniques (Fig. 71-2). Over the years, more than 100 mutations of the AAT gene have been identified by IEF and/or DNA sequencing. Once all the letters of the alphabet were consumed, names were added based on the city of discovery and other characteristics. A group of these variants produces no measurable AAT protein. This group is known as the PI Null alleles. In all, approximately one third of the mutations to the AAT gene appear to cause the production of a Null, deficient, or dysfunctional AAT protein. The most common variant in the United States and Europe is the PI S allele, which leads to a mild deficiency of AAT in the circulation of individuals who are homozygote for this allele. The most commonly identified severe deficiency allele remains the PI Z variant. Table 71-1 lists the best-characterized AAT genotypes and their characteristics.

DISEASE MECHANISMS

Lung Injury in α_1-Antitrypsin Deficiency

Exogenously administered elastolytic proteases were shown as early as 1964[15] to be capable of causing emphysema in a variety of laboratory animal species. It was not until the first description of HNE in 1968[16] that an endogenous source of elastase was identified that might play a role in the lung destruction of human emphysema. During the 1970s, intratracheal administration of HNE was shown to be quite effective at producing emphysema in laboratory animals and AAT was shown to be an effective inhibitor of this protease and its emphysema-producing properties.[17,18] In addition, it was demonstrated that components of cigarette smoke, primarily oxidants, were capable of destroying the antielastase capacity of AAT.[19] Thus, a "protease pathogenesis" model of human

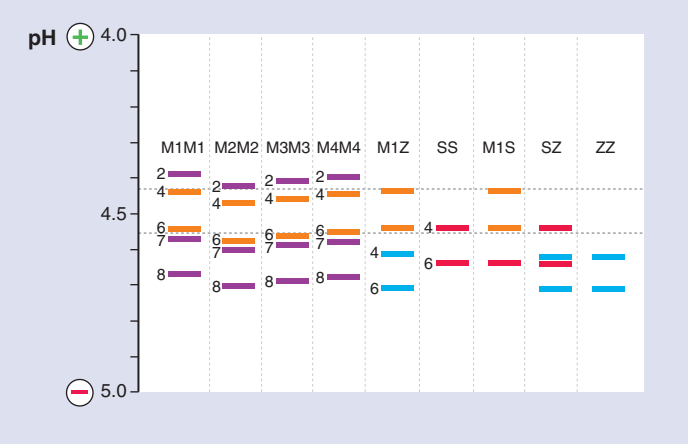

Figure 71-2 Diagrammatic representation of the banding patterns of common AAT phenotypes when evaluated using serum protein isoelectric focusing from pH 4.0 to 5.0.

pulmonary emphysema was proposed: Unbridled HNE activity is the cause of the lung destruction characteristic of pulmonary emphysema. In most individuals, the antielastase activity of AAT is used to protect against this destruction. In those with insufficient antielastase activity, due to the action of cigarette smoke on AAT or its hereditary deficiency, normal pulmonary connective tissue can be destroyed by HNE. Although most dinicians still accept that this model explains the lung destruction associated with AATD, the picture in smoking-related COPD is now considerably more complex, with contributions from other connective tissue degrading proteases and more complex oxidant–antioxidant interactions.

Several explanations have been proposed to account for the predilection for the lung as the primary target organ associated with a systemic deficiency of this important protein. The lung is an organ that is exquisitely dependent on its connective tissue architecture, and destruction of this architecture tends to be irreversible. The lung has the largest capillary bed of any organ, and its function depends on putting this large blood supply in intimate contact with the outside world. The neutrophil is one of the primary sentries guarding the lung from invasion by bacteria and other inhaled agents. While diapedesis and phagocytic ingestion of bacteria looks elegant under the microscope, in fact, neutrophils have been shown to spill their proteolytic contents into the surrounding environs during this process. In most individuals, there is sufficient AAT bathing the pulmonary connective tissue to prevent this destructive cocktail from degrading normal lung tissue. This appears to be true even in individuals with AATD. However, when the protease load is too large or there has been local inactivation of AAT by environmental oxidants such as cigarette smoke, destruction of elastin and other connective tissue will occur. In most other organs of the body, such environmental factors do not play as direct a role.

Clearly, the coexistence of AATD and cigarette smoking is to be avoided. But the other side of the protease-antiprotease balance is upset in AATD as well. Individuals with AATD, even without documented lung disease, have a higher percentage and number of neutrophils in their lungs, as judged by bronchoalveolar lavage.[20] Events that stimulate the migration of neutrophils to the lungs such as pulmonary bacterial infections move this balance even farther in the direction favoring accelerated connective tissue destruction. Whereas most investigations have focused on this connective tissue destruction, recent studies have evaluated the cellular components that make up the alveolar unit and found that pulmonary epithelial apoptosis is also increased during processes that produce connective tissue injury.[21]

Liver Injury in α_1-Antitrypsin Deficiency

Our understanding of the pathophysiology of the liver disease of AATD has taken longer to evolve and is still incomplete. When the association between AATD and neonatal liver disease was first described, an unusual histologic feature was noted during microscopic evaluation of livers from affected individuals. Large inclusions were found in the periportal hepatocytes of these specimens. These inclusions stained with periodic acid–Schiff (PAS) and were diastase resistant.[2] Speculation about the nature of these inclusions ended when immunostaining demonstrated that this material was predominantly AAT.[22]

When the three-dimensional structures of PI M and PI Z AAT were evaluated and compared, the differences between the two forms suggested the possibility that the PI Z form might be susceptible to polymerization.[23] This was demonstrated in vitro, and polymerized PI Z AAT was also identified by immunoelectron microscopy within the hepatocyte inclusions from the livers of affected individuals.[24,25] Using these techniques, it was concluded that the PAS-positive hepatocyte granules represent rough endoplasmic reticulum engorged with polymerized AAT. These inclusions exist in all individuals with PI Z AATD, and in those heterozygous for this abnormal allele (PI MZ). There does not appear to be a relationship between the size or the number of these inclusions and the development of liver disease. In contrast, however, individuals with two Null genes, whose hepatocytes make no AAT protein, have no hepatocyte inclusions and do not appear to have an increased risk of liver disease, suggesting that these inclusions are at least necessary for the development of liver injury. Recent preliminary data have suggested that a second inherited defect in the intracellular trafficking of misfolded proteins may account for the severe perinatal liver disease seen in about 2% of those born with AATD (Richard Sifers, Baylor University, personal communication).

GENETICS

As with most non–sex-linked genetic traits, each individual carries two AAT genes, one inherited from each parent. The expression of the AAT trait is codominant rather than recessive. In codominant expression, each gene appears to contribute equally to the quantity of translated protein made in the cell. Thus, whereas an individual with AATD has about 10% to 15% of the normal AAT level in serum, a heterozygote for AATD, such as PI MZ, will have a level intermediate between normal and deficient. Certain heterozygote combinations have an increased risk of lung disease including PI SZ and PI MNull. There are about 8 million individuals in the United States with the PI MZ phenotype. A meta-analysis of case-

Table 71-1
Well-Characterized Abnormalities of the α_1-Antitrypsin Genome

Allele	Background	Exon	Mutation
Normal Level and Function			
M1(Ala213)*			
M2*	M3	II	Arg101 CGT to His CAT
M3*	M1(Val213)	V	Glu376 GAA to Asp GAC
B alhambra	?	?	Lys to Asp
L frankfurt	M2	II,III	Gln156 CAG to Glu GAG/Pro255 CCT to Thr ACT
L offenbach	M1(Val213)	V	Pro362 CCC to Thr ACC
M1(Val213)	M1(Ala213)	III	Ala213 GCG to Val GTG
M2 obernburg	M1(Ala213)	II	Gly148 GGG to Trp TGG
M4	M1(Val213)	II	Arg101 CGT to His CAT
M5 karlsruhe	M1(Val213)	II	Ala34 GCC T to Thr ACC
M5 berlin	M1(Val213)	II	Pro88 CCG to Thr ACC
M6	M1(Val213)	II	Ala60 GCC to Thr ACC
P st albans	M1(Val213)	III,V	Asp341 GAC to Asn AAC/Asp256 GAT to Asp GAC
P st. louis	M2	III	Met221 ATG to Thr ACG
V	M1(Val213)	II	Gly148 GAC to Asn AAC
V donauworth	M1(Val213)	V	Asp341 GAC to Asn AAC
V munich	M1(Val213)	II	Asp2 GAT to Ala GCT
X	M1(Val213)	III	Glu204 to Lys
X christchurch	?	V	Glu363 to Lys
Deficient Level			
I	M1(Val213)	II	Arg39 CGC to Cys TGC
M heerlen	M1(Ala213)	V	Pro369 CCC to Leu CTC
M malton	M2	II	Phe52 TTC to delete
M mineral springs	M1(Ala213)	II	Gly67 GGG to Glu GAG
M procida	M1(Val213)	II	Leu41 CTG to Pro CCG
M palermo	M1(Val213)		Phe51 TTC to delete
M nichinan	M1(Val213)	II	Phe52 TTC to delete/Gly148 GGG to Arg AGG
P lowell	M1(Val213)	III	Asp 56 GAT to Val GTT
P duarte	M4	III	Asp256 GAT to Val GTT
S	M1(Val213)	III	Glu264 GAA to Val GTA
Siiyama	M1(Val213)	II	Phe53 TTC to Ser TCC
T	M2	III	Glu264 GAA to Val GTA
W bethesda	M1(Ala213)	V	Ala336 GCT to Thr ACT
Ybarcelona	?	III/V	Asp256 GAT to Val GTT, Pro391 to His391
Z	M1(Ala213)	V	Glu342 GAG to Lys AAG
Z ausburg	M2	V	Glu342 GAG to Lys AAG
Dysfunctional			
F	M1(Val213)	III	Arg223 CGT to Cys TGT
M pittsburgh†	?	V	Met358 to Arg
Null			
QO bellingham	M1(Val213)	III	Lys217 AAG to stop 217 TAG
QO bolton	M1(Val213)	V	Pro362 CCC to delete C to 5′ shift to stop 373 TAA
QO bonny blue	M1(Val213)	*	DG deletion at position 1 of intron II splice acceptor
QO cairo	M1(Ala213)	III	Lys259 AAA to stop 259 TAA
QO clayton	M1(Val213)	V	Pro362 CCC to insert C to 3′ shift to stop 376 TGA
QO granite falls	M1(Ala213)	II	Tyr160 TAC to delete C to 5′ shift to stop 160 TAG
QO hong kong	M2	IV	Leu318 CTC to delete TC to 5′ shift to stop 334 TAA
QO isola di procida	?	II-V	10-kb deletion of exons II-V, DII-V
QO kowloon	M1(Val213)	II	Tyr38 TAC to stop TAA
QO lisbon	M1(Val213)	II	Thr68 ACC to IleATC
QO ludwigshafen	M2	II	Ile92 ATC to AsnAAC
QO mattawa	M1(Val213)	V	Leu353 TTA to insert T to 3′ shift to stop 376 TGA
QO new hope	M1(Ala213)	IV,V	Gly320 GGG to Glu GAG/Glu342 GAG to LysAAG
QO riedenburg	?	II-V	Deletion of exons II-V, DII-V
QO saarbruecken	M1(Ala213)	V	Pro362 CCC to insert C to 3′ shift to stop 376 TGA
QO trastevere	M1(Val213)	III	Trp194 TGG to stop TGA
QO west	M1(Val213)	*	G-to-T position 1 of intron II splice donor substitution

*Classic "normal" alleles.
†Has anti–thrombin III activity.
Data courtesy of Dr. Mark Brantly, University of Florida College of Medicine, Gainesville, Florida.

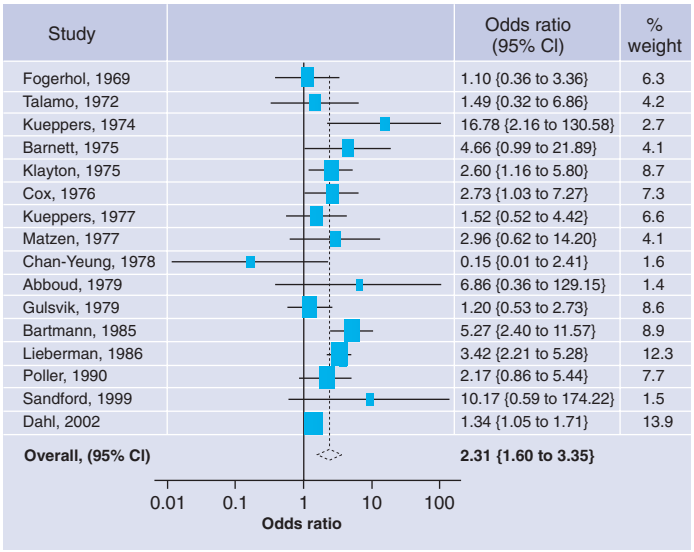

Figure 71-3 Summary results of meta-analysis of case-control and cross-sectional studies of COPD in AATD heterozygotes. (From Hersh CP, Dahl M, Ly NP, et al: Chronic obstructive pulmonary disease in α_1-antitrypsin PI MZ heterozygotes: A meta-analysis. Thorax 59:843, 2004, reproduced with permission from the BMJ Publishing Group.)

control studies in individuals with PI MZ demonstrated an increased risk of developing COPD compared with the general population (odds ratio, 2.31; 95% confidence interval, 1.60 to 3.35)[26] (Fig. 71-3).

CLINICAL FEATURES

When AATD is detected in the pediatric setting, it is usually because of liver disease in the child or because a family member has been diagnosed and family screening has been recommended. The majority of infants born with severe AATD (PI ZZ) will have abnormal liver function tests as an infant, primarily characterized by transaminase elevations.[27] Approximately 5% will develop clinically significant liver disease during their first year of life and, of these, approximately 40% (2% overall) will develop liver failure, with the remainder returning to normal liver function. While elevated transaminase levels are usual, when overt liver disease occurs in AATD, it is often accompanied by jaundice, an enlarged liver, and failure to thrive. A predominantly cholestatic picture can be seen, usually in those with more severe disease. Whether the presence of AATD can aggravate typical neonatal hyperbilirubinemia has not been fully evaluated.

Early studies suggested a strong family clustering of childhood liver disease, and, in fact, some recommended that parents of a child with AATD-related liver disease should strongly consider avoiding having additional children.[28] However, although there is a degree of this clustering, more recent data have shown that these early studies represented an extreme not seen in common practice.

Lung disease associated with AATD is extremely rare before the age of 20, and even those cases reported as AATD-related lung disease during childhood may well represent congenital cysts or blebs, rather than true emphysema due to AATD. The role of AATD as a risk factor for childhood and adult asthma is not well established. Whereas it is true that most individuals who develop lung disease as an adult have a history of childhood or adult asthma, until a prospective evaluation of asthma incidence is performed, it is difficult to evaluate these self-reported data. Animal studies have found that AAT can decrease bronchial hyperreactivity.[29] In humans, early research suggested airway hyperresponsiveness was associated with certain specific heterozygous phenotypes of AATD.[30] Recent work, however, with larger numbers of patients has not supported AATD as a risk factor for asthma.[31]

Whether a major inflammatory lung disease such as severe pneumonitis could overwhelm the antiprotease capacity of the child with AATD and lead to more lung damage than might otherwise take place seems a possibility but has been difficult to study. Recent epidemiologic reports have concluded that one risk factor associated with lung disease in adults with AATD is parental smoking during childhood.[32] This suggests that lung injury occurring during childhood may manifest itself later in life in those with AATD.

Neonatal screening for a variety of genetic conditions is becoming more common, and it is likely that testing for AATD will be included in such panels. Therefore, it will become more common for the pediatrician to be confronted with a healthy baby diagnosed with AATD and be asked to discuss the implications and risks associated with this finding. Currently, recommendations for the healthy child identified with AATD include immunization against influenza and viral hepatitis, smoking prevention, avoidance of second-hand smoke, and rapid treatment of pulmonary infections.

Because AATD is a condition that can affect the entire family of the identified individual, screening of family members is often recommended. Currently, there are risks associated with screening of healthy individuals; these risks are primarily related to potential genetic discrimination in obtaining health or life insurance or in employment. Some states have provided full or partial remedy to these risks through legislation that prohibits such discrimination. Another form of testing risk relates to studies that have demonstrated that some parents of healthy children identified as having AATD have reported treating those children differently from their other children without AATD, viewing the child with AATD as more vulnerable or ill.[33] All these potential risks must be weighed against the benefits of preventing future lung and liver disease.

The majority of adults identified with AATD, when not identified by family screening, are diagnosed because of precocious emphysema or emphysema out of proportion to their smoking history. Unfortunately, this diagnostic bias toward those with early onset disease often prevents the clinician from considering the testing of individuals with more usual COPD. Individuals with mild lung disease due to AATD may have normal spirometry and other tests of pulmonary physiology but have emphysema noted on computed tomography of the chest (chest CT). Bronchiectasis, often asymptomatic, is a frequent additional finding on chest CT of adults with AATD. Testing for AATD should be included in the work-up of any individuals with unexplained bronchiectasis.[34]

Autopsy studies from Sweden have demonstrated that liver disease is more common in adults with AATD than previously thought. In that study, more than 50% of adults over 65 years of age with AATD had histologic evidence of

liver scarring, although these changes were asymptomatic in most individuals.[35]

DIAGNOSIS

In the mid-1990s, Stoller and coworkers.[36] found that, on average, it took evaluations by at least three different physicians over approximately 7 years from the time symptoms first appeared until the diagnosis of AATD was made. Follow-up studies published in 2006 found little had changed over the decade since that original publication.[37,38]

The diagnosis of AATD can be made with a simple blood test, but the choice of which test(s) to do and how to interpret the results may not be simple (Table 71-2). The least expensive and most widely available test is a blood or serum level of AAT protein and usually requires drawing a tube of blood. However, even this simple test has its limitations. As mentioned, the results of an AAT level can be expressed using three different units of measurement. These are milligrams per deciliter (mg/dL), micromoles (μmol/L), and grams per liter (g/L, used mostly in Europe). Thus, it is important to check which units are being used by the laboratory performing the test and to check that laboratory's normal range, because these are laboratory specific. Assuming the units have been considered, a level measurement can identify individuals with severe AATD such as PI ZZ, PI ZNull, and PI NullNull. Although AAT is an acute phase reactant and even severely deficient individuals can raise their levels somewhat in response to stress such as inflammation or infection, in general, individuals with a severe deficiency cannot raise their level into the normal range. Severe deficiency is generally defined as a level at or below 58 mg/dL, 11 μmol/L, or 0.58 g/L. In most settings, the risk of adult lung disease is a function of the level of AAT in the blood and tissues and the phenotype/genotype predicts the level for the most common abnormalities of the AAT gene (Fig. 71-4).

Level testing has other limitations as well. Because heterozygotes can have levels approaching or within the normal range, level testing is not the best way to detect these carriers of a single abnormal gene or individuals with mutations that do not cause severe deficiency. In addition, there are rare phenotypes such as PI F and PI $M_{pittsburgh}$ that lead to production of normal or near-normal levels of a dysfunctional protein.

When an unusual variant is suspected or when carriers of a single abnormal gene need to be detected, such as in family screening, additional testing in the form of *phenotyping* (electrophoretic evaluation of the circulating AAT protein) or *genotyping* (evaluation for abnormal AAT genes) should be done. Phenotyping requires a tube of blood to obtain a plasma

Table 71-2
Testing Methodologies

Test Type	Method	Sample Needed	Benefits	Limitations
Level	Quantification of α_1-antitrypsin antigen in blood or serum (results expressed in μmol or mg/dL)	Tube of blood	Inexpensive, readily available	Confusion regarding units and normal range. Cannot definitively detect heterozygotes or unusual mutations.
Phenotype	Isoelectric focusing of α_1-antitrypsin protein in plasma or serum	Tube of blood	Detects most molecular variants of α_1-antitrypsin. Detects heterozygotes.	Expensive. Requires training and experience to read accurately. Will miss Null variants.
Genotype	Nucleotide probes used to identify mutations of interest in α_1-antitrypsin gene of leukocytes	Tube of fresh blood, or dried blood spot on special filter paper, or buccal swab	Automated, high-volume testing requiring minimal experience to read.	Can only detect variants for which probes are available. Often uses only probes for Z and S alleles. Will miss rarer variants and nulls as method is usually applied.

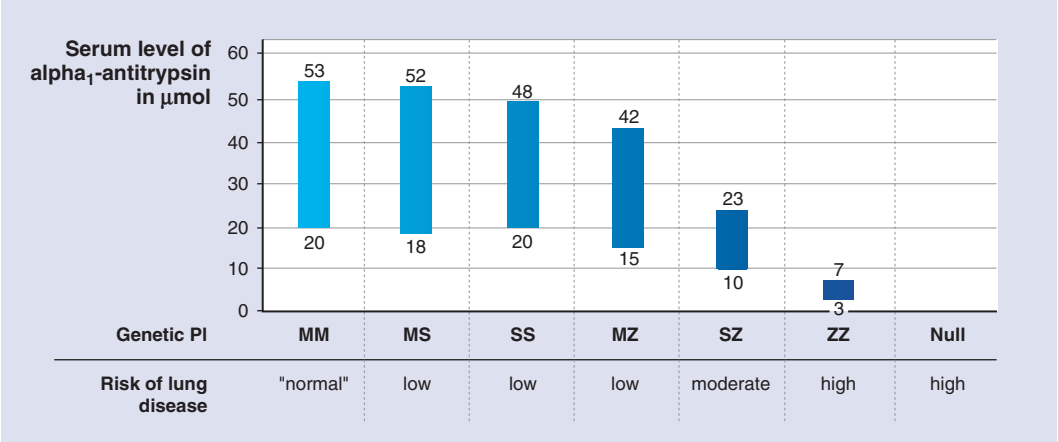

Figure 71-4 Relationship between AAT phenotype, blood, and risk of lung disease in adults with AAT deficiency.

or serum sample. Genotyping can be performed using a fresh tube of anticoagulated blood or a specific finger stick or buccal swab kit. One might assume that genotyping would be the gold standard in testing, because it looks at the AAT gene itself. However, as currently implemented in most laboratories, genotyping uses probes for specific abnormal genes, usually the genes coding for the Z variant and the S variant. Thus, other, rarer abnormal genotypes can be missed using this technique.

For most testing situations requiring more than a simple blood level, phenotyping of circulating AAT protein using isoelectric focusing is the test of choice. Many commercial laboratories offer this service. It is a very labor-intensive methodology and requires experience on the part of the person reading the gels to identify rarer phenotypes.

One specific area of some concern to the pediatrician is identification of carriers of a Null allele. When two Null genes are present, the diagnosis is readily apparent, for the patient has no circulating AAT protein. A carrier of a single Null gene presents a silent gene to phenotyping and usual methods of probe-based genotyping. Thus, a physician can be presented with the situation in which the child of a parent identified as PI MM is tested and reported to be PI ZZ. Questions of paternity or hospital nursery error are often the first thoughts that come to mind. However, if, in fact, one parent is actually PI MNull, it is possible this parent and his or her PI ZNull child were incorrectly identified as homozygotes for the more easily identified M and Z genes.

For the most unusual or questionable cases, reference laboratories studying AATD can perform gene sequencing. To identify sites with extensive experience in identifying unusual phenotypes/genotypes and where sequencing can be done, one can call the Alpha-1 Foundation (888-825-7421). Regardless of the method used to detect an individual with AATD, it is generally recommended that positive results be repeated for confirmation.

TREATMENT

The treatment of AATD depends on the clinical presentation of the affected individual. Individuals identified with AATD but demonstrating no clinical disease need no treatment except education and regular follow-up for signs of liver or lung problems. Family testing should be considered. Risk factors for disease should be reduced or eliminated. This includes smoking prevention or cessation, avoidance of second-hand cigarette smoke, avoidance of chronic exposure to dusts or organic fumes, and prevention and treatment of target organ infection. The role of alcohol consumption in the promotion of liver disease is assumed but not well documented. The best evidence for this is the fact that adults with AATD and elevated serum liver enzymes often see a normalization of their liver function with abstinence from alcohol. Therefore, moderation of ethanol intake should be recommended.

The liver disease associated with AATD does not have a specific therapy at present. Usual supportive therapy for liver injury is the norm. This includes promotion of adequate nutrition, prevention of vitamin deficiency, treatment for ascites if present, and control of potential hemorrhagic complications associated with coagulopathy and/or portal hypertension. Those with liver failure due to AATD may be candidates for liver transplantation. AAT deficiency is a major cause of liver transplantation in children and a growing cause in adults. Successful liver transplantation provides an interesting result in AATD because replacing the failing liver with a normal donor liver also corrects the plasma and tissue deficiency AAT. Although the other cells of the body still have the abnormal genotype, and thus such transplant recipients can still pass an abnormal gene on to their offspring, the transplanted liver now has a normal genotype and releases normal amounts of AAT protein.

Avoidance of risk factors for liver injury is key, although no specific risk factors for severe neonatal cirrhosis have been identified. In older children and adults with AATD, exposure to infectious agents that target the liver and exposure to liver toxins should be prevented by appropriate immunization and counseling in the avoidance of excessive alcohol consumption and occupational exposures to certain organic chemicals, primarily cyclic/aromatic molecules.

Similar to liver disease, the treatment of the lung disease of AATD is based on the usual treatment of chronic obstructive lung disease from any cause (Table 71-3). Smoking cessation is of primary importance in individuals with lung disease due to AATD, as is avoidance of second-hand smoke. Prevention of pulmonary exacerbations is paramount in slowing the progression of COPD in general, including those with COPD due to AATD. Inhaled therapies with bronchodilators and steroids have been documented to reduce the incidence of such exacerbations. Treatment of exacerbations should be aggressive to minimize the time that lung tissue is exposed to an increased protease burden. Many recommend immediate initiation of antibiotic therapy and short burst oral steroids for severe exacerbations.

In addition and in contrast to the liver disease of AATD, there is specific therapy available for AAT deficient individuals with emphysema. This therapy, known as augmentation or replacement therapy (currently in the United States: Prolastin from Talecris Biotherapeutics, Aralast from Baxter Healthcare, and Zemaira from CSL Behring), relies on intravenous infusion of purified human AAT protein derived from the plasma of healthy donors. Given as a weekly infusion of 60 mg/kg, augmentation therapy is widely used in the United States and Europe. It is only approved for use in adults with documented pulmonary emphysema. Emphysema due to

Table 71-3
Treatment of Lung Disease Due to α_1-Antitrypsin Deficiency

Treatment	Goal	Improve Survival?
Smoking cessation	Reduce inflammation	Yes
Immunizations	Reduce infection	Not documented
Avoid inhaled agents	Reduce risks	Not documented
Bronchodilators	Prevent exacerbations	Not documented
Inhaled corticosteroids	Prevent exacerbations	Not documented
Pulmonary rehabilitation	Improve quality of life	Not documented
Antibiotics	Treat exacerbations	Not documented
Supplemental oxygen	Reverse hypoxemia	Yes
Augmentation therapy	Replace deficient protein	Yes

AATD rarely occurs in individuals younger than the third decade.

Based on the known pathophysiology of the lung destruction of AATD, it is widely accepted that augmentation therapy slows the progression of emphysema in AATD. Although no randomized controlled trial has supported the efficacy of augmentation therapy, a number of large case-control studies have demonstrated significant beneficial effects on such outcomes as rate of decline of lung function,[3,39,40] incidence of pulmonary exacerbations,[41] and survival[3] for individuals receiving augmentation therapy compared with similar AATD patients not receiving such therapy.

The most severely lung-affected individuals are often candidates for surgical intervention. Lung transplantation, either single or double, is effective at improving the pulmonary function and quality of life in individuals with a successful procedure. It now appears likely that survival is also prolonged in those receiving a lung transplant, although the documentation of this improved survival is just now accumulating. Lung volume reduction surgery (LVRS) is also considered in some patients. The National Emphysema Treatment Trial (NETT) suggested that the classic AATD patient is unlikely to be a good candidate for LVRS, however. NETT demonstrated that individuals with diffuse destructive lung disease and/or a low diffusing capacity of the lung for carbon monoxide (DLCO) are likely to have a significantly higher mortality from LVRS than those managed without surgery.[41] The lung disease of AATD is often characterized by its diffuse nature (panlobular emphysema) and resultant low DLCO.

CLINICAL COURSE AND PROGNOSIS

As with many medical conditions, especially those with gene by environment interactions, the clinical course of individuals with AATD is highly variable. While it was initially assumed that all individuals with AATD would develop precocious, life-shortening pulmonary emphysema, this is now considered the exception rather than the rule. As more affected individuals are identified, the spectrum of "disease" includes a population of unknown total size who will never develop any medical problems related to their AATD; those with liver disease, from mild to severe and with an age of onset from the newborn to elderly; and those with lung problems ranging from mild asthma to severe emphysema and/or bronchiectasis beginning in the early decades of adult life and extending to individuals whose symptoms start in their eighth or ninth decades.

Augmentation therapy appears to improve the prognosis of those with the lung disease of AATD. In addition, it has been documented that an integrated patient-directed disease management program has beneficial effects on both quality of life and health care utilization in this same population. Still, as a whole, individuals with AATD tend to have shortened life span, increased disability, and poorer quality of life compared with the general population. In addition, there is the added psychological burden of passing this condition on to one's children (Box 71-1).

SUMMARY

AAT is one of the body's major defenses against proteolytic attack and has potent anti-inflammatory properties. The hereditary deficiency of this protein is among the most prevalent genetic risk factors for disease in humans and the most common genetic cause of COPD. AATD increases the risk of lung and liver disease and predisposes to a variety of other clinical sequelae. Still, the diagnosis is often delayed, with many affected individuals complaining of significant symptoms for many years before being identified. A variety of interventions have proved to be effective at improving quality of life and slowing the progression of symptoms.

BOX 71-1 Pitfalls and Controversies

Controversy	Results in:
Underdiagnosis	• Incorrect follow-up and therapy • Tens of thousands of individuals with undiagnosed AATD • No appropriate genetic counseling
Effectiveness and cost/benefit of augmentation therapy in question	• Expensive therapy without definitive documentation of effectiveness • General impression of and case-control evidence for effectiveness • Therapy not available in many countries
Potential for genetic discrimination	• Cases of employment discrimination • Individuals denied health insurance and life insurance

SUGGESTED READINGS

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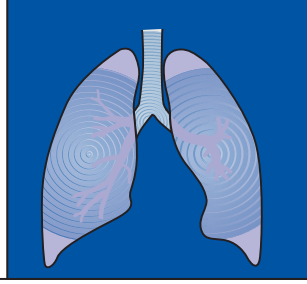

CHAPTER 72 Thoracic Tumors

Robin R. Deterding and Gregory S. Montgomery

TEACHING POINTS

- Pediatric thoracic neoplastic tumors can present with subtle clinical findings that mimic other disease.
- Consideration of the most likely types of thoracic lesion by location can guide differential diagnosis and the evaluation.
- Examination with computed tomography scanning or magnetic resonance imaging plays an important role in the evaluation of pediatric thoracic lesions.
- Tumors of the mediastinum and thoracic wall are more commonly malignant.
- Malignant masses found in the pulmonary parenchyma are often secondary metastatic disease from solid tumors.

Each year, 166 of every 1 million children aged 0 to 19 years are diagnosed with malignancies.[1] Fortunately, with therapeutic advances, the overall 5-year survival for these children is now greater than 75%. Primary and secondary thoracic tumors are even more rare, although they result in significant morbidity and mortality. Early recognition is desirable and requires clinicians to consider a tumor diagnosis in the context of the patient's history, physical examination, and evaluation. Diagnosis can be complicated by signs and symptoms that mimic more common and less concerning pulmonary disease.

Malignant tumors are classically described as primary, originating from the site of occurrence, or secondary, metastasizing from another primary site. This classification is helpful, once a diagnosis is established, to understand the nature of the tumor and clinical course. However, patients present clinically with different signs and symptoms depending more on thoracic location, which drives the generation of a differential diagnosis and evaluation. This chapter reviews pediatric thoracic tumors by thoracic location to focus attention on diagnosis and evaluation. A discussion of primary verus secondary malignancy is included for each section. Table 72-1 provides an overview of malignant pediatric thoracic tumors by anatomic location, malignancy type, and possible signs and symptoms.

AIRWAY TUMORS

Tumors arising from the conducting airways are almost exclusively primary tumors. They often manifest in affected children as nonspecific signs and symptoms of bronchial obstruction, masquerading as asthma.[2,3] Findings may include chronic cough and wheezing that fail to completely respond to asthma-focused therapy. Clinicians must have a high index of suspicion to make the diagnosis of an endobronchial tumor. Poor response to medical therapy, fixed obstructive airflow on pulmonary function testing, and associated findings that may include recurrent or persistent localized pulmonary infections, chest pain, and hemoptysis should prompt the consideration of an airway tumor. Investigations geared toward confirming the diagnosis include bronchoscopy and computed tomography (CT) scans of the chest. Specific diagnoses are confirmed by histology at the time of resection. Malignant airway tumors in children are often classified within two broad categories: bronchial adenomas and bronchogenic carcinomas.

BRONCHIAL ADENOMAS

Endobronchial tumors within this classification arise from the airway epithelium and tend to display glandular histologic features. Importantly, many "adenomas" in this category are actually slow-growing tumors that possess the potential for malignant transformation. Commonly occurring malignant airway tumors in this category include bronchial carcinoids, cylindromas, and mucoepidermoids.

Bronchial Carcinoid

The most common airway tumor in children is the bronchial carcinoid, representing nearly half of all malignant pediatric primary lung tumors.[2,4] These tumors arise from abnormally proliferating neuroendocrine cells within the bronchial epithelium, often appearing as polypoid projections into the airway lumen (Fig. 72-1*A*, *C*). For carcinoid tumors, somatostatin receptor scintigraphy (SRS), using the somatostatin analogue octreotide, may have a higher diagnostic yield than conventional imaging for localizing primary and metastatic tumor sites[5] (Fig. 72-1*B*). Final diagnosis and prognosis are assessed through pathologic classification. The more common "typical" or well-differentiated carcinoid tumor generally suggests a reduced likelihood of metastasis and excellent long-term survival. The less common "atypical" or poorly differentiated carcinoid is considerably more aggressive, often with metastatic lesions notable at the time of presentation. Therapy in children is frequently limited to local surgical resection of the tumor. Often, sleeve resection of the tumor (Fig. 72-1*D*) allows substantial preservation of functional lung

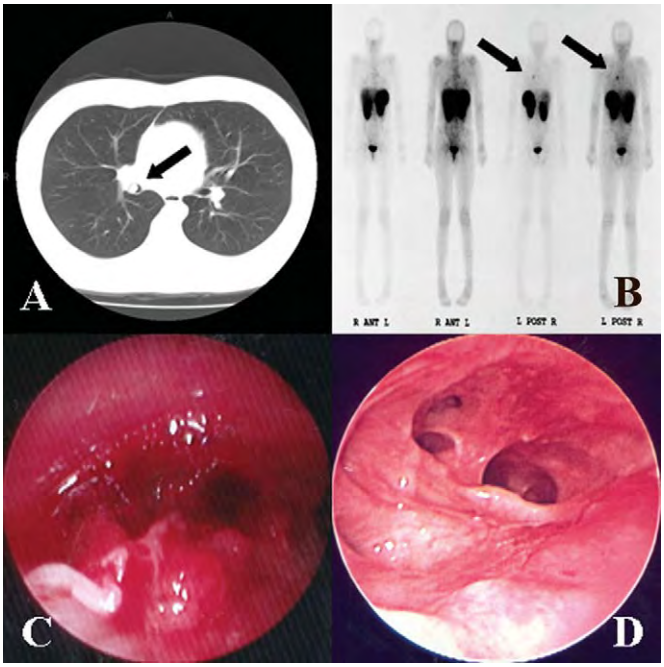

Figure 72-1 Radiographic assessments and surgical intervention in three cases of childhood bronchial carcinoid tumor. **A,** A 1.5-cm endobronchial lesion within the bronchus intermedius of an 18-year-old man as noted on computed tomography scan of the chest. **B,** Scintigraphy with a radiolabeled somatostatin analogue identified residual carcinoid tissue in the right lung of an 11-year-old girl, despite previous surgical removal. Rigid bronchoscopy demonstrated an obstructing polypoid mass **(C)** in the bronchus intermedius of a 7-year-old girl but a widely patent airway **(D)** following sleeve resection of the carcinoid tumor.

parenchyma. The "carcinoid syndrome" of excessive secretion of vasoactive peptides from carcinoid tumors has rarely been reported in association with pediatric lung tumors.

Cylindroma/Adenoid Cystic Carcinoma

Few cases of cylindroma tumors have been reported in children.[6] These tumors are perhaps the most malignant of the bronchial adenomas, with a predisposition for local infiltration, metastasis, and recurrence. Treatment options concentrate on complete surgical resection.

Tracheobronchial Mucoepidermoid

The mucoepidermoid is a slow-growing bronchial tumor arising from mucus glands within the bronchial submucosa. Histologically similar tumors occur within the salivary glands. Cytogenetic analysis of mucoepidermoid tumors often identifies the chromosomal translocation t(11;19).[7] These tumors may be locally invasive, but evidence of low-grade histologic findings suggests a favorable long-term prognosis in children.[8] As with other bronchial adenomas, treatment is focused on complete surgical resection.

BRONCHOGENIC CARCINOMAS

In children, bronchogenic carcinomas occur much less frequently than in adults. Most tumors in this category are of the undifferentiated or adenocarcinoma variety.[6] Squamous cell tumors are notably rare given the prevalence among adult tumors. As in adults, bronchogenic carcinomas are typically

Table 72-1
Malignant Pediatric Thoracic Tumors

Anatomic Location	Malignancy	Possible Signs and Symptoms
Airways	Bronchial adenomas	Asymptomatic
	Bronchial carcinoid	Cough, wheeze, fixed obstruction, hemoptysis, atelectasis, persistent pneumonia
	Cylindroma	
	Mucoepidermoid	
	Bronchogenic carcinomas	
Anterior mediastinal	Lymphoma or leukemia	Cough, airway compression, superior vena cava compression, atelectasis
	Germ cell tumors	
	Teratoma	
Posterior mediastinal	Ganglion cell	Asymptomatic
	Neuroblastoma	Incidental finding
	Ganglioneuroma	Respiratory distress
	Ganglioneuroblastoma	Cord compression
Parenchymal	Metastatic solid tumor	Asymptomatic
	Wilms tumor	Respiratory distress
	Hepatoblastoma	Solitary pulmonary nodule
	Osteosarcomas	Multiple nodules
	Rhabdomyosarcoma	
	Papillary thyroid cancer	
	Lymphoma	
	Hodgkin disease	
	Non-Hodgkin lymphoma	
	Posttransplantation	
	Lymphoproliferative disease (PTLD)	
	Primary tumors	
	Bronchioloalveolar carcinoma	
	Pleuropulmonary blastoma	
Chest wall	Ewing sarcoma	Cough, dyspnea, painful and palpable chest wall mass
	Askin tumor	
	Rhabdomyosarcoma	
	Lymphoma	

aggressive in children. Metastases are frequent at the time of presentation, often associated with symptoms of systemic involvement—weight loss, bone pain, and anemia. Radical surgical excision remains the mainstay of therapy; no standardized chemotherapy regimen has been developed.[9] The prognosis in children is generally poor.

BENIGN AIRWAY TUMORS

A number of benign endobronchial lesions may occur in children. The capillary hemangioma is a developmental proliferation of tightly packed, trabeculated blood vessels that may arise along the surface of the conducting airways. Bronchoscopic or surgical removal may be indicated in children with symptoms of airway obstruction or hemoptysis. Inflammatory myofibroblastic tumor, also known as pulmonary inflammatory pseudotumor and plasma cell granuloma, is a non-neoplastic reactive lesion.[3] The majority are benign and amenable to complete surgical resection. Other benign pediatric airway tumors described in the literature include true mucous gland adenomas, leiomyomas, and myoblastomas.

MEDIASTINAL TUMORS

The mediastinum is traditionally conceptualized as anterior, middle, and posterior compartments based on a lateral chest radiograph. This provides a framework for addressing underlying structures and predicting disease processes and symptoms. Because the majority of malignant mediastinal tumors arise from the anterior and posterior compartments, the middle mediastinum, which can contain abnormalities associated with adenopathy or foregut malformations, is not discussed here.

Anterior Mediastinum

The *anterior mediastinum* is defined as the area posterior to the sternum and anterior to the heart and contains the thymus.[10] Masses in this region can be asymptomatic or potentially life threatening from airway compression depending on mass size and must be approached very cautiously during evaluation.[11] Nonspecific signs and symptoms of cough (especially when the child reclines), atelectasis, and superior vena cava obstruction can be seen.[12]

LYMPHOMA

Lymphomas are one of the more common pediatric malignancies with an incidence of 11.3 per 1 million for Hodgkin lymphoma (or Hodgkin disease [HD]) and 8.4 per 1 million for non-Hodgkin lymphoma (NHL) (ages 0-19 years) and the most common cause of mediastinal masses in children.[1,13] Both NHL and HD frequently present with a primary mass and adenopathy in the anterior mediastinum.[14] Chest radiographs can be abnormal with an enlarged thymic or unusual shadow anteriorly (Fig. 72-2*A*), and calcifications are rare. A contrast CT scan provides the best characterization of the mass.[12] A complete review of the different subtypes of HD and NHL is beyond the scope of this review. In general, treatment consists of combination therapy with radiation and chemotherapy regimens.[15-17] Prognosis has markedly improved over the past three decades with improving therapeutic advancements, resulting in 5-year survival rates of 95% for HD and 81% for NHL (ages 0 to 19 years).[1]

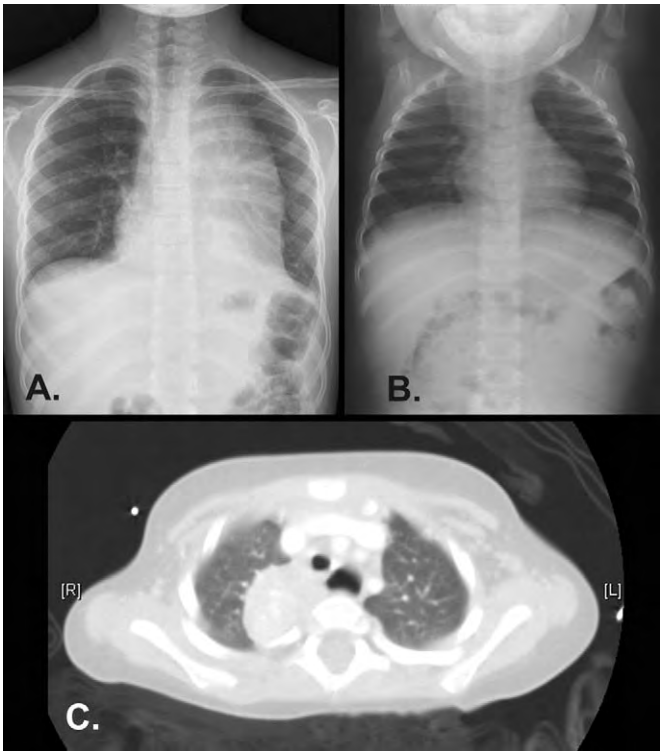

Figure 72-2 Radiographs of mediastinal neoplasms. **A,** Large T-cell lymphoblastic lymphoma arising from the anterior mediastinum seen on a chest radiograph in a 12-year-old. A posterior mediastinum neuroblastoma in a 3-year-old seen on a chest radiograph **(B)** and a computed tomography scan of the chest **(C),** which also demonstrates calcifications.

GERM CELL TUMORS

Germ cell tumors are the third most common tumor of the pediatric mediastinum, accounting for 6% to 18% of tumors in this location.[18] Germ cell tumors have varied histology, with the most common being different grades of teratomas. Other nonteratoma germ cell tumors include seminoma, embryonal carcinoma, choriocarcinoma, yolk sac tumors, and mixed types. Most germ cell tumors arise in the anterior compartment and, like lymphoma, can cause respiratory symptoms and distress from airway compression. Masses can be large and visible on chest radiographs. CT images are helpful for localizing the lesion and determining the attenuation of fluid, soft tissue, calcium, and fat, which can be suggestive of the diagnosis.[12] Survival has improved with treatment approaches that focus on a tailored surgical resection and neoadjuvant chemotherapy.[19]

NONMALIGNANT MISCELLANEOUS DISORDERS

Other differential diagnoses to consider in the anterior mediastinum include thymus and vascular abnormalities, infections, benign tumors, and miscellaneous disorders.[12]

Posterior Mediastinum

The *posterior mediastinum* is defined as the area posterior to the heart and trachea to the thoracic vertebral margins.[10] Normally occurring structures include the thoracic aorta, esophagus, azygos veins, autonomic ganglia and nerves, thoracic duct, and lymph nodes.

Masses in this region account for 30% to 40% of pediatric mediastinal tumors, and 90% of these tumors are of neuro-

genic origin.[12,20] Patients with posterior tumors can be asymptomatic and the tumor found incidentally on a chest radiograph or symptomatic from local mass effect or intraspinal extension. All unusual masses in the posterior mediastinum must be investigated regardless of the presence of symptoms.

GANGLION CELL TUMORS

Ganglion cell tumors are the second most common pediatric mediastinal tumor and include neuroblastomas, ganglioneuromas, and ganglioneuroblastomas.[21] Radiographically, ganglion cell tumors are not distinguishable. One of the most important considerations for distinguishing between the different tumors is median age of occurrence, with neuroblastoma occurring at a median age of 2 years and 95% by 10 years, ganglioneuroblastomas occurring at a median age of 5.5 years, and benign ganglioneuromas occurring later in childhood, after 10 years.[12]

Neuroblastoma is a major pediatric malignancy, accounting for 10% of all childhood cancers and 15% of cancer deaths.[22] It is commonly found as a primary in the thorax. Patients may be asymptomatic with an incidental chest radiograph finding (Fig. 72-2*B*), symptomatic with respiratory distress or cord compression from the primary tumor, or symptomatic with symptoms of disseminated disease such as fever, weight loss, or bone pain.[21,23] A CT scan is commonly used to assess the soft tissue in the paraspinal area and may show calcifications up to 80% of the time[12] (Fig. 72-2C). Magnetic resonance imaging (MRI) can be useful to determine the extent of tumor involvement in the chest, and nuclear scintigraphy is helpful to further stage the disease. Survival is best determined by age at diagnosis and stage of disease.[23]

OTHER MISCELLANEOUS DISORDERS

Although less common, non-neurogenic primary malignant posterior mediastinal masses can include Ewing sarcoma, germ cell tumor, and rhabdomyosarcoma. Less frequent nonmalignant disorders to consider in the differential diagnosis include vascular abnormalities, infections, adenopathy, benign tumors, and miscellaneous conditions.[12]

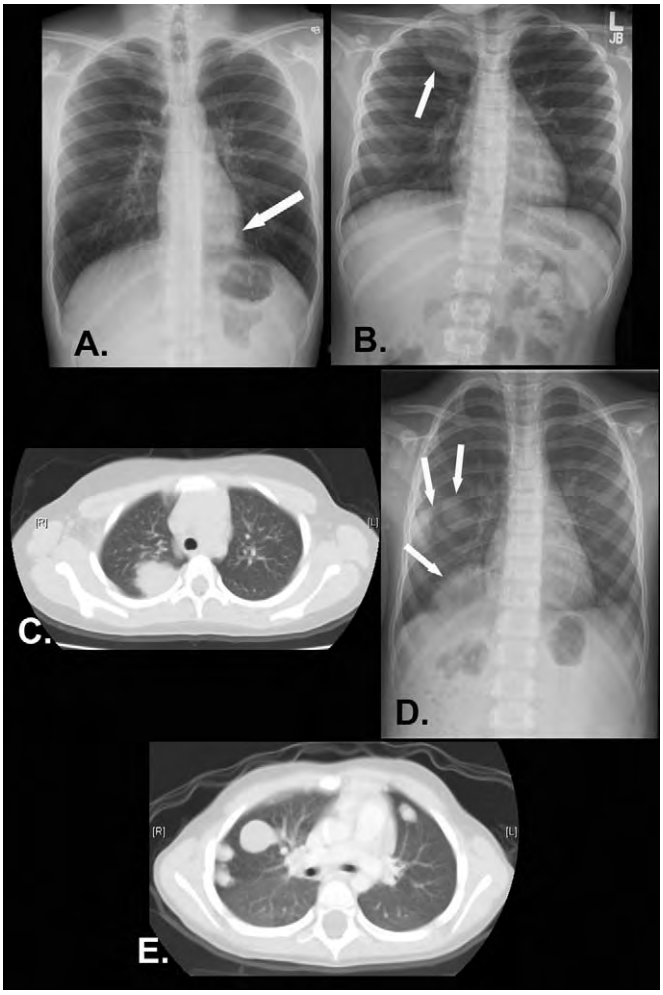

Figure 72-3 Radiographs of pulmonary parenchymal lesions. **A,** A 1.7-cm solitary pulmonary nodule seen on a chest radiograph in an 18-year-old man, ultimately diagnosed with a rare and benign pulmonary sclerosing hemangioma. A single metastatic lesion from a Wilms tumor in an 8-year-old seen on a chest radiograph **(B)** and a computed tomography scan of the chest **(C).** Multiple metastatic Wilms tumor lesions in a 5-year-old seen on chest radiograph **(D)** and a computed tomography scan of the chest **(E).**

PARENCHYMAL TUMORS

Unlike mediastinal and chest wall tumors in children, the majority of parenchymal nodules usually represent a granulomatous infection and are rarely neoplastic. Secondary metastatic nodules or masses are much more common than are primary tumors. When parenchymal malignancies occur, patients can be asymptomatic or have only mild or nonspecific complaints. Large masses create more symptoms that can progress to respiratory distress. Because of their rarity and subtle findings, most thoracic malignancies are diagnosed at advanced stages.[8] Important history such as malignancy or transplantation and radiographic information can help guide clinical reasoning and structure the diagnostic evaluation.

PULMONARY NODULES

Solitary pulmonary nodules (SPNs), or "coin lesions," are defined as round lesions that are surrounded by lung parenchyma and less than 3 cm in diameter[24] (Fig. 72-3*A*). The majority of coin lesions are benign in healthy children, representing infectious granulomas or hamartomas. Although less common, malignant lesions to consider in the initial differential would include carcinoid tumor, very rarely a bronchogenic carcinoma, post transplant lymphoproliferative disease (PTLD), and a solitary metastatic lesion in a child with a current or previous malignancy.[6,9,24-27] Previous chest radiographs can be examined, and if the nodule has not grown in size over 2 years, there is a high likelihood that the nodule is benign.[28] High-resolution CT is better than chest radiographs in providing current clues to the diagnosis. Certain findings support the diagnosis of a benign lesion, such as calcifications within a nodule, a laminated or central pattern consistent with a granuloma, a classic "popcorn" pattern, or evidence of intranodular fat suggestive of a hamartoma.[24,29] If lesions remain suspicious, noninvasive evaluations for malignancy and granulomatous infections can be undertaken, and the healthy patient with low probability of malignancy can be followed with serial radiographs. Positron emission

tomography (PET) is usually not indicated in healthy children who have a low likelihood of malignancy and are more likely to have an infection (which results in a false-positive PET scan) or a carcinoid tumor (which results in a false-negative PET scan).[30] For nodules that remain suspicious and carry a higher probability for malignancy, surgical removal and histologic evaluation are necessary to make the diagnosis.

PULMONARY MASSES

In contrast to nodules, lesions larger than 3 cm are considered masses. Masses are more likely to be malignant than are nodules. Except for a small percentage of pediatric lymphomas that can present with pulmonary parenchymal involvement,[14] most masses are associated with metastatic disease from a known solid tumor in children. Common childhood solid tumors that metastasize to the lung include Wilms tumor, osteosarcoma, rhabdomyosarcoma, hepatoblastoma, and, rarely, thyroid cancer.[23,25,26,31] Metastatic masses or nodules can be solitary (Fig. 72-3*B*, C) or multiple (Fig. 72-3*D*, *E*) and could be found at the time of diagnosis of the malignancy or as a recurrence of disease.[26] One fourth of hepatoblastomas present with metastatic disease, and 30% of these metastases occur in the lung.[23] Osteosarcoma has a high recurrence rate in the lung.[32] Wilms tumor can be associated with metastatic disease at the time of diagnosis and as recurrent disease.[33] The primary treatment, if possible, for lung metastases is resection. Survival is dependent on the underlying primary malignancy.

Nonmalignant conditions to consider depending on the clinical presentation include infectious etiologies, inflammatory noninfectious etiologies (Wegener granulomatosis), vascular lesions, and congenital abnormalities.[29]

OTHER CONDITIONS

Congenital cystic adenomatoid malformations (CCAMs) have been associated with primary pulmonary malignancy transformation into bronchioloalveolar carcinoma, rhabdomyosarcoma, and pleuropulmonary blastoma (PPB).[34-36] Type 1 CCAMs have been found to contain microscopic foci of bronchioloalveolar carcinoma.[34] Type 4 CCAMs have demonstrated some histologic overlap with PPB and malignant transformation has also been postulated.[37] Thus, resection of CCAMs and careful histologic evaluation are required for an appropriate diagnosis.

PPB is a rare and aggressive primary parenchymal tumor in early childhood that carries a poor prognosis. Patients present with a pulmonary- or pleural-based cystic mass and respiratory symptoms, with or without fever.[35] Pleural or mediastinal involvement is associated with worse outcomes. Resection is the primary therapy but recurrences are common. Five-year survival ranges from 42% to 83% depending on the PPB tumor classification, which is based on cystic or solid tumor characteristics.[35]

An aggressive form of lymphoma associated with immunosuppression after transplantation is PTLD. Epstein-Barr virus (EBV) infections are associated with the development of this life-threatening condition. EBV-PTLD can involve the lung and other extrapulmonary sites. In the lung, the lesions can vary from single to multiple nodules or masses. In bone marrow transplant patients, the highest risk period appears 5 months post transplant with associated risk factors for PTLD including T-cell depletion of the donor marrow, unrelated or mismatched donor, and use of anti–T-cell antibodies for graft-versus-host disease (GVHD).[27] EBV-DNA load in peripheral blood can be measured by quantitative PCR and provide support for a diagnosis of PTLD. Histology confirms the diagnosis. Treatment is directed at lowering immunosuppression; rituximab has also been successfully used.[27,38]

CHEST WALL TUMORS

Primary chest wall tumors are also rare in children, but a high percentage of these tumors are malignant.[39] These aggressive tumors can primarily arise from the soft tissues of the chest wall or as extensions from bony structures or the mediastinum. Symptoms of neoplastic chest wall lesions include a painful, palpable chest wall mass, cough, and dyspnea.[40] Conversely, benign lesions tend to be asymptomatic. Imaging plays a central role in evaluation and diagnosis.

The most common chest wall tumors are a group of tumors called either Ewing sarcoma family of tumors (ESFT) or malignant small round cell tumor (MSRCT).[40,41] This group includes primitive neuroectodermal tumors of the chest wall known as Askin tumor, Ewing sarcoma of bone, and extraosseous Ewing. Pulmonary metastasis can also be found at the time of diagnosis. Imaging with CT, which is better at demonstrating lung metastasis, and MRI, which can be superior to CT for showing invasion into the chest wall, often shows a thoracic lesion with adjacent rib erosion.[39] ESFT or MSRCT are aggressive tumors with a poor prognosis and a high rate of recurrence.[41] Complete tumor resection provides the best possibility for cure.

Rhabdomyosarcomas constitute the second most common group of chest wall tumors and are also very aggressive with a poor prognosis.[40] Imaging usually demonstrates a large heterogeneous mass with rib destruction and occasionally a pleural effusion. Resection is the primary treatment. Lymphomas appear as a primary within the chest or as a direct extension from the mediastinum with evidence of lytic destruction of the ribs or the sternum. Likewise, neuroblastomas can also invade the chest wall from the posterior mediastinum. Less common malignant chest wall tumors include congenital fibrosarcoma, chondrosarcomas, and primary osteosarcomas.[40]

Other, more benign chest wall lesions to consider in the differential diagnosis in children include a wide range of possibilities such as lipomas, neurofibromas, lymphangiomas, hemangiomas, hamartomas, tuberculosis, Langerhans cell histiocytosis, osteochondromas, and anatomic variations of the thoracic cage.[42]

CONCLUSION

Pediatric thoracic tumors are a rare group of diverse disorders that can be associated with significant morbidity and mortality. Patients may present with only subtle signs and symptoms requiring a high index of suspicion. Understanding the most common disorders in each thoracic location can aid the diagnosis and evaluation.

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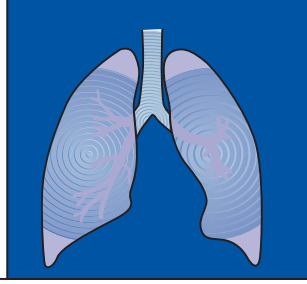

CHAPTER 73

Bronchiolitis Obliterans*

Rees L. Lee and Carl W. White

TEACHING POINTS

- The pathogenesis of bronchiolitis obliterans often relates to infection, especially adenovirus or *Mycoplasma pneumoniae;* drugs, inhaled toxins, and toxic gases; transplant (lung, heart-lung, bone marrow); or collagen vascular diseases.
- Bronchiolitis obliterans is suspected in a patient with a consistent history, airways obstruction without reversal by inhaled β-adrenergic agents, or "burst" glucocorticoids, usually with increased lung volumes.
- High-resolution chest computed tomography scan shows a variegated or mosaic pattern with persistent areas of alternating hyperinflation and hypoinflation.
- Lung biopsy may reveal bronchiolar obstruction by fibroblasts and/or myofibroblasts.
- Immunosuppressive therapy often has limited success.

Bronchiolitis obliterans (BO) is a rare, irreversible obstructive lung disease resulting from bronchiolar inflammation and luminal obliteration by circumferential peribronchiolar fibrosis. It can be the uncommon aftermath of a severe pulmonary infection. More recently, BO has gained prominence as the major cause of lung transplant failure beyond the immediate post-transplant period. It is also a significant cause of morbidity after bone marrow transplants. Few treatments have been shown to be effective and a fatal progression can occur, particularly in post-transplant patients.

HISTOPATHOLOGY

BO is a primary bronchiolar disease process[1,2] characterized by the circumferential peribronchiolar fibrosis leading to constriction of the bronchiolar lumen and, in the worst case, complete luminal obliteration[3-5] (Fig. 73-1). Synonymous terms are *constrictive bronchiolitis* and *obliterative bronchiolitis*.

There has been significant confusion regarding the term *bronchiolitis obliterans*. Many early descriptions of BO, including the first description by Lange,[6] would today be termed *cryptogenic organizing pneumonia* or *bronchiolitis obliterans organizing pneumonia* (BOOP).[1] Despite the very similar terminology of BO and BOOP, these disease processes have very different histologies (Table 73-1). BOOP is a distinct histopathologic disease with bronchiolar intraluminal polyps composed of mucopolysaccharide-rich fibroblasts that can extend into the alveolar ducts and alveoli, leading to organizing pneumonia.[3,5] In fact, the involvement of the bronchioles may be relatively minor with the organizing pneumonia being the primary pathology.[7]

By contrast, BO is a uniquely bronchiolar disease. There are no changes to the distal alveoli or lung parenchyma.[3] Instead, there is circumferential bronchiolar thickening of the submucosa from collagenous scarring. This results in distortion of the airway architecture and narrowing of the lumen. In a Brazilian study of children with the clinical presentation of BO, 97% showed evidence of constrictive bronchiolitis. Mucous stasis further complicated the luminal narrowing and one third had evidence of bronchiectasis.[4] Chronic inflammation can be seen and may account for the progressive nature of BO. Inflammatory infiltrates of foamy macrophages and lymphocytes are observed in the majority of postinfectious BO biopsy specimens.[4] Increases in both $CD4^+$ and $CD8^+$ lymphocytes are observed.[8]

A submucosal lymphocytic infiltrate (lymphocytic bronchitis/bronchiolitis) also characterizes post-transplant BO.[9] The accumulation of myofibroblasts and fibroblasts with collagen deposition results in granulation tissue and ultimately a fibrous scar that obstructs the bronchiole.[10] The presence of lymphocytic bronchiolitis in post–lung transplant patients is a significant risk factor for the development of BO.[11,12]

PATHOGENESIS

Because BO is a common cause of death after lung transplantation, a significant amount of effort has been expended trying to understand the pathogenesis of BO. BO may be an injury response of repeated or chronic insults to the airway epithelium.[13,14] In human lung transplant patients, even mild rejection (grade A1) experienced recurrently increases the risk of developing BO.[15]

Epithelial damage appears to be important. In a heterotopic tracheal allograft rat model, marked lymphocytic infiltration with loss of the epithelium precedes complete fibrous

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obliteration of the graft airway.[16] Similarly, 2 weeks after proteolytic removal of the tracheal epithelium, airway obliteration is noted. Reseeding the grafts with epithelial cells significantly mitigates the obstructive changes,[17] emphasizing the importance of epithelial layer disruption to the development of BO. In human transplant patients, detection of specific antibodies to the donor airway epithelial cells precedes development of BO and may contribute to airway epithelial damage.[18] In an intriguing animal study, progression to BO was prevented by reepithelialization of the donor graft with *recipient-derived* epithelium,[19] reinforcing the hypothesis that immune-mediated injury to the epithelium is key to BO development.[20,21]

Epithelial damage with the loss of basement membrane integrity could allow lymphocyte access to the airway mucosa similar to the lymphocytic bronchiolitis noted in pathologic specimens. Infiltrating $CD4^+$ and $CD8^+$ T-lymphocytes[22] release a variety of inflammatory cytokines, especially Th1 cytokines such as interferon-γ and interleukin-2 (IL-2).[23] As part of this inflammatory response, fibroblasts and myofibroblasts lay down collagenous scar tissue as documented by increases in profibrotic factors[24] and procollagen I and III mRNA[25] in BO animal models.

The inflammation, epithelial damage, and fibroblastic response leading to BO appear to be a T-cell–mediated process. $CD8^+$ T cells may play a particularly important role in the fibroblastic response as depletion of $CD8^+$ T cells significantly reduces the fibrosis and airway obliteration in the mouse model.[26] Activation of T cells depends on (1) recognition of MHC class I and II antigens on antigen presenting cells (APC) by $CD8^+$ and $CD4^+$ T-lymphocytes, respectively; and (2) co-stimulatory interactions between CD28 on the T cells and B7 ligands on the APC. Both arms of T-cell activation are important. Alloreactivity against the donor MHC-I and II antigens by the recipient $CD4^+$ and $CD8^+$ T-lymphocytes can induce BO in experimental animal models,[27] and MHC mismatch remains a significant risk factor for development of BO in human transplant recipients.[28,29] Blockade of CD28 binding to the B7-2 ligand results in a significant decrease in airway obliteration in the rat model,[30,31] emphasizing the importance of the co-stimulatory interactions. Additional studies supporting the importance of the T cell–APC interaction have used the compound FTY720 to reduce the T-cell population by inducing apoptosis and sequestering circulating lymphocytes. Similar to CD28/B7-2 blockade, rats treated with FTY720 also show decreased obliterative airway changes.[32] Simultaneous blockade of CD28/B7-2 together with the administration of FTY720 not only prevents airway obliteration but also preserves the airway epithelium.[32] Finally, interference with the interaction of activated T cells with B cells by blocking the CD40 co-stimulatory pathway can mitigate the development of BO.[33]

The importance of microvascular changes in the development of BO has recently been appreciated. Angiogenesis and vascular remodeling are important aspects of the fibroproliferative process,[34] and transplant patients with BO show significant increases in airway microvascular vessel counts compared with patients without BO.[35] In rat tracheal allografts, overexpression of vascular endothelial growth factor (VEGF) results in luminal occlusion. This obstructive

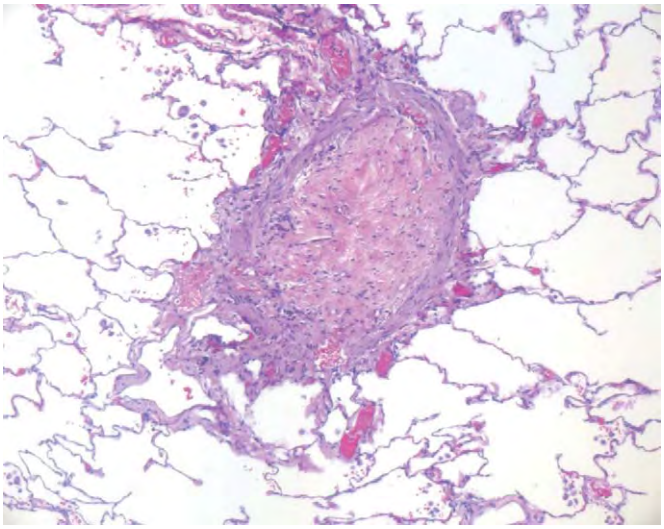

Figure 73-1 Pathology of bronchiolitis obliterans (BO): Bronchiole with a thickened airway wall and collagenous scar tissue which has obliterated the lumen. Note the sparing of the alveolar spaces in this pure form of BO. (Courtesy of Dr. Carlyne Cool, University of Colorado Health Sciences Center.)

Table 73-1
Comparison of Bronchiolitis Obliterans and Bronchiolitis Obliterans Organizing Pneumonia

	Bronchiolitis Obliterans*	Bronchiolitis Obliterans Organizing Pneumonia†
Presentation	Asymptomatic to chronic cough and wheeze	Insidious onset of hypoxia, dyspnea, and/or cough
Lung function	Irreversible obstruction Decreased FEV_1	Restrictive changes
Chest radiography	Normal or hypolucent areas	Consolidation
High-resolution CT	Mosaic hypolucencies indicative of air-trapping Bronchiectasis	Patchy consolidation and ground-glass opacities
Primary pathology	Concentric or asymmetric bronchiolar constriction from submucosal scar tissue with partial or complete airway lumen obliteration	Bronchiolar and alveolar filling with fibrous polypoid mass

*From Couture C, Colby TV: Histopathology of bronchiolar disorders. Semin Respir Crit Care Med 24:489-498, 2003; Mauad T, Dolhnikoff M: Histology of childhood bronchiolitis obliterans. Pediatr Pulmonol 33:466-474, 2002; and Myers JL, Colby TV: Pathologic manifestations of bronchiolitis, constrictive bronchiolitis, cryptogenic organizing pneumonia, and diffuse panbronchiolitis. Clin Chest Med 14:611-622, 1993.
†From Schlesinger C, Koss M: The organizing pneumonias: An update and review. Curr Opin Pulm Med 11:422-430, 2005.

process appears to operate through platelet-derived growth factor (PDGF) as inhibition of this pathway with imatinib (a PDGF tyrosine kinase inhibitor) prevents luminal occlusion.[36] Despite this animal finding, the significance of VEGF in human BO pathology remains unclear. Instead of increased VEGF, the BAL from lung transplant patients has significant depressions in VEGF, especially immediately after transplantation, during periods of rejection, and in patients with active BO.[37] In fact, low BAL VEGF levels at 6 months post-transplant were significantly correlated with the development of BO (BO patients: 86 ± 19 pg/mL versus non-BO patients: 158 ± 18 pg/mL)[37] and may be most useful as a marker of at-risk patients rather than being causal in the etiology of BO.

More recent investigations have explored VEGF-*independent* chemokine-mediated angiogenesis. A series of investigations by Belperio and colleagues[38] examined the role of CC chemokines and ELR$^+$ CXC chemokines. ELR$^+$ CXC chemokines contain a Glu-Leu-Arg immediately before the first cysteine residue at the NH_2 terminus and serve as important mediators of early neutrophil and monocyte inflammation and later angiogenesis as part of the fibroproliferative response. In murine models, the CC chemokine monocyte chemoattractant protein 1 (MCP-1) operating through the receptor CCR2 has been related to the mononuclear cell recruitment associated with BO formation.[39] In humans, elevated BAL levels of MCP-1 has been found in patients with acute and chronic rejection.[39] With regard to vascular remodeling and angiogenesis, research using the mouse tracheal allograft model of BO indicates that the ELR$^+$ CXC chemokine receptor 2 (CXCR2) and its ELR$^+$ CXC ligands are significant. In CXCR2$^{-/-}$ animals, the angiogenic and fibrotic response to tracheal allografts is dramatically reduced compared to CXCR2$^{+/+}$ wild-type animals.[35] A similar effect occurs if ELR$^+$ CXC chemokine binding to CXCR2 is blocked by anti-CXCR2 antibodies.[35] In human transplant patients, significant elevations of ELR$^+$ CXC chemokines in the BAL fluid are present in patients with bronchiolitis obliterans syndrome (BOS) compared with healthy transplant patients.[35] This elevation persists in some ELR$^+$ CXC chemokines (especially CXCL8) despite treatment of the BOS. This BAL fluid from BO patients has substantial biologically active angiogenic activity when assessed by human lung microvascular endothelial cell chemotaxis assay. This angiogenic activity can by neutralized with specific antibodies to CXCR2 but antibodies to VEGF have no effect.[35] This exciting research into VEGF-independent angiogenesis may ultimately lead to anti-angiogenic/antifibrotic therapies that target the ELR$^+$ CXC chemokines or their receptors.[40]

The etiology of BO in nontransplant patients is less clear but, similar to the post-transplant situation, is likely the result of a chronic inflammatory insult to the airway epithelium. In children with postinfectious BO, biopsy specimens show increases in CD4$^+$ and CD8$^+$ T-lymphocytes as well as prominent foamy macrophages.[4,8] Comparing an animal model of toxin-induced BO[41] to a tracheal transplant model, both sets of animals show similar increases in cytokines including TGF-β and interferon-γ.[42] The histology of the BO is identical in the two models. However, the rapid increase in osteopontin seen after toxicant injury but not seen in the transplant model implies that although the mechanisms leading to BO are similar, they are not necessarily identical.[42] Instead, BO likely represents a "final common pathway" following severe and/or repeated airway injury.[14] This injury induces a primarily lymphocytic, T-cell–mediated inflammatory response that includes fibroproliferation leading to the classic circumferential scar formation and progressive obliteration of the airway lumen (see Fig. 73-1).

PREVALENCE

The incidence of nontransplant BO is difficult to estimate due to its rarity. In a large retrospective review of 2897 autopsies and 244 lung biopsies at a children's hospital, only 19 cases of BO were documented, 12 of which were clinically diagnosed prior to death/biopsy.[43] This would give a prevalence in this selected sample of 0.6%. By contrast, post-transplant BO is relatively common and accounts for the majority of lung graft failures outside of the immediate post-transplant recovery period. Approximately 40% to 50% of lung transplant patients who survive 5 years develop BO and it remains the most common cause of death beyond 1 year post-transplant (approximately 40% of pediatric deaths and 27% of adult deaths).[44,45] The recent use of induction suppressive therapy does not appear to have affected this prevalence.[45] In bone marrow transplants, the prevalence of BO is approximately 9%.[46] The prevalence after allogeneic hematopoietic stem cell transplantation is 1.7%.[47]

ETIOLOGIES AND RISK FACTORS

Few large studies of nontransplant BO have been conducted from which to derive good estimates for developing risk assessments. Box 73-1 lists the reported etiologies of BO. Infection remains the most commonly identified etiology of BO, with adenovirus being the most prevalent infectious agent,[4,48-51] followed by *Mycoplasma pneumoniae*.[49] Perhaps due to the fact that BO may be diagnosed well after the acute phase of the illness, the etiology is often not determined with certainty (idiopathic BO).

Currently, the most common cause of BO is post-transplant BO, particularly after lung transplantation. A number of risk factors have been identified predisposing to more rapid development of BO.[52] Primary among these is the occurrence of acute rejection.[52] The presence of lymphocytic bronchiolitis has also been associated with BO,[11] but it may simply represent the pathologic correlate of graft rejection. Supportive of the importance of inflammation related to graft rejection is the observation that the development of BO is associated with subtherapeutic cyclosporine levels.[11] Nonimmunologic risk factors are less well defined. Early associations noted with cytomegalovirus infection[53,54] may be less important with the increased use of ganciclovir prophylaxis.[55,56] The role of other viruses such as RSV, parainfluenza, metapneumovirus, and adenovirus remains controversial, but a number of recent studies have documented trends toward the development of BO in patients contracting these infections post-transplant.[57-59]

Gastroesophageal reflux (GER) is very common in transplant patients, and aspiration of the refluxed material may contribute to BO.[60] In a retrospective study of 128 lung

Box 73-1 Etiologies of Bronchiolitis Obliterans

- Post-transplant BO
  - Lung transplant
  - Heart-lung transplant
  - Bone marrow transplant
  - Hematopoietic stem cell transplant
- Postinfectious
  - More common
    - Adenovirus[48-50]
    - *Mycoplasma pneumoniae*[49,135,136]
  - Less common
    - Cytomegalovirus
    - Respiratory syncytial virus[137]
    - Influenza
    - Parainfluenza
    - Measles[138]
    - Legionella
- Collagen vascular disease/autoimmune disease
  - More common
    - Rheumatoid arthritis[88,91,139,140]
  - Less common
    - Juvenile rheumatoid arthritis[141,142]
    - Scleroderma[143]
    - Crohn disease[144]
    - Ulcerative colitis[145,146]
    - Stevens-Johnson syndrome[147-149]
    - Systemic lupus erythematosus[150,151]
    - IgA nephropathy[152]
    - Castleman disease[153]
- Inhalation injury (NO_2, sulfur dioxide, ammonia, chlorine, phosgene, hot gas, fly ash)
  - Sulfur mustard (mustard gas)[154,155]
  - Dust/silicosis[156,157]
  - Popcorn worker's disease[158,159]
  - World Trade Center dyspnea[160]
- Ingested toxins
  - *Sauropus androgynus*[161,162]
  - Asian shrub leaf[163]
- Drugs (penicillamine, lomustine, cocaine, gold)[140,143,164]
- Radiation exposure[165]
- Ataxia-telangiectasia[166]
- Paraneoplastic disease
  - Neuroendocrine cell hyperplasia/carcinoid tumor[167,168]
  - Paraneoplastic pemphigus[169-171]
- Idiopathic

transplant patients, 73% had pH probe-confirmed GER disease (GERD). Those who underwent fundoplication showed an average of 24% improvement in FEV_1 when assessed 6 months later.[61] Early identification and treatment of GERD appears to yield better outcomes.[62] While it is reasonable to speculate that GERD may play a significant role in nontransplant BO, such an association has not been reported.

Box 73-2 lists risk factors that have been associated with post-transplant BO. Causal relationships have yet to be definitively determined.

Box 73-2 Potential Risk Factors for Post-Transplant Bronchiolitis Obliterans[52]

- Immunologic risk factors
  - Acute rejection
  - Subtherapeutic immunosuppression
  - Lymphocytic bronchiolitis
  - HLA mismatch between donor and recipient
- Nonimmunologic risk factors
  - Post-transplant viral infection
  - Recipient of young age
  - Donor of older age
  - Prolonged graft ischemia
  - Gastroesophageal reflux
  - Positive methacholine challenge[172]

CLINICAL PRESENTATION AND DIAGNOSIS

The clinical onset of BO is often insidious. Following an acute respiratory insult such as a viral pneumonitis or toxic inhalation exposure, the patient may appear to show recovery. However, the exertional dyspnea, chronic cough, and wheeze persist. While sometimes the physical examination results normalize, the majority of cases have abnormal physical examination findings (Table 73-2). Even in patients who are asymptomatic, the classic finding is an irreversible decline in FEV_1. In a study of Korean and U.S. nontransplant BO patients, 26% presented with hypoxia at rest and an additional 22% had evidence of nocturnal or exercise-induced hypoxia.[49]

In transplant patients, there is usually an initial period of good graft function. However, there is an insidious onset of exertional dyspnea and chronic cough. Occasionally, patients can present with acute wheezing and low-grade fever and may initially be diagnosed with asthma. Unlike asthma, these patients show an irreversible decline in FEV_1 and the response to oral corticosteroids is minimal or nonexistent. Occasionally, BO patients may have a reactive, bronchodilator, and/or corticosteroid responsive component in addition to the predominantly irreversible fixed airways obstruction. The pulmonary functions of these patients never normalize.

The clinical diagnosis of BO relies on the presence of irreversible obstruction (decreased FEV_1) on spirometry. In the absence of a definitive biopsy diagnosis and in the appropriate clinical situation, irreversible decline in FEV_1 may be sufficiently suggestive of BO to diagnose BOS. In a 1993 consensus statement from the International Society for Heart and Lung Transplantation, BOS was defined as a 20% or greater drop in FEV_1 compared with the baseline.[63] Baseline is the mean of the two highest post-transplant FEV_1 values obtained 3 to 6 weeks apart, and the drop in FEV_1 must be documented for more than 1 month in the absence of acute infection, acute rejection, or airway anastomotic stenosis. BOS is graded from BOS 0 (no BOS) to BOS 3 (severe BOS) (Table 73-3). More recently, a "potential BOS" stage was added (BOS 0-p).[64] BOS 0-p is defined as a drop in FEV_1 of 10% to 19% below baseline *or* a drop in $FEF_{25-75\%}$ greater than or equal to 25% below baseline. The BOS 0-p stage includes the recognition that declines in $FEF_{25-75\%}$ may be a more sensi-

tive measure of early BOS in some patients as well as the importance of even a mild FEV_1 decline in identifying at-risk patients. While controversy remains as to the best spirometric value to measure (FEV_1 or $FEF_{25-75\%}$), it appears that BOS 0-p has post-transplant prognostic value (sensitivity 71% to 80%, specificity 83% to 93%).[65,66] In one study, 81% of patients who met BOS 0-p FEV_1 criteria went on to develop BOS or died.[65]

The chest radiograph findings are nonspecific. In patients with early BO, chest radiographs may appear normal or show mild hyperinflation. More advanced disease may show areas of volume loss, atelectasis, bronchiectasis, and linear opacities.[67,68] High-resolution chest CT (HRCT) has become a very useful tool in the diagnosis of BO. A mosaic pattern of hypolucencies due to air-trapping is noted,[67,69-71] which becomes more prominent on expiratory-phase HRCT views[72] (Fig. 73-2). Expiratory-phase HRCT has a sensitivity of 80% to 93% and a specificity of 80% to 94%.[72-74] Unfortunately, a prospective trial of adding HRCT to the annual post-transplant patient evaluation did not enhance the ability to detect BO.[75] The extreme form of air-trapping with unilateral hypolucency is the Swyer-James/MacLeod syndrome.[76] Vascular attenuation, bronchiectasis, and atelectasis can also be noted on HRCT.

Ventilation-perfusion ($\dot{V}/\dot{Q}$) scans of the lung show matched defects.[77,78] Regional hypoperfusion is likely due to reflex vasoconstriction secondary to hypoxia in the affected hypoventilated lung segment. Routine $\dot{V}/\dot{Q}$ scans of post-transplant patients do not enhance the ability to detect BO.[79]

Exhaled nitric oxide (eNO) may be a useful adjunct in the diagnosis and monitoring of BO. In a 2-year observation trial of post–lung transplant patients, 12 of 13 patients who developed BOS had two or more eNO measurements above 15 ppm, whereas only 3 of 19 without BOS satisfied this

Table 73-2
Presenting Symptoms and Signs of Nontransplant Bronchiolitis Obliterans

	Percent ($N = 31$)
Symptoms	
Cough	94
Wheezing	87
Exercise intolerance	87
Tachypnea	77
Frequent respiratory illnesses	77
Signs	
Crackles	87
Wheezing	71
Tachypnea	61
Retractions	45
Poor air entry	35
Clubbing	10
Oxygen Saturation	
Hypoxia at rest	26
Hypoxia only with sleep/exercise	22
Normal oxygen saturation	52

Adapted from Kim CK, Kim SW, Kim JS, et al: Bronchiolitis obliterans in the 1990s in Korea and the United States. Chest 120:1101-1106, 2001.

Table 73-3
Diagnostic Criteria for Bronchiolitis Obliterans Syndrome (BOS)

BOS 0	$FEV_1 > 90\%$ of baseline and $FEF_{25-75\%} > 75\%$ of baseline
BOS 0-p	FEV_1 81% to 90% of baseline and/or $FEF_{25-75\%} \leq 75\%$ of baseline
BOS 1	FEV_1 66% to 80% of baseline
BOS 2	FEV_1 51% to 65% of baseline
BOS 3	$FEV_1 \leq 50\%$ or less of baseline

From Estenne M, Maurer JR, Boehler A, et al: Bronchiolitis obliterans syndrome 2001: An update of the diagnostic criteria. J Heart Lung Transplant 21:297-310, 2002.

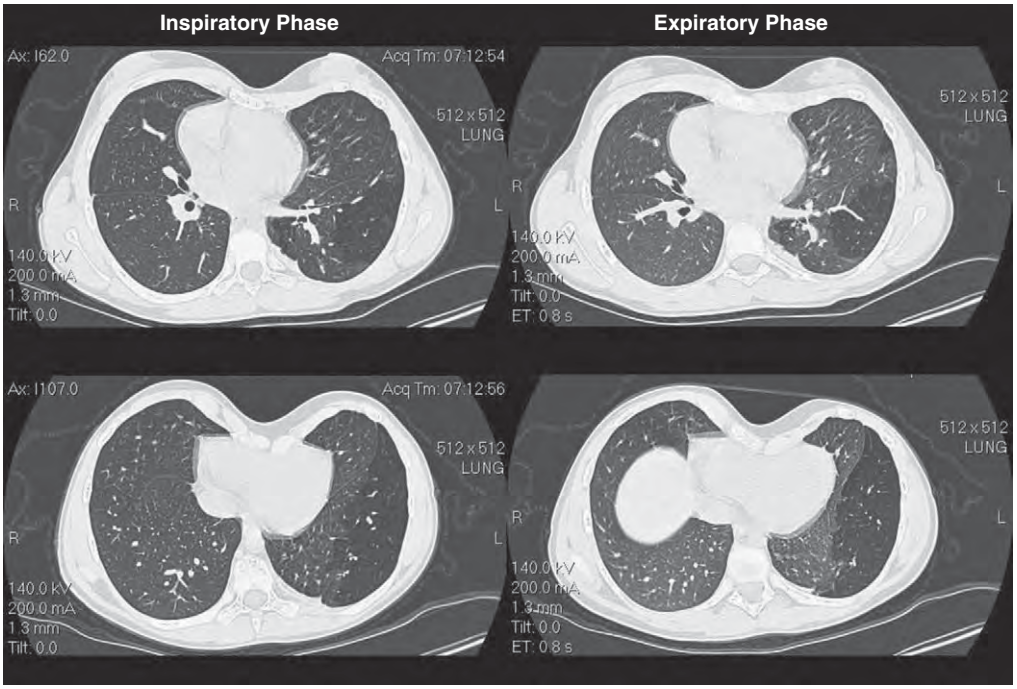

Figure 73-2 A 12-year-old girl with irreversible obstructive lung disease consistent with bronchiolitis obliterans (Swyer-James changes). Large hypolucent areas of the left lower lobe are noted which become more prominent on expiratory phase CT scan. Failure of these areas to compress significantly during expiratory phase is consistent with air-trapping. (Child also has moderate pectus excavatum. The round opacity within the right lung field of the lower right CT scan is the diaphragm extending upward during expiratory phase.)

criteria.[80] Using eNO to guide immunosuppressive treatment has also been suggested.[81,82]

The definitive diagnosis of BO requires a lung biopsy specimen showing the characteristic histology described previously. The pathologist may need to evaluate multiple sections through one or more blocks in order to find the *focal* pathognomic obstructive airway lesion. The clinician must maintain a high index of suspicion, especially with a suggestive history, physical findings, and HRCT. The pathologist should be encouraged to continue the search if classic findings are not immediately apparent. Due to the patchy nature of BO, the sensitivity of a transbronchial biopsy is quite variable (15% to 82%) and cannot be used to reliably rule out the diagnosis.[83-85] However, a positive result from a transbronchial biopsy specimen may be helpful in confirming the diagnosis of BO because such a positive finding has high specificity and predictive value.[84] With the advent of video-assisted thoracoscopic surgery (VATS) techniques for both adults and children, lung biopsies may be better tolerated than previously reported[86] and make a definitive diagnosis through lung biopsy a more realistic goal.

TREATMENT AND PROGNOSIS

Nontransplant Bronchiolitis Obliterans

The natural history of nontransplant BO is difficult to determine due to the varied etiologies, relatively small numbers of affected patients, and the widely variable outcomes noted in the literature. Postinfectious BO is the most common form of BO in children. In a retrospective study by Kim and associates[49] of 31 Korean and U.S. children with mostly postinfectious BO, only one patient (3%) had died of the disease over a follow-up period of 1 to 10 years. However, three patients (10%) required lung transplantation. The authors noted that nontransplant BO in children has "a good overall prognosis and a relatively low mortality rate."[49] By contrast, Hardy and colleagues[43] noted 9 deaths in 19 cases of BO (47% mortality) between 1960 and 1985. In a series of 31 Brazilian children with postinfectious BO followed for an average of 3.5 years, two-thirds had persistent symptoms, 23% showed clinical remission, and 10% died.[87]

No specific treatment exists for postinfectious BO. The use of both inhaled and oral corticosteroids is controversial, but benefits have been reported in some patients.[49] Despite being on steroids, lung inflammation often persists.[8] The use of bronchodilators may be counterintuitive in a disease defined as irreversible airway obstruction. However, regular use of bronchodilators in some patients may be beneficial.[49] In our personal experience, we find that the majority of postviral BO patients have some reactive airways component and benefit from bronchodilators and/or steroids. Patients with severe obstruction, hypoxia, and functional impairment may require lung transplantation.

Rheumatoid arthritis (RA) is the most common collagen-vascular disease leading to BO.[88] It is sometimes unclear whether this is a direct result of RA or a result of the medications used to treat it, such as penicillamine or gold salts. Unlike postinfectious BO, which can stabilize or even have some remission, most patients with RA-associated BO die within 1 to 5 years.[88-90] Treatment with corticosteroids or other immunosuppressive agents has been disappointing. Regular use of erythromycin was shown in a small study of 15 patients to stabilize or improve symptoms.[91] A recent case report of a 55-year-old woman with rapidly progressive BO and RA documents marked improvement after use of methotrexate and etanercept (TNF-α inhibitor).[92]

Post-Transplant Bronchiolitis Obliterans

The greatest challenge in the treatment of BO has been the attempt to halt its development in transplant patients, especially those receiving lung transplants. BO remains the most common cause of death more than 1 year post–lung transplant.[44,45] Despite improvements in immediate post-transplant survival, the ability to either prevent BO or alter the progression of BO has met with only marginal success.

Three distinct patterns of pulmonary function decline have been described in post-transplant patients.[93] The first pattern is one of rapid, relentless decline in FEV_1 with no stabilization. A second pattern also has an initial rapid FEV_1 decline but is followed by a period of partial stabilization. The final group shows a slow but inexorable decline in pulmonary function. In no group is there improvement or recovery of lung function (Fig. 73-3).

Since the occurrence of acute rejection episodes and inadequate immunosuppression has been correlated with BO development, preventive strategies have concentrated on determining the optimal immunosuppressive regimen. The traditional immunosuppressive regimen has consisted of cyclosporine, azathioprine, and corticosteroids. There has been evidence that tacrolimus (FK506) and mycophenolate mofetil (MMF) may provide superior prevention and treatment of BO in lung-transplant patients.

Tacrolimus is a calcineurin inhibitor similar to cyclosporine. It acts to inhibit lymphokine production by helper and cytotoxic T-lymphocytes.[94] Tacrolimus use as part of the post-transplant immunosuppressive regimen has shown some superiority versus using cyclosporine. In vitro studies on cul-

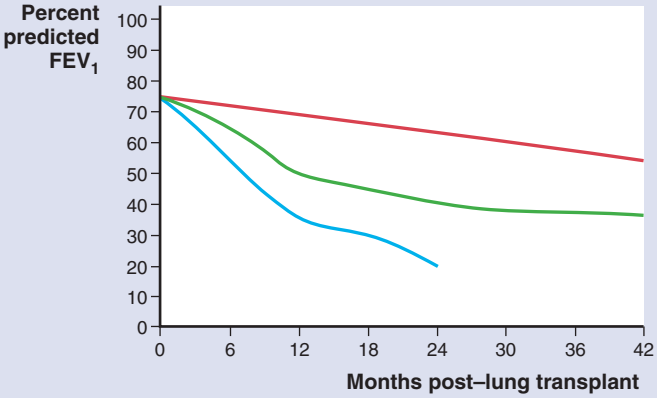

Figure 73-3 Stereotypical patterns of pulmonary function decline in single lung–transplant recipients. *Blue line*: Rapid, relentless decline in FEV_1 with no stabilization. *Green line*: Initial rapid FEV_1 decline followed by period of partial stabilization. *Red line*: Slow, inexorable decline in pulmonary function. (Based on data from Nathan SD, Ross DJ, Belman MJ, et al: Bronchiolitis obliterans in single-lung transplant recipients. Chest 107:967-972, 1995.)

tured $CD4^+$ T-lymphocytes show that tacrolimus is at least 100 times more potent than cyclosporine in inhibiting cytokine secretion, including the cytokines IL-2, IL-3, IL-4, and interferon-γ.[95] In the pig lung transplantation model, transplant survival was superior in the tacrolimus-treated animals.[96] Early prospective clinical trials in humans comparing tacrolimus to cyclosporine as part of post–lung transplant maintenance therapy showed fewer episodes of acute rejection[97,98] and development of BO.[98] Additionally, observational data from the Registry of the International Society for Heart and Lung Transplantation shows that the combination of tacrolimus and MMF has the lowest overall rate of rejection.[44] However, more recent prospective randomized trials have been less impressive but may be limited due to the short follow-up period to date. An open randomized trial in progress involves MMF and steroids with either tacrolimus or cyclosporine as the calcineurin inhibitor. Induction therapy consisted of rabbit antithymocyte globulin for 3 days. Reports after 6 and 12 months post–lung transplant show no significant differences in the number of patients free of acute rejection.[99,100] A trend toward a decrease in the number of rejection episodes treated per 100 patient-days in the tacrolimus group was noted. Of interest, 11% of the cyclosporine group had to be switched to tacrolimus in order to control ongoing rejection, but none of the tacrolimus group switched to cyclosporine. Perhaps a longer follow-up period will reveal more substantial differences between the two therapies. Regardless, the data supporting the superiority of tacrolimus (versus cyclosporine) have been sufficiently persuasive to prompt a clear trend among lung-transplant centers toward using tacrolimus as part of the post-transplant maintenance immunosuppressive therapy. In 1999, about 70% of lung-transplant patients at 1 year were receiving cyclosporine and only 26% received tacrolimus.[101] In 2005, this ratio had shifted such that 23% were on cyclosporine while tacrolimus had expanded to be part of 62% of the patients' immunosuppressive regimens.[44] A similar trend has been noted in pediatric lung-transplant patients.[45]

The use of tacrolimus as part of the post-transplant maintenance therapy also delays the onset of BO. In a prospective trial of 133 patients comparing tacrolimus and cyclosporine, BO developed in significantly fewer patients in the tacrolimus group (21.7%) compared with the cyclosporine group (38%).[98] A more recent trial (reported in abstract form) of 110 patients also found that those treated with tacrolimus had a lower incidence of BOS (10%) compared with those treated with cyclosporine (41%).[102] Tacrolimus presumably affects BOS by more effectively controlling the graft inflammation, which is the causal event leading to BO.

In addition to being used in the post-transplant maintenance regimen, tacrolimus has become an accepted part of the rescue therapy for lung graft rejection as well as BOS. However, no prospective trials involving large numbers of patients have evaluated the switch to tacrolimus. Multiple nonrandomized observational studies have documented partial stabilization of pulmonary function in patients with BOS or recurrent rejection as well as a decrease in the frequency of rejection after switching from cyclosporine to tacrolimus.[103-108] A retrospective study of 244 patients with either recurrent rejection or BOS showed significant decreases in the frequency of rejection within 3 months of switching from cyclosporine to tacrolimus as well as short-term stabilization of FEV_1.[109] Stabilization of exhaled nitric oxide levels once tracrolimus is started mirrors the effect on pulmonary function.[82] Taken as a whole, the current literature appears to support the use of tacrolimus in the treatment of BOS and recurrent/chronic graft rejection.

MMF is an purine synthesis antagonist (inosine monophosphate dehydrogenase inhibitor) that suppresses T- and B-cell proliferation. A large, retrospective study of 303 lung-transplant patients showed that the risk of developing BOS 2 or 3 was reduced by half (odds ratio 0.51) in those receiving MMF.[110] However, in prospective studies evaluating MMF versus azathioprine as part of maintenance immunosuppressive therapy, no significant differences in the two groups have been noted with respect to the frequency of acute rejection or the development of BO out to 3 years of follow-up.[111-113] MMF does appear to be better tolerated by patients than is azathioprine.[111] As a combination therapy with tacrolimus, MMF has the lowest rate of acute rejection episodes[44] and has become the preferred purine synthesis antagonist (MMF: 46% of lung transplant patients at 1 year; azathioprine: 30%).[44]

Numerous other agents have been investigated as treatments for BO, but only a few of the more interesting therapies are discussed here. Steroids have always had a role in the treatment of post-transplant BO. High-dose pulse therapy has been used with some success. In post-BMT patients with BO, high-dose pulse methylprednisolone led to stabilization of lung function in 7 of 9 patients.[114] Inhaled therapies hold the promise of delivering high doses of medications to the airway while minimizing systemic absorption and side effects. A small clinical trial (N = 10) of patients with BOS showed significantly higher FEV_1 values while on 2000 μg/day inhaled fluticasone propionate versus placebo.[115] However, a larger study (N = 30) with a dosage of 1500 μg/day fluticasone propionate could not reproduce these findings.[116] It remains to be determined if even higher doses of inhaled steroids would be beneficial. Currently, inhaled steroids cannot be routinely recommended but may be useful in individual patients. Other inhaled medications being explored include inhaled cyclosporine.[117] In a 2-year randomized controlled study (N = 58) of aerosolized cyclosporine (300 mg 3 days per week) started within 6 weeks of lung transplantation, significant improvements in overall survival and BOS-free survival were noted.[118] Only 3 deaths among the aerosolized cyclosporine group were noted whereas there were 14 deaths in the placebo group (relative risk = 0.20). BOS-free survival was also improved significantly as evaluated by spirometry (RR = 0.38) or by histology (RR = 0.27). The long-term effect of inhaled cyclosporine on BO is not known, but these early results are very encouraging. Further studies involving larger number of patients are clearly needed to confirm the benefits of inhaled cyclosporine.

Animal models have indicated that tumor necrosis factor-α (TNF-α) appears to be an important aspect of the inflammatory cascade and its blockade can halt the progression to BO.[24,119-121] In an exciting case report involving a post-BMT child with BO, the monoclonal anti-TNF-α antibody infliximab showed dramatic resolution of the BO and no recurrence over a 9-month follow-up period.[122] Further study is clearly indicated.

Macrolide antibiotics have been shown to have anti-inflammatory properties, which have been useful in the treatment of diffuse panbronchiolitis and cystic fibrosis.[123,124] Recent trials of azithromycin in post-transplant patients have suggested similar benefits. In a retrospective study examining azithromycin as part of a rescue therapy for BOS in lung transplant patients, 250 mg azithromycin every other day resulted in FEV_1 increases after 3 months that persisted for the 11-month follow-up period in many patients.[125] Similar findings have been documented by other studies.[126-128] Studies involving large patient numbers or evaluating the ability of azithromycin to prevent or delay the onset of BO have not been conducted. However, the early data are encouraging and warrant further study.

Development of bronchiolar fibrosis is an important part of the pathology of BO. Antifibrotic medications hold the promise to stem this aspect of BO. In a mouse model of BO, the antifibrotic drug pirfenidone was able to prevent the onset of obstructive airway changes[129] and may serve as a model for future drug development in humans.[130] The mammalian target of rapamycin (mTOR) is a downstream protein kinase of the phosphatidylinositol 3′-kinase–Akt signaling pathway.[131,132] mTOR may drive or contribute to fibromuscular proliferation. Antagonism of mTOR with medications such as sirolimus and everolimus may be beneficial. A pilot study of post-transplant BO patients added sirolimus to a calcineurin inhibitor and prednisone and demonstrated stabilization of pulmonary function but at the cost of significant adverse effects.[133] Everolimus used in lieu of azathioprine for maintenance therapy results in fewer acute rejection episodes and BOS at 12 months post-transplant. At 24 months post-transplant, the BOS effect is lost and only the decline in acute rejection remains.[134] Similar to sirolimus, there are significant side effects of the medication. The dosing and indications for the use of sirolimus and everolimus need to be more fully explored before they can become part of routine care. Finally, with the new knowledge regarding the role of angiogenesis in the fibroproliferative phase of BO, development of antiangiogenic compounds, especially those which target the ELR^+ CXC chemokines, may provide additional therapies in the future.[40]

CONCLUSION

Although is an entity rarely seen by most physicians outside of the pulmonary specialties, the expanded use of lung transplantation in both the adult and pediatric populations makes continued research in this area vital. With the growing understanding of the pathophysiology of BO, we can anticipate exciting novel therapies. It is hoped that such understanding and new therapies will yield longer post-transplant survival.

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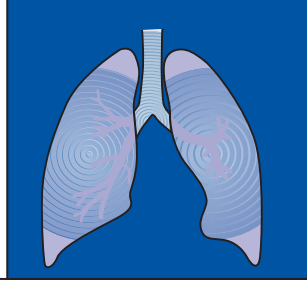

CHAPTER 74

Psychiatric Aspects of Respiratory Symptoms

Frederick S. Wamboldt and Marianne Z. Wamboldt

TEACHING POINTS

- Central nervous system (CNS) reflexes devoted to protecting respiration can at times become hyperactive and dysfunctional, producing breathing disorders.
- The process of "central sensitization" may explain how intense or repeated stimulation of CNS reflexes designed to protect respiration can become hyper-responsive.
- The "somatic" anxiety disorders (panic attacks, hyperventilation, and panic disorder) likely arise due to induced hyperresponsiveness of brainstem respiratory control centers and mid-brain "fear" centers.
- Vocal cord dysfunction likely arises from central sensitization of reflexes designed to protect the glottis.
- Habit cough may function similarly, with central sensitization of reflexes, but also needs to be distinguished from a phonic tic, which has a different etiology and treatment.
- All of these disorders, once recognized and appropriately diagnosed, respond well to simple, targeted treatments that improve quality of life and decrease iatrogenic morbidity and wasteful health care utilization.

> Each person is born to one possession which outvalues all his others—his last breath.
>
> MARK TWAIN—*Following the Equator* (1897)

An important subset of patients presenting to pediatric pulmonologists, as well as these children's parents, suffer from knowing this quote by Mark Twain all too intimately, having pondered the possibility of losing their, or their child's, last breath during respiratory crises. It is not surprising that having an episode of breathlessness, or observing such in your child, may be one of the most anxiety-provoking experiences that many people ever have. This chapter reviews the etiology, pathophysiology, and treatment of two common disorders of breathing—"somatic" anxiety disorders and paradoxical vocal cord dysfunction (VCD)—in which the prominent concurrence of psychiatric and respiratory symptoms is caused by hyperresponsiveness of the intricate set of controls, monitors, and protective reflexes in the central nervous system (CNS) that link the control breathing with affective, anxiety, and cognitive centers. Understanding this CNS physiology will help the physician successfully treat pediatric patients presenting with these common respiratory syndromes. We also review the frequent pediatric problem of habit cough. Although certain cases of chronic cough, including habit cough, also fit very nicely into this model of CNS reflex hyperresponsiveness, as will be seen, a more extensive differential diagnosis is required to effectively manage and treat patients with habit cough.

"CENTRAL SENSITIZATION" OF CENTRAL NERVOUS SYSTEM RESPIRATORY CONTROL CENTER

The basic dynamics of respiration, such as rate and rhythm, are controlled by medullary and pontine centers in the brain. These same centers monitor not only the status of respiration but also other associated systems, such as the status of the airway. When respiration is in danger (e.g., smoke inhalation) these centers use a variety of short-term protective reflexes (e.g., cough, glottic closure, and "fight-or-flight" panic anxiety) to protect the individual until the source of respiratory danger has ended. Considerable evidence has accrued that CNS respiratory control centers can become sensitized so that these short-term protective reflexes become hyperactive, leading to a family of related clinical syndromes in which neuropsychiatric factors produce and maintain common respiratory symptoms, such as cough, dyspnea, and wheezing, thereby mimicking or confounding asthma and other pulmonary disorders.

Some of the best evidence supporting this hypothesis comes from animal models in which early exposure to various lung irritants (e.g., capsaicin, environmental tobacco smoke, upper respiratory viruses) can cause central sensitization of CNS respiratory centers, resulting in persistent hyperactivity of respiratory reflexes.[1,2] For example, Bonham and colleagues[1] exposed juvenile guinea pigs to environmental tobacco smoke for 5 weeks and elegantly demonstrated that this exposure activated vagal C-fiber afferents to the nucleus tractus solitarius (NTS), causing increased responsiveness of caudomedial NTS neurons to subsequent respiratory irritant exposure. Furthermore, these animals also displayed CNS hyperactivity outside of irritant exposure, including altered respiration (more rapid and shallow breathing), lowered cough threshold, increased mucus production, and increased bronchial hyperresponsiveness. This increased CNS excitability was sustained throughout the life of the exposed animals.

Morrison and colleagues[3] have invoked a similar model of CNS "neural plasticity" to explain the irritable larynx syndrome (ILS). Specifically, they hypothesized that ILS develops due to "CNS changes that leaves sensorimotor pathways in a hyperexcitable state" with the underlying mechanisms proposed as being either an adaptive response to "nerve or tissue injury" or "repeated noxious stimulation." In a series of 39 patients diagnosed in their clinic, the most common probable etiologic factors were reported to be gastroesophageal reflux disorder (GERD), recent viral upper respiratory infection (URI), "psychogenic," and concurrent chronic respiratory disorder. Once such CNS changes have placed the larynx in a "spasm-ready state," they observed that a wide variety of nonspecific triggers can produce symptoms, with airborne odors (especially perfumes and cleaning products), GERD, foods, emotions, voice use, coughing, and exertion described as particularly frequent triggers.

These concepts of *central sensitization* and *neural plastic hyperexcitability* are widely accepted as important mechanisms in chronic pain syndromes[4,5] but, in general, are not widely invoked as neuropsychiatric mechanisms in the production of respiratory symptoms. We review relevant literature for three common clinical syndromes frequently encountered in pulmonary clinics, "somatic" anxiety disorders, paradoxical VXD, and habit cough, in which these CNS mechanisms often play an important pathophysiologic role.

"SOMATIC" ANXIETY DISORDERS: PANIC ATTACKS, PANIC DISORDER, AND HYPERVENTILATION

These common conditions are discussed together for two reasons. First, there exists great overlap between the phenomenologic and pathophysiologic expression of these conditions, despite the fact that they are not totally overlapping syndromes. Second, principles of effective treatment are more or less the same across these disorders.

In general, all these conditions include some combination of the following clinical paroxysmal signs and symptoms: (1) intense feeling of discomfort or fear; (2) autonomic arousal; (3) vague, diffuse, "atypical" bodily sensations; (4) overbreathing; (5) catastrophic cognitions (e.g., fear of losing control, going crazy, or dying); and (6) avoidance behavior. The onset of full criteria for these conditions is most common in late adolescence or early adult years, although prepubertal onset has been reported.[6-9] However, subsyndromal symptoms are common in younger children, and early identification and intervention may help prevent progression to full disorder. All are prevalent yet underdiagnosed disorders in primary care as well as pulmonology and cardiology specialty clinics. They are major sources of preventable morbidity and mortality in these settings because safe, reliable, and effective treatment strategies exist.

Panic Attacks and Acute Hyperventilation

Panic attacks are an extremely common experience, with one quarter to one third of the U.S. population reporting lifetime occurrence of at least one panic attack.[10-12] The term *panic attack* refers to an acute episode of sudden intense fear or discomfort that rapidly builds in a crescendo fashion over a period of minutes and that is associated with a number of somatic or cognitive symptoms. Accordingly, the diagnostic label *panic attack* is a phenomenologic or descriptive one, implying nothing about etiology or pathophysiology. The specific *DSM-IV-TR* diagnostic criteria for panic attack are listed in Box 74-1.[13]

It is important to note according to these criteria that the patient needs to report either intense fear or *discomfort*. Up to 40% of patients presenting to medical (as opposed to psychiatric) settings have been reported to have "panic without fear"; that is, although they feel intense somatic discomfort during attacks, they do not experience anxiety or fear, typically remaining stoic.[14-16] Such patients also tend to develop less avoidance behavior in response to recurrent panic attacks but otherwise are indistinguishable from patients with fearful responses during panic attacks. What does this mean that one can have a panic attack without fear? The likely answer is that during a panic attack the vast majority of patients hyper-

BOX 74-1 Signs and Symptoms of a Panic Attack

A. A discrete period of intense fear or discomfort
B. During which four or more of the following symptoms developed abruptly and reached a peak within 10 minutes:
   1. Palpitations, pounding heart, or accelerated heart rate
   2. Sweating
   3. Trembling or shaking
   4. Sensations of shortness of breath or smothering
   5. Feeling of choking
   6. Chest pain or discomfort
   7. Nausea or abdominal distress
   8. Feeling dizzy, unsteady, lighthearted, or faint
   9. Derealization or depersonalization
   10. Fear of losing control or going crazy
   11. Fear of dying
   12. Paresthesias
   13. Chills or hot flushes
C. Other signs/symptoms associated with panic attacks hyperventilation:
   1. Electrocardiogram changes (e.g., ST-segment depression, T-wave inversion)
   2. Musculoskeletal pain, stiffness, "fibrositis"
   3. Weakness, listlessness, exhaustion
   4. Poor concentration, forgetfulness, confusion
   5. Euphoria
   6. Frequent sighing, yawning, thoracic breathing
   7. Dry mouth, aerophagia, flatulence
   8. Blurred vision
   9. Syncope, seizures
   10. Focal neurologic signs and symptoms (often left sided)
   11. Extreme sensitivity to stimulant side effects of medications
   12. Hallucinations (rare)
   13. Tetany (rare)

Criteria A and B are required to make a diagnosis of panic attack using *DSM-IV* criteria.

ventilate.[17] Hyperventilation, as is described in detail later, is the direct cause of most of the somatic sensations that arise during a panic attack. Fear develops during a panic attack when a patient misattributes these somatic sensations as indicating that they are in danger.[18] In other words, patients suffering from panic without fear perceive the physiologic effects of hyperventilation but have benign cognitive appraisal of these sensations.

Acute hyperventilation is the physiologic state of overbreathing in which breathing is occurring in excess of metabolic requirements, leading to an acute reduction in $PaCO_2$ and the consistent set of physiologic changes that occur in response to this state. Most typically, acute hyperventilation occurs because of a modest increase in tidal volume (e.g., 750 mL/min) in conjunction with a "normal" respiration rate (e.g., 16 to 17 breaths/min). Hence, clinically significant overbreathing is often not grossly visible.[19]

The multiple physiologic changes that occur during and in immediate response to acute hyperventilation are the proximal cause of many of the somatic and CNS symptoms that occur during a panic attack. The immediate effect of overbreathing is that the $PaCO_2$ drops, blood pH rises, and an acute state of hypocapnic, respiratory alkalosis is induced, typically in 1 minute or less. In response to this state of respiratory alkalosis, a variety of secondary physiologic changes occur in a rapid, sequential cascade.[20-22] First, there is a shift in the oxyhemoglobin dissociation curve so that oxygen is bound more tightly (the Bohr effect), resulting in less efficient delivery of oxygen. Second, hypocapnia leads to CNS vasoconstriction. The resulting reduced cerebral flow is assumed to be the cause of a variety of the CNS symptoms observed, such as light-headedness, dizziness, depersonalization, blurred vision, confusion, and even focal neurologic signs. Third, paresthesia and pain symptoms commonly arise in response to the combination of direct effect of persistent alkalosis on peripheral nerves, mechanical muscle fatigue, and peripheral vasoconstriction and spasm. Fourth, mouth breathing and aerophagia can contribute to the symptoms of dry mouth, abdominal distress, and flatulence. Fifth, as the patient attempts to interpret these sensations a variety of catastrophic cognitions can (but, as mentioned earlier, do not always) arise, feeding back to lower brain centers and worsening the attack. Finally, this physiologic cascade is mitigated or terminated as renal compensation restores normal arterial pH by increasing bicarbonate excretion and as relative cerebral hypoxia induces vascular dilation restoring CNS blood flow.

Several important long-term effects can occur as a result of the renal compensation of the acute hyperventilation episode that increase the likelihood that a diathesis toward future panic/hyperventilation episodes is maintained. First, although renal compensation restores normal blood pH, both arterial $PaCO_2$ and bicarbonate levels remain low. Because the chemoreceptor system's control function for CO_2 is nonlinear (i.e., whereas at $PaCO_2$ levels above 35 mm Hg any rise in $PaCO_2$ is strongly opposed by the chemoreceptor system promptly increasing ventilation, at $PaCO_2$ levels below 35 mm Hg this system provides virtually no change in ventilatory drive), in the "compensated" state, small changes in ventilation can rapidly lower an individual's $PaCO_2$ with no opposition from the control system.[22] Furthermore, if episodes of acute hyperventilation continue long enough, continued renal compensation can lead to depletion of the bicarbonate buffer system, thereby amplifying the physiologic effects of low $PaCO_2$.[21] Hence a vicious cycle can be established in which a few sighs or deep breaths can lead to intensified and continued episodes of acute panic and hyperventilation.[19,22] Indeed, chronic hyperventilation has been purported to underlie various states of chronic fatigue and incapacity.[21,23]

Panic Disorder

Panic disorder is diagnosed when there is the presence of recurrent, unexpected panic attacks followed by at least 1 month's duration of persistent concern about having another panic attack, worry about possible implications or consequences of the attacks, or a significant behavioral change as a result of the attacks. Two features of panic disorder should place it near the top of a physician's differential diagnostic list in most patients suffering from recurrent panic attacks or hyperventilation. First, panic disorder is an extremely prevalent condition. Epidemiologic research suggests a lifetime prevalence rate of 2% to 5%.[10,24,25] Furthermore, panic disorder is estimated as the major clinical problem in 10% to 15% of patients entering primary care as well as pulmonology, cardiology, and gastroenterology subspecialty practices.[16,26-30] Second, the pathophysiology of panic disorder has become increasingly clear with safe and effective treatments available.[20,31,32]

The leading current pathophysiologic models of panic disorder posits that a hyperresponsive mid-brain "fear center" (most likely in the amygdala) responds in an exaggerated fashion to incoming "danger" signals, in particular to false "suffocation alarms" from brainstem respiratory control and monitoring centers (primarily in pons and medulla), leading to prompt activation of associated defense and escape systems (e.g., in the locus ceruleus and periaqueductal gray region).[20] This hypersensitive response to perceived respiratory danger triggers a 2- to 3-fold increase in minute ventilation leading to the physiologic cascade of a panic attack.[20,32,33] In support of this proposition, inhalation of CO_2 or sodium lactate infusion causes increased ventilation, and both challenges are potent and specific panicogens in susceptible individuals.[34,35] Furthermore, effective antipanic treatment (using either medication or cognitive behavior psychotherapy) has been shown to be able to block the respiratory stimulatory and panic-inducing effects of these laboratory challenges.[36] Finally, patients with panic disorder have greater baseline evidence of chronic, compensated hyperventilation as well as more chaotic breathing patterns at rest and during sleep, than normal controls, indicating observable abnormalities in the control of breathing even outside of panic episodes.[35,37,38]

Klein[39] proposed a useful temporal and logical sequence for the symptom clusters that are seen in panic disorder. First is the acute panic anxiety elicited during the panic attack. Such anxiety is especially potent given its intense visceral, bodily nature and the sense of inexplicable catastrophe that typically accompanies the episode. Individuals who suffer from panic attacks tend to be oversensitive to interoceptive signals, usually have no solid, logical explanation of why the

event occurred, and therefore with recurrent attacks can feel helpless and confused and often grasp for answers that will allow them to escape from these attacks.

The second feature, anticipatory anxiety, arises as a response to the intense conditioning stimuli of an acute panic attack. In more common terms, the patient's level of chronic anxiety or "nervousness" rises out of the uncertainty and worry about when the next attack will occur. Three important clinical correlates of this more generalized and chronic anxiety state are that such patients may be more likely to (1) appear to have "excessive stress" or "psychologic overlay" as they enter the health care setting, thereby receiving poorer quality of care[27]; (2) establish a state of chronic hyperventilation, thereby being vulnerable to experience more frequent and intense recurrences[22,35]; and (3) have higher cortical learning involved in the pathophysiology of their panic attacks. The relevance of this last point is highlighted by recent findings from CO_2 inhalation challenges demonstrating that aspects of the social context in which the challenge is conducted (e.g., the patient's perceived level of control or the presence of a "safe person," can influence the likelihood that the patient will have a panic attack during the challenge).[40,41]

Third, up to one third of patients begin to phobically avoid situations that they come to believe trigger acute episodes (e.g., leaving their house, driving their car, or taking baths or showers), likely as a conditioned-fear response.[20] Such agoraphobic behavior greatly increases the psychosocial morbidity of panic disorder because of the interpersonal and sociovocational difficulties that arise as the patient's significant others, friends, and employers react to this seemingly "irrational," avoidance behavior.[42] Additionally, significant demoralization or frank depression frequently arises. Up to three quarters of patients with panic disorder become clinically depressed, and suicide rates for patients with panic disorder are among the highest for any psychiatric disorder.[43,44]

Panic, Hyperventilation, and Chronic Pulmonary Illness

It is well established that these "somatic" anxiety disorders are especially common comorbid psychiatric disorders in patients with chronic pulmonary illness.[26,28,30,45,46] Indeed, the CNS-lung connections described here lead to a very complex intertwining of these anxiety disorders and chronic respiratory disease. Hyperventilation (even when isocapnia is maintained) can precipitate bronchial constriction, with isocapnic hyperventilation often used to measure airway hyperresponsiveness.[47] Conversely, the $PaCO_2$ increase during an acute asthma attack can trigger a panic attack in patients with panic disorder.[48] Additionally, although the symptoms of air hunger, shortness of breath, chest discomfort, and acute fear are similar across these conditions, the treatments are not. In fact, certain asthma treatments, such as β-agonists, can increase autonomic arousal, thereby precipitating or worsening panic attacks. Hence, both patients and their health care providers need to discriminate these two entities during acute episodes,[46,49] as well as recognize and aggressively treat comorbid "somatic" anxiety to effectively manage chronic pulmonary patients over time.[29,48,50,51]

Treatment

Fortunately, acute panic attacks and hyperventilation, as well as more chronic panic disorders, even when complicated by significant agoraphobia, are readily treated. Basic guidelines for treatment follow.

BEGIN WITH EDUCATION

Panic attacks and episodes of acute hyperventilation are horribly frightening experiences. Patients are generally frightened, confused, and very uncomfortable. They may feel that something is terribly wrong with their bodies. The physician can greatly improve chances of a successful outcome by taking several minutes with the patient, and with the child patient's parents, to cover the following points, thus providing them with a clear, cogent explanation of the panic attack. First, panic attacks are extremely common, even though most people never talk about them. They are not a sign of impending insanity or a flawed character. Second, panic attacks cause a real bodily experience because "hyperactive breathing control centers in the brain" have given the body a "false alarm," but the body has had no way of knowing that the alarm was not a true one. Using the analogy of the relationship between a furnace (lungs) and its thermostat (CNS breathing control centers) can help many pulmonary patients grasp this systemic relationship between CNS control and monitoring and lung function in a fashion that gets their "head" into the equation without implying that their problem is "all in their head." Third, certain medical problems can cause symptoms similar to those the patient has experienced (Box 74-2), but these already have been considered, checked, and ruled out by the physician. Fourth, although such attacks may disappear without treatment, safe and effective treatment exists, and it is highly recommended that patients begin these treatments. Such treatment consists of medication and some breathing and behavioral changes, the combination of which will help patients gain control over their attacks over a period of several weeks.

PHARMACOLOGIC BLOCKAGE OF PANIC

Medication treatment should be instituted to block or blunt the attacks. For the vast majority of adult patients with panic disorder, the medication of choice is a selective serotonin reuptake inhibitor (SSRI).[31,52] A number of other commonly prescribed antidepressant medications, most notably trazadone and bupropion, have little to no antipanic activity. Because a potentially large subset of patients with panic disorder are inordinately sensitive to the stimulatory effects of these antidepressant medications (e.g., agitation, restlessness, insomnia),[53] therapy should begin with low dosages (e.g., paroxetine 5 mg every morning in adults). In adults, aggressive use of antidepressant medications is particularly necessary in the case of panic disorder complicated by major depressive disorder because depression appears to significantly diminish the efficacy of the behavioral treatments described in the following sections.[54] Due to important concerns about the risks of using SSRIs in children and adolescents, the behavioral interventions described below should always be attempted first in pediatric populations.[55]

A recent meta-analysis found that in adults, the commonly used, high-potency benzodiazepine alprazolam is less effec-

BOX 74-2 Causes of Hyperventilation

Respiratory Disorders

Asthma
Pneumonia
Pulmonary embolism
Interstitial lung disease
Chronic obstructive lung disease
Respiratory dyskinesia/diaphragmatic flutter
Pulmonary hypertension
Pneumothorax

Central Nervous System and Psychiatric Disorders

Panic disorder (via a hypersensitive "suffocation alarm")
Phobias
Generalized anxiety disorder
Central neurogenic hyperventilation
Hiccup/palatal myoclonus
Central nervous system lesion (especially brain stem; e.g., tumor, post–cerebrovascular accident, meningitis)
Factitious (consciously induced or simulated)

Pharmacologic Agents

Aspirin and other salicylates
Alcohol withdrawal
Neuroleptics (via respiratory dyskinesia)

Other

Chronic, severe pain
Adaptation to higher altitude
Pyrexia/sepsis
Heat exhaustion/heatstroke
Pregnancy/luteal phase of menstrual cycle (via progesterone)
Liver disease/failure

tive treatment of panic attacks than are the SSRIs.[56] Furthermore, given the potential for benzodiazepines to cause tolerance, dependence, and respiratory depression, their use should be limited in individuals with milder pulmonary illness (1) who have very infrequent panic attacks not requiring daily medication or (2) during the initial weeks of treatment in patients with more intense anxiety symptoms while awaiting the response to SSRI medication. Benzodiazepines are *not* recommended as a first-line medication for children with panic anxiety.

RESPIRATORY CONTROL, COGNITIVE BEHAVIORAL, AND EXPOSURE TREATMENTS

Coincident with the start of pharmacologic treatment, patients should be instructed in respiratory control strategies to prevent or limit the hyperventilation that occurs during an attack.[51,57-59] There are two important aspects to such training. First, patients should be informed that once a CNS breathing alarm occurs, the body's natural response is hyperventilation, and that it is this hyperventilation that causes most of the discomfort experienced during a panic attack/hyperventilation episode. Second, patients benefit from training in slow, regular, diaphragmatic breathing, with specific comments to avoid mouth breathing, thoracic breathing, or excessive sighing or yawning as appropriate. Patients often require practice and the help of a coach (therapist or family member) to remember to commence such breathing during the "heat" of an impending panic attack. Training in more general relaxation techniques is often advocated, although such training is most likely a nonspecific adjuvant therapy.

In addition to respiratory control techniques, formal cognitive behavioral therapy for panic disorder also focuses on reframing how the patient interprets the frightening, somatic symptoms that arise during a panic attack.[57,60,61] Such treatment clearly lessens the catastrophic thinking usually seen during acute panic, and also most likely promotes higher cortical learning effects that over time inhibit or reduce the hypersensitivity of mid-brain fear and/or brainstem breathing control centers. As stated above, successful cognitive behavioral treatment for panic does alter the hyperresponsiveness to CO_2 seen in panic patients.[36]

Given that significant avoidance (agoraphobic) behavior complicates the clinical presentation in up to 30% of patients with panic disorder, in vivo exposure treatment of the avoidance behavior is often required for recovery. Principles of such treatment are well described.[54,57] In essence, exposure treatment involves graduated real-life exposure of the patient to the fear-producing situation until he or she becomes desensitized to the discomfort of being in the situation. The patient uses respiratory control and cognitive reframing techniques to manage the panic experienced during the exposure. Typically, ability for the patient to tolerate the previously dreaded and avoided situation occurs after 2 to 10 repetitions of the exposure. For children, often it is avoidance of school that is seen with this type of anxiety, and it is necessary to teach the parent(s) how to coach their child with breathing exercises and positive cognitions to get them over the transition to school. Typically, once in school, these children do fine.

Additional treatments, such as family therapy, should be considered when appropriate, especially if the parents, themselves, are too anxious about the child's symptoms to be able to appropriately coach them. Treatment ends by reemphasizing the "tools" that the patient has learned to gain control over their panic anxiety symptoms, with the explicit prediction that although relapse is possible, any recurrence of symptoms would diminish promptly once the patient reinstitutes these newly learned cognitive-behavioral strategies.

VOCAL CORD DYSFUNCTION

Paradoxical VCD is a common, poorly understood condition in which the vocal cords paradoxically close on inspiration, producing airflow obstruction at the larynx and causing audible wheeze or stridor. VCD most frequently is diagnosed as a mimic or confound in difficult-to-treat asthma or another chronic respiratory disorder, but also can be seen in diverse groups of patients including "perfectionistic" teenagers, elite athletes, active duty military personnel, and patients with other allergic and/or inflammatory disorders involving the upper airway (e.g., GERD, sinusitis, occupational irritant exposures, and post-URI). Typical clinical episodes range from transient, mild asthma-like symptoms (i.e., chest tightness, shortness of breath, wheezing, and cough) to total upper

airway occlusion. Although arterial blood gases usually are normal during symptomatic episodes, both hypoxia and hypocapnia have been reported. The acute presentation is often dramatic and misdiagnosed, leading to unnecessary intubation, tracheotomy, or treatment with high doses of corticosteroids, often resulting ultimately in iatrogenic complications.[62-64]

Clinical Presentations and Prevalence

The clinical syndrome was first documented in 1842 by Dunglison,[65] who described it as an adduction of the laryngeal muscles in hysterical female patients and called it "hysteric croup." The prescribed treatment was "cold water thrown over the face and neck and compound spirit of ammonia held to the nostrils." "Functional upper airways obstruction without organic abnormalities" was described in three patients in 1981,[66] all of whom had acute upper airway obstruction, hypoxia, and tracheotomies. These were the first patients in whom the vocal cord abnormalities were documented by visualization of the adduction of the true and false vocal cords during symptomatic episodes. The term *vocal cord dysfunction* was coined by Christopher and associates[67] in 1983, who described five cases of adults in whom paroxysms of wheezing and dyspnea were refractory to standard therapy for asthma. Laryngoscopy confirmed that wheezing was caused by adduction of the true and false vocal cords throughout the respiratory cycle, which was essentially normal when patients were asymptomatic. The patients could not reproduce the vocal cord abnormality voluntarily.

Although the exact prevalence of VCD is unknown, it does not appear to be rare. The literature is almost entirely comprised of myriad case reports describing VCD-like clinical conditions, from a variety of disparate and nonoverlapping literatures (e.g., anesthesia, otolaryngology, emergency medicine, psychiatry, pulmonology, and pediatrics), often with highly evocative names such as Munchausen stridor,[68] factitious asthma,[69] emotional laryngeal wheeze,[70] and episodic laryngeal dyskinesia.[71] In terms of quantitative data, Newman and colleagues reported that nearly 40% of adult patients presenting to a prominent national pulmonary referral center for evaluation of asthma that failed to respond to aggressive treatment ultimately were diagnosed with VCD, with essentially half being diagnosed with VCD alone and half with VCD associated with chronic asthma.[63] The patients with VCD alone had been misdiagnosed as having asthma on average for 4.8 years, and at intake were taking an average oral corticosteroid dose equalling nearly 30 mg of prednisone. In the prior year they averaged nearly 10 emergency department visits and 6 hospital admissions. Young adults, females, health care workers, and individuals with stressful life circumstances and/or psychiatric illness are overrepresented in reports of VCD, but this disorder is clearly not limited solely to such populations.[64,72] For example, Rundell and Spiering[73] reported presence of inspiratory stridor (and presumed VCD) during exercise challenge in 5% of elite athletes training at the Lake Placid United States Olympic Training Center. Such inspiratory stridor commenced soon after onset of intense physical performance, resolved within 5 minutes after cessation, and showed no response to inhaled β_2-agonist. Females competing in outdoor sports predominated. Slightly over half also had coexistent exercise-induced bronchospasm. Similarly, VCD confirmed by laryngoscopy has been reported as the cause of nearly 10% of children and adolescents presenting with exercise-induced dyspnea.[74]

VCD can cause stridor, shortness of breath, wheezing, chest tightness, and cough. The syndrome is suspected when the patient does not reveal an organic cause of upper airway obstruction or respond to adequate asthma therapy. The symptoms often start and cease abruptly, and the patient is asymptomatic between attacks. Often patients indicate that they feel throat tightness or that their voice changes during an acute attack. Patients who have "pure" VCD may indicate that bronchodilators do not help, and often worsen their breathing. Although stridorous wheezing can sometimes be heard over the larynx, it also can be transmitted to the lower airways from the larynx; thus the physical examination can be unreliable in distinguishing a VCD attack from an asthmatic episode. However, if at the time of acute symptoms the patient is able to hold his or her breath or pant, this is suggestive of VCD because patients suffering an acute asthma attack will be unable to comply. While asymptomatic, patients with pure VCD have normal pulmonary function tests, which may help distinguish them from asthmatics, who often have increased residual volumes, indicating air trapping from small airways closure. During acute symptoms, the patient with VCD may have a truncated inspiratory or expiratory limb of the flow-volume loop, indicating variable obstruction. The ratio of expiratory flow to inspiratory flow at 50% of forced vital capacity is usually greater than 1.5. However, even during an acute VCD attack, the alveolar-arterial oxygen difference is usually normal. It is important (and relatively easy) to exclude other conditions that can cause acute stridor and wheezing in children and adolescents, including a foreign body in the upper airway, epiglottitis and croup, and hereditary angioedema[75] (Fig. 74-1).

The diagnosis is definitively established by laryngoscopic visualization of the vocal cords while the patient is having symptoms. "Classic" VXD is characterized by adduction of the anterior two thirds of the vocal cords with a characteristic "posterior chink" observed during inspiration. Wood and Milgrom[64] provide an excellent description of this procedure, including recommendations of how to differentiate true VCD from vocal cord movement induced by the laryngoscopy procedure itself (e.g., via the cough or gag reflex, or through inadequate anesthesia). It is important to note that

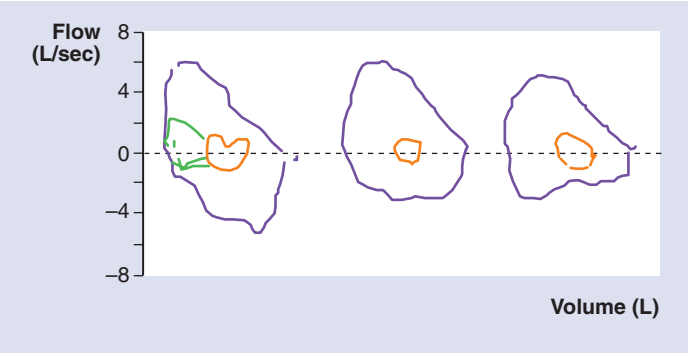

Figure 74-1 Characteristic spirometric abnormalities seen in VCD: Variable notching and truncation of the inspiratory portion of the flow-volume loop.

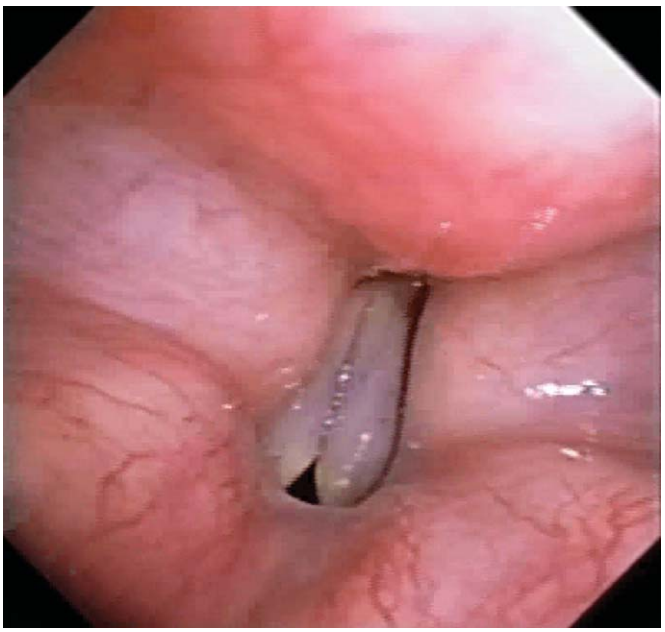

Figure 74-2 Photograph of classic vocal cord adduction during inspiration with posterior chink.

a normal laryngoscopy in the absence of symptoms does not exclude the diagnosis of VCD. In one series approximately half of the unstimulated laryngoscopies done on patients ultimately diagnosed with VCD were normal.[63] Accordingly various challenge procedures have been recommended prior to laryngoscopy, including methacholine or histamine, specific irritant, and exercise.[64,72,76] If the vocal cords are not seen to adduct during an acute episode, the diagnosis of VCD must be seriously questioned (Fig. 74-2).

Pathophysiology

The etiology and pathophysiology of VCD remain largely unknown. It is widely recognized, however, that one of the primary physiologic functions of the larynx is protection of the airway via the cough, glottic closure, and other CNS reflexes. Morrison's "irritable larynx syndrome" does provide a clinically useful integration of the various pathways whereby various "threats" to breathing that are of sufficient intensity and/or sustained over time could cause these normally protective reflexes involving the vocal cords to become sensitized, hyperresponsive, and dysfunctional.[3] Evidence supporting some of the most common threat pathways that may be causally related to VCD are discussed below.

RESPIRATORY IRRITANTS, INFLAMMATION, AND ALLERGY

The best support for the role of irritant and inflammatory processes in VCD comes from Bucca and colleagues, who have described a syndrome of extrathoracic hyperresponsiveness (ETHR) in over 500 patients with asthma-like symptoms that bears strong resemblence to VCD.[77-79] Specifically, following a histamine challenge when asymptomatic, they have demonstrated that the vast majority of patients exhibited some type of airway hyperresponsiveness: approximately 25% of patients had only ETHR, as defined by the provocative concentration of histamine required to produce a 25% drop in maximal mid-inspiratory flow rate from baseline ($PC_{25}MIF_{50}$) being less than 8 mg/mL; around 10% had only lower airway reactivity, as defined by a provocative concentration of histamine to produce a 20% drop in FEV_1 ($PC_{20}FEV_1$) of less than 8 mg/mL; and another 40% of patients demonstrated both. Results of laryngoscopy revealed that although all examinations of the glottis were normal at baseline, following histamine challenge marked mucosal edema, pharyngoconstriction, and adduction of the vocal cords during inspiration were observed in patients showing ETHR but not in those showing only bronchial hyperreactivity. ETHR was associated with postnasal drip, dysphonia, and sinusitis, suggesting that it is sustained by chronic irritation and/or inflammatory processes affecting the upper respiratory tract. Over 75% of subjects with ETHR were female. Similar findings have also recently been reported in children.[80] Even more important, successful treatment of coexistent rhinosinusitis and GERD improves ETHR.[79-81] It seems likely that ETHR occurs across a spectrum, with severe VCD residing at one extreme endpoint.

Perkner and associates have described 11 patients who developed onset of VCD within less than 24 hours after a single, albeit often intense exposure to occupational respiratory irritants.[82] All cases were confirmed to have the pathognomic laryngoscopic findings including a "posterior chink" despite the fact that these examinations were performed weeks to months after the occupational exposure. Our experience working with such patients suggests that sometimes the exposure results in permanent damage to the airway that produces ongoing activation of the glottic closure and/or cough reflex, thereby perpetuating the VCD symptoms. However, much more commonly, the initial exposure and airway injury sets up a vicious cycle of cough, mucous drainage, inflammation, and vocal cord sensitivity that prevents adequate resolution, thereby sustaining itself. Similar mechanisms may explain VCD onset after viral URIs[3,83,84] and during postsurgical recovery.[85-87]

During Intense Athletic Competition and Military Experience

A second set of "threats" to breathing come from various case studies and series reporting on VCD occurring in healthy, physically fit individuals in contexts that demand intense, peak-level physical performance.

McFadden and Zawadski[88] reported seven cases of elite athletes in whom acute exercise-induced dyspnea was ultimately determined to be due to VCD based on spirometric and/or laryngoscopic testing during bronchoprovocative challenges. Interestingly, exercise-induced VCD also could be differentiated from exercise-induced bronchospasm (EIB) by the clinical history of the attacks, with VCD episodes coming on during rather than after intense exercise, not consistently occurring with exposure to similar stimuli, and not responding to prophylactic or rescue asthma treatments. The patients were described as "highly competitive, success oriented, and either personally intolerant of failure or . . . the offsprings of parents so inclined." The authors conclude that the cause of these VCD episodes was "psychological stress" leading to "choking" during competition (in both the medical and sports connotations), and "probably a conversion disorder."

Rundell and Spiering[73] found the prevalence of exercise-induced inspiratory stridor (confirmed only by laryngeal auscultation) to be slightly greater than 5% in a cohort of 370 elite athletes participating in training through the U.S. Olympic program at Lake Placid, New York. Similar to the aforementioned report, they also found that these presumed cases of VCD could be differentiated from EIB by onset during, not after, exercise; rapid resolution following cessation of exercise; and lack of response to bronchodilator treatments. Inspiratory stridor was most common in female athletes participating in outdoor sports. The authors do not make any specific causal statements about why inspiratory stridor occurred in these world-class athletes, but do mention that competition is a "psychologically stressful" situation.

Morris and colleagues[89] found a 15% prevalence rate of laryngoscopically confirmed VCD in a group of young U.S. Army soldiers who were unable to pass a required 2-mile running physical fitness task due to exertional dyspnea. They acknowledge that many have suggested that VCD represents a conversion reaction, or another form of psychopathology, and comment that the Army training undertaken by the young recruits of their cohort is "generally considered to be a time of great emotional, psychological, and physical stress."

Another feature of exercise-induced VCD that likely has contributed to investigators seeing this as a psychologically induced problem is that exercise-induced VCD episodes are not reliably provoked by hyperventilation or methacholine challenges; instead, variable responses to differing challenges commonly are observed both within and across subjects.[76,88,89]

Despite the assertion that psychological factors have a direct causal role in exercise-induced VCD, several other observations argue against this. First, brief, simple speech therapy and breathing retraining interventions appear to be extremely effective for exercise-induced VCD, with the vast majority of those affected being able to return to baseline performance during competition.[90,91] Although effective treatments exist for psychological disorders, such interventions are almost universally more time and effort intensive, and except in a few specific disorders, somewhat less effective. Second, VCD-like episodes have been observed in thoroughbred race horses exhibiting stridorous breath sounds during competition,[92] suggesting that the CNS mechanisms do not require either higher levels of conscious psychological or unconscious psychodynamic processes. Third, a leading cause of pulmonary barotrauma in military personnel being trained in SCUBA diving is laryngeal closure arising as an involuntary panic reaction during ascent, consistent with a hypothesis that VCD arises when protective reflexes misfire at inappropriate times.[93] Fourth, VCD has been described as a side effect in patients treated with vagal nerve stimulation for intractable seizure disorders,[94,95] suggesting that VCD arises from a dysfunctional CNS reflex response, rather than from psychological maladjustment. It is important to remember that many body reflexes are augmented by both psychosocial stress and increased muscle tension, so the observed association of VCD with stress may simply reflect reflex facilitation rather than direct causation. Consistent with this supposition are the clinical observations that patients with VCD typically focus their attention on the larynx and airway, and indeed, have palpable tension of the laryngeal musculature.[3,96]

PSYCHIATRIC DISORDERS AND VOCAL CORD DISORDER

The role of psychological stress in VCD has been discussed earlier. In this section, we turn to the issue of overt psychiatric disorders in VCD. Despite the fact that VCD is quite frequently labeled a "functional" or "psychogenic" disorder in the literature, the role of psychiatric factors in the pathophysiology of VCD remains murky, with many seriously flawed assertions (e.g., patients with VCD use a lot of medical services, patients with somatization disorder use a lot of medical services, therefore patients with VCD have somatization disorder). We examine the evidence around two key questions: Are any specific psychiatric conditions associated with VCD? Are any causally related to VCD?

Cormorbidity of Psychiatric Disorders in Vocal Cord Disorder

A very wide range of specific and phenomenologically distinct psychiatric diagnoses have been reported to occur in patients with VCD, including conversion disorder, family conflict, depression, anxiety disorder, factitious disorder, personality disorders, and posttraumatic stress disorder. Several studies have compared patients with VCD to patients with moderate to severe asthma and reported no group differences in overall rates of psychopathology.[63,71] Rates of psychopathology in these studies ranged up to 73% in the Newman study, but it is also clear that VCD exists in patients without psychopathology, arguing against a causal role of psychiatric factors in VCD.[62,63] Virtually all prior reports of psychiatric problems are limited by their methodologic reliance on retrospective chart reviews, and their use of self-report or clinical interview assessments of psychopathology rather than research-grade measures.

One exception is the report of Gavin and colleagues,[97] who examined panic anxiety symptoms in adolescent patients admitted to an inpatient tertiary care pulmonary program with a diagnosis of severe, chronic asthma. Children whose primary discharge diagnosis was changed to VCD were matched to a group of adolescents whose discharge diagnosis remained severe, chronic asthma and who showed no clinical evidence of VCD. Medical records for these children were reviewed by a pediatric pulmonologist to ensure that an appropriate work-up had been performed to rule in and rule out VCD in these two groups. Research-grade assessments of anxiety were obtained before the diagnoses of VCD were established. Patients subsequently diagnosed with VCD were found to have higher levels of self-reported and parent-reported panic anxiety and received a higher number of panic anxiety diagnoses during a structured psychiatric interview than the patients with asthma. Two thirds of patients with VCD (i.e., 8 of 12) received such diagnoses, versus 2 of the 12 asthma patients. Furthermore, the vast majority of the VCD patients had onset of their anxiety symptoms prior to onset of their respiratory problems, whereas this was true for none of the asthma controls. Given the evidence presented above that panic disorder may share similar etiologic roots in protective brainstem respiratory reflexes gone awry, the findings of this study deserve replication and extension.

Conversion Disorder and Factitious Disorder

Because virtually all early and many recent reports claim that the patients with VCD have either conversion disorder or factitious disorder (aka Munchausen's syndrome), these disorders are discussed in more detail. Both diagnoses are highly overused, and typically inaccurate. Factitious disorder is diagnosed when a patient intentionally produces or feigns symptoms in order to assume the sick role. The judgment that a symptom is intentionally produced is made by direct evidence and by excluding other causes of the symptom. The presentation may include fabrication of subjective complaints, self-inflicted conditions, or exaggeration or exacerbation of a preexisting medical condition.[13] The motivation is to assume the sick role. If there is an obvious external incentive (e.g., to be out of jail, economic gain, avoiding legal responsibility), the condition is labeled "malingering." Key features of conversion disorder are "the presence of symptoms or deficits affecting voluntary motor or sensory function that suggest a neurological or other general medical condition . . . The initiation or exacerbation of the symptom or deficit is preceded by conflicts or other stressors . . . and the symptoms are not intentionally produced or feigned."[13] Symptoms of conversion disorders do not generally conform to known anatomic pathways or physiologic mechanisms and the diagnosis of conversion disorder should not be given if the symptoms can be fully explained by a neurologic or other general medical condition.[13]

In contrast, in VCD there is a documented physical abnormality, the paradoxical adduction of the vocal cords, which conforms to known neurologic reflex pathways (the enervation of the musculature involved with upper airway muscles includes cranial nerves 5, 7, 9, and 10 and cervical nerves 1, 2, and 3).[98] Concerning factitious disorder, it is doubtful that VCD episodes can be voluntarily feigned or purposely induced. Christopher and colleagues[67] reported that when patients were asked to duplicate their symptoms while the vocal cords were being visualized, they were not able to do so. Conversion disorder is an involuntary (indeed usually considered an unconscious psychodynamic process) but should not be used when a known reflex mechanism exists as a competing explanation. Hence, in most cases where the vocal cords are seen to have the characteristic posterior chink while the patient is symptomatic, conversion or factitious disorders are probably not accurate diagnoses. Some patients may feign wheezing or stridor at times when the cords are not truly adducted, meeting the criteria of purposeful exaggeration of an existing medical condition. These patients could then be appropriately diagnosed as having factitious disorder or malingering depending on the circumstances. Finally, both conversion disorder and factitious disorder are notoriously difficult to treat or interrupt, and most patients with the disorder are severely psychologically disturbed. This is not the case in most patients with VCD, where the available, albeit sparse, evidence suggests that a majority of patients respond to brief and focused treatment.[90,91,96]

Treatment

Martin and associates[84] emphasize the role of a multidisciplinary team (pulmonologist, otolaryngologist, psychiatrist, and speech therapist) in the evaluation and treatment of patients with VCD. The interventions described in the literature for VCD range from simple and quick educational approaches to invasive surgical procedures, and include explanation and reassurance; behavioral medicine, speech therapy, and psychiatric interventions (i.e., breathing exercises, biofeedback, hypnosis, individual or family psychotherapy, psychotropic medication); breathing helium-oxygen mixtures; CPAP; botulinum toxin; bilateral nerve blocks; posterior fossa cystectomy; and tracheotomy.

For most patients, receiving the diagnosis of VCD requires them to change the beliefs they have developed about their illness from prior medical diagnosis and therapeutics, including a sizable number of patients who have suffered iatrogenic harm from misdiagnosis. In general, patients who are pleased and adapt well to being told the nature of their condition usually are more accepting of appropriate therapy and have a better outcome. Therefore, much care should be taken in explaining the diagnosis of VCD to the patient. For example, for those patients who have been previously diagnosed with asthma, they should be told that they do not have asthma, or asthma alone, but another medical condition called VCD. Viewing the videotape of their own or another patient's vocal cords closing on inspiration is often a powerful aid in explaining the medical aspects of this disorder. We find it helpful to suggest to patients that the main pathophysiologic mechanism is a reflex designed to protect their breathing that now has become hyperactive and dysfunctional, although we acknowledge that this is just a reigning hypothesis, not an established fact.

The cornerstone of outpatient VCD therapy is various speech exercises, designed to accomplish two key goals.[64,91] First, a set of rescue techniques that open the cords during episodes and allow patients to regain control over their symptoms which are based on substituting a voluntary and competing behavior, such as panting or sibilant breathing, whenever the vocal cords adduct. Practiced whenever symptoms are triggered, and coached by supportive persons in the environment, these techniques are very specific and effective. Second, patients are coached in techniques (e.g., slow, relaxed, abdominal breathing) to change their breathing outside of episodes (i.e., throughout the day) in such a way so as to refocus their breathing efforts away from the larynx and airway, thereby reducing laryngeal tension and potentially decreasing feedback to the CNS that drives and maintains the hyperactive reflexes.

Evidence exists that biofeedback, relaxation, and hypnosis can be effective, but since they are not as specific and efficient as the speech therapy exercises, they probably are best reserved for patients requiring additional assistance in their recovery. For patients who have associated psychiatric problems, or whose VCD symptoms have become incorporated into their self-image or entangled in interpersonal conflicts, the addition of formal psychotherapy is sometimes required to manage the illness. Antidepressant/antipanic medications are useful in cases when depression and/or panic anxiety are present, and may be helpful more generally. One group has found that pretreatment with an anticholinergic inhaler (ipratroprium) helped all six pediatric patients with exercise-induced VCD control their episodes and continue their sports activities.[90]

Most of the literature suggests that the vast majority (>70%) of patients with VCD have a good outcome with some combination of education/reassurance, speech or breathing exercises, and psychotherapy, including two recent reports of longer term outcomes,[90,91] although in one 10-year follow-up of three patients, all continued to have recurrent symptoms despite speech therapies and psychotherapies, indicating that some minority of the group may be refractory to treatment.[99]

HABIT COUGH

The syndrome of habit cough is characterized by a barking or honking cough that is persistent and disruptive to normal activity. By definition, there are no laboratory, radiographic, bronchoscopic, or pulmonary function abnormalities. The patient does not show bronchoconstriction on methacholine challenge test or other provocative tests for asthma. The cough does not respond to usual antitussive therapies, bronchodilators, or anti-inflammatory medications. Nonetheless, the cough can become chronic and debilitating, preventing the child from attending school or social activities or impairing the adult's sociovocational functioning. The major morbidity from habit cough is iatrogenic, resulting from misdiagnosis and excessive medical treatment. It is not unusual for children to have been hospitalized for this disorder or to receive extensive evaluations. Two features that distinguish this cough from most of the pulmonary causes of cough is that it usually disappears once the patient is soundly asleep, and it seldom is exacerbated by exertion, as are coughs of most respiratory etiologies.

The prevalence of habit cough seems to be low, but it is not rare. There have been well over 100 cases of habit cough reported in the pediatric literature, at times labeled "psychogenic cough," "barking cough of puberty," "honking or psychogenic cough tic," "operant cough," or "respiratory tic"[100-103]; a handful of cases have been reported in adults.[104,105]

Diagnostic Considerations

Because the diagnosis of habit cough is essentially a diagnosis of exclusion, care should be taken to exclude all other causes of cough.[106] The differential diagnosis should include cough variant asthma,[107,108] bronchitis, pneumonia, allergic tracheitis, tuberculosis, cystic fibrosis, congenital pulmonary abnormalities, foreign bodies, and other intrinsic and extrinsic pulmonary disorders.[109,110] These pulmonary disorders would usually cause some abnormalities on laboratory, radiographic, or pulmonary function testing. Occasionally, the only abnormality may be noted on bronchoscopic examination, as in localized tracheomalacia.[111]

In understanding the pathophysiology of habit cough, it may be useful to understand its different eponyms because each of these three key terms implies a different mechanism: *habit*, *tic*, and *psychogenic cough*. Although the initial explanation to the patient and his or her family, as well as the first clinical intervention, in any of these instances may be similar, in general, the major reason to make these distinctions is that the likely treatment plan and overall prognosis will differ for each type of habit cough.

HABITS

Habits are generally semivoluntary activities, often reinforced either because they are self-soothing or because of the response they elicit from people in the environment. Although some habits (e.g., habit cough) disappear during sleep, not all habits do (e.g., bruxism or teeth grinding). In most cases of habit cough, children first develop a cough of infectious etiology, which lingers long after the infection usually should be resolved. Repeated cough continues to irritate the airways and stimulate the cough receptors, lowering the threshold for continued coughing.[109] Another frequently reported source of continued irritation is tobacco smoke exposure. Although never considered in the existing literature on habit cough, due to this common association with URIs and respiratory irritants, it behooves subsequent work in this area to examine whether such cases represent a true "habit" as opposed to cases of central sensitization of protective CNS reflexes, as discussed above, for somatic anxiety disorders and VCD. According to the cases reported in the literature, when a simple suggestive intervention is given and patients are shown how to suppress the urge to cough habit, the cough threshold returns to normal and the condition is "cured."

TICS

Tics are sudden, rapid, recurrent, nonrhythmic, stereotyped motor movements or vocalizations. Like habit cough, tics most often disappear during sleep and are exacerbated by stress, yet are defined as involuntary or semivoluntary. Tics are classified as *simple* or *complex* and as *motor* (movement) or *phonic* (sound producing). Tics may appear to be exaggerated fragments of ordinary motor or phonic behaviors that occur out of context. Simple tics usually involve a single muscle or functionally related group of muscles and are generally brief, lasting less than half a second each. However, they often occur in bouts of rapid succession, each bout lasting seconds up to minutes. Complex tics involve more muscle groups, often have a sustained duration or orchestrated pattern, and may appear purposeful. Complex phonic tics involve linguistically meaningful speech and language at times, whereas simple phonic tics are most often brief sounds, including coughing. Table 74-1 lists common motor and phonic tics. Occasionally, the first presentation of a tic disorder may be the single motor tic of coughing.[112]

Tic disorders involve a spectrum that includes transient tic disorder of childhood on the mild end, chronic motor or vocal tics in the moderate range, and Tourette's syndrome (TS) in the severe range. Transient tic disorder is common, occurring in 5% to 24% of schoolchildren.[112] By definition, tics in this disorder last more than 2 weeks but less than 12 consecutive months. Chronic multiple motor or vocal tics (there may be more than one tic, but all tics are in the same category) appear to represent a mild form of TS because both are transmitted as inherited traits within the same family. The severe end of the spectrum is Tourette's syndrome, in which more than one motor tic and at least one vocal tic occur in the same person, which are not due to the effects of a substance (e.g., stimulants) or a general medical condition (e.g., Huntington's disease or postviral encephalitis).[13] Onset must occur before age 21 (the median age of onset is 7 years), and the tics must be present for at least 1 year. Symptoms that may, but need not necessarily occur, include coprolalia, echo-

Table 74-1
Examples of Simple and Complex Tics

	Simple	Complex
Phonic tics	Coughing	Single words or phrases
	Sniffing	Speech blocking (e.g., stuttering or other interruptions)
	Barking	Palilalia (repeating one's own words)
	Throat clearing	Echolalia (repeating last heard word or sounds)
	Screaming	Coprolalia (inappropriate expression of socially unacceptable words or phrases)
	Sucking	
	Clicking	
	Snorting	
	Chirping	
	Blowing	
	Snorting	
Motor tics	Eye blinking	Jumping
	Jaw thrusting	Touching
	Nose wrinkling	Stomping
	Shoulder shrugging	Squatting
	Eyebrow twitching	Retracing steps
	Wrist snapping	Twirling
	Limb jerking	Hand gestures
	Facial grimacing	Copropraxia (a sudden, tic-like, vulgar gesture)
	Abdominal tensing	Echopraxia (repeating someone else's movements)

lalia, and complex motor tics, such as touching or picking. Approximately one third of individuals diagnosed with TS have resolution of tics by late adolescence; in another third, the tics diminish markedly; and in the remaining third the tics persist into adulthood.

In a child with habit cough, a tic disorder should be considered when more than one tic is noted, or if there is a family history of tics or other disorders genetically associated with tic disorders. These disorders include obsessive-compulsive disorder, attention deficit/hyperactivity disorder, and learning disorders. The vulnerability to Tourette's disorder is transmitted in an autosomal dominant pattern, with approximately 70% penetrance for female gene carriers and 99% penetrance for male gene carriers. Family members often have transient motor and vocal tics without full-blown Tourette's disorder.[113] Interestingly, in the pediatric reports of habit cough, there is note of some obsessive-compulsive symptoms in two of the patients, which is part of the genetic spectrum of tic disorders.[114]

The course of the cough symptom over time, comorbid psychiatric conditions, and family history will be most helpful in distinguishing a tic from a habit cough. Of note, antihistamines and sympathomimetic substances have been associated with exacerbation of motor tics in persons with preexisting tic disorders. These widely used agents could potentially bring on a motor tic in a genetically susceptible child and should be discontinued during evaluation of habit cough for that reason.[115]

Psychiatric Aspects

As discussed earlier in the section of VCD, the term *psychogenic* implies psychological causation. In the case of cough, psychoanalysts in the past have argued that a cough (as also was purported for asthma) can arise to express unconscious conflict: "The automatic cough reflex is expropriated by the voluntary muscle system in an effort to protect the ego. Just as weeping serves the dual function of washing irritants out of the eyes and expressing unhappiness, so does the cough share overlapping roles in discharging emotions and clearing the lungs."[105] Some early psychoanalytic reports suggested that the child's cough may be expressing a single, relatively circumscribed conflict (e.g., a way to protest to an overbearing mother),[100] whereas others indicated more complex motives (e.g., to avoid anxiety-provoking experiences at school).[116] It is important to underscore that outside of the rhetoric of psychoanalysis, there is no scientific evidence base to support psychological causation of cough.

A more evidence-based approach is to recognize that once started through other mechanisms, a cough can become entangled in psychological processes, and/or become entrenched and confounded by preexistent psychopathology. In one description of nine cases of habit cough, eight of the nine children had school phobia, possibly indicating an underlying anxiety disorder.[116] Several other authors described comorbid family conflicts or school phobia, and successful treatment of the patient included psychotherapy[101,117,118] or antidepressant medication.[119] These reports indicate that at least some children with habit cough have significant comorbid psychological problems and benefit from psychosocial intervention.

On the other hand, the existing literature also contains numerous examples that, in many children, reassurance and simple suggestive therapy are very effective in extinguishing the habit cough, usually within minutes to days and without emergence of other emotional or somatic symptoms.[102,103,114,120] Similar to pediatric VCD, many of these children are described as being conscientious, good students, and high achievers. These outcomes suggest that often habit cough is not associated with either underlying or concurrent psychopathology and can be easily treated with simple education and suggestion therapy.

As with VCD, there is a paucity of objective information with which to judge the actual prevalence of comorbid psychiatric problems in children with habit cough. None of the reports used blinded, objective raters to evaluate the presence of psychologic problems. There are no published reports of standardized ratings of emotional or behavioral problems among children with habit cough. None of the studies used control groups to compare rates of psychological or family problems, or overt psychopathology. Until this is done, one should not view habit cough as being caused by psychologic problems. Rather, it is likely that cough starts for a physiologic reason (e.g., post-URI), then gets sustained due to habit (or central sensitization?), and may be complicated and confounded by either preexisting psychological problems or via sickness reinforcing secondary gain, such as being able to stay home from school or receive extra attention from health care personnel. Even more important, if left untreated, it is possible that the habit cough itself may lead to psychosocial complications that become severe and take on a life of their own (e.g., secondary depression or markedly deficient social skills).[104,116]

Treatment

What is the natural course of habit cough? In the largest sample of habit cough syndrome reported, Rojas et al[121] followed up 60 patients (34 males and 26 females) an average of 7.9 years after diagnosis. The mean age at diagnosis was 10.5 years, with a range of 4.6 to 15.6 years. Mean duration of cough before diagnosis was 7.6 months, and mean duration until complete resolution was 6.1 months. In their sample, 73% had complete resolution of cough. However, 16 patients were still coughing a mean of 5.9 years after diagnosis. Because none of these patients was given specific treatments for the cough, this may reflect the natural course over time. The authors argue that more direct intervention would most likely shorten the course and limit the morbidity. It is important to clearly inform the patient and family of the diagnosis and intervene in some behavioral way to expedite recovery of these children, so that they do not form secondary problems from an unresolved habit.

Several types of interventions for habit cough and tic cough have been described in the literature. Treatment for simple motor tics is similar to that reported for habit cough. Current behavioral interventions use a combination of education and suggestion, for example, "This cough started with a cold. It has now become a habit in part because each time you cough, it irritates your throat and you are more likely to cough again. We will teach you how to stop doing that." The child is then taught a voluntary behavior that is incompatible with maintenance of the cough, such as diaphragmatic breathing, panting, or swallowing.[96,114,120] We often recommend that children carry a water bottle and have them swallow water each time they feel the urge to cough, which both inhibits the cough and may enhance mucus drainage at the same time. Finally, the parents are asked to monitor the child's progress (i.e., keep track of how many times an hour the child coughs) and reward the child for decreased coughing. Behavioral therapy has been demonstrated to be effective for most children with habit cough; overall, habit reversal has been found to reduce habit cough and simple phonic tics by 80% to 90%.[122] Pharmacologic interventions are not often used today for transient motor or vocal tics.

Some children and adults require more intensive psychosocial intervention, including hypnosis.[104,105,123,124] The few reported adult cases appeared to have more consistent psychopathology and were more difficult to treat than the pediatric and adolescent cases.[96] Nonetheless, with persistent therapy over 6 to 12 months, the overall morbidity of the disorder was greatly decreased, even if the symptom was not entirely extinguished.[104]

Prognosis and treatment for Tourette's disorder is very different than that for habit cough or simple transient tic disorder, and the patient suspected of having TS should be referred to a neurologist or psychiatrist. Treatment for TS usually includes psychopharmacologic interventions in addition to psychotherapy focused on behavioral strategies to decrease tics and how to cope with the illness in general. At least 20 agents have been tested for the more severe tics of TS. The most effective are pimozide, haloperidol, and clonidine. These are occasionally used for chronic tics. For example, in one description of nine cases of psychogenic cough tic six of nine children were treated with tranquilizers to alleviate symptoms.[116]

Habit cough should be in the differential of every cough persisting more than 2 weeks without any laboratory, pulmonary function, or radiographic abnormalities. Children and parents should be informed that the cough does not reflect any dangerous pathology and is indeed a habit at this point. Children should then be given a behavioral intervention that teaches them to suppress the cough and that allows a face-saving way out of the now dysfunctional habit/pattern. For most children, this approach is successful. If, however, evidence of more than one tic or strong family history for tic disorder exists, referral to a neurologist or pediatric psychiatrist should be considered. Likewise, if a straightforward behavioral approach is unsuccessful or if comorbid secondary psychiatric problems seem now to contribute to maintenance of the cough, referral to a pediatric psychiatrist or psychologist for further evaluation and treatment would be recommended.

CONCLUSION

This chapter has reviewed several common clinical syndromes in which CNS processes lead to respiratory symptoms. In each, a collaborative, potentially multidisciplinary, biopsychosocial orientation toward diagnosis and treatment is indicated because the existing research suggests that these disorders are based in hyperresponsive CNS reflexes, which although intended to protect respiration, can in certain circumstances misfire and produce episodes of cough, dyspnea, and breathing difficulty. As opposed to the notion that these problems are psychogenic and "all in the head," this chapter has argued that an informed clinical approach acknowledges both the central pathophysiologic importance of brain reflexes gone awry as well as the frequent confounding role of psychological stress and psychiatric disorders in the course and prognosis of these conditions. Given the relatively high prevalence rates, frequency of misdiagnosis and iatrogenic harm, significant degree of preventable morbidity, and availability of effective treatments for these

disorders, a clear understanding of the pathophysiology and treatment of the disorders discussed in this chapter will foster the clinical success of pulmonologists with what otherwise can be a difficult and frustrating group of patients to understand and treat.

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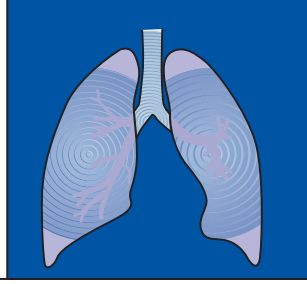

CHAPTER 75

Pulmonary Manifestations of Systemic Disorders

Laura S. Inselman

TEACHING POINTS

- Obesity and malnutrition can cause pneumonia, atelectasis, respiratory muscle weakness, alterations in control of breathing, and respiratory failure.
- Diabetes mellitus is associated with hypoplastic, polyalveolar lungs; increased amounts of collagen and elastin that are also structurally abnormal; and altered lung architecture, mechanics, and function.
- A recurrent left lower lobe pneumonia with chronic pancreatitis may indicate a pancreaticobronchial fistula.
- Liver disorders can cause pulmonary arterial hypertension and hypotension.
- Renal failure associated with collagen vascular disease is often accompanied by pulmonary vasculitis and alveolar hemorrhage.
- Metastatic pulmonary calcification occurs when an alkaline environment in the lung promotes calcium deposition.
- Sickle cell chronic lung disease often results from multiple episodes of the acute chest syndrome but may occur without a prior acute injury to the lung.
- A hemothorax may be present in thalassemia when extramedullary hematopoiesis develops in the chest wall.
- Familial dysautonomia is associated with aspiration pneumonia, bronchiectasis, airway reactivity, pneumothoraces, and apnea.

Pulmonary physiology and function reflect not only the physiology and function of the lung itself but also that of other tissues and organs in the body. Although the lung's primary roles are the exchange of oxygen (O_2) and carbon dioxide (CO_2) between the environment and the body and the maintenance of acid-base balance within the body, the lung also has metabolic, endocrinologic, and growth-mediating actions that interact in different ways with other organs. Modifications, dysfunction, and malfunction in other tissues and organs may be reflected in alterations in lung growth, structure, function, and physiology. In particular, the lung can be affected by disorders of nutrition; dysfunction of the pancreas, liver, and kidneys; the presence of hemoglobinopathies; and familial dysautonomia.

NUTRITIONAL DISORDERS

Obesity

DEFINITION, RISK FACTORS

Obesity is defined by a body mass index (BMI) ≥ 30 kg/m^2 and is characterized by excessive adipose tissue.[1-5] It may be exogenous, that is, diet-induced, or endogenous, that is, secondary to an underlying disorder. It is associated with a protein, leptin, that helps regulate fat metabolism and satiety. Adipocytes synthesize and secrete leptin under the control of the *OB*, or *LEP*, gene on chromosome 7q31.[5-8] Leptin receptors occur in large airways and alveolar epithelial type II cells in the lung and are identified prenatally and postnatally, during childhood, and in the adult.[9,10] Leptin, its receptors, and its interactions with other proteins, such as neuropeptide Y, insulin, glucocorticoids, and estrogen, regulate appetite, fat deposition, and weight gain.[5,6,8,11-13] Congenital leptin deficiency, genetic mutations, and target organ, that is, adipocyte, resistance are associated with excess caloric intake, diminished fat metabolism, and severe obesity.[2,12,14]

PATHOGENESIS

Developmental, biochemical, structural, and functional changes occur in the lung with obesity.[15-30] The lungs of young obese rats fed a high-fat diet are large when measured by the lung volume/body weight ratio (Table 75-1). They have cellular hyperplasia, indicated by elevations in lung deoxyribonucleic acid (DNA) content; enlarged alveoli, measured by alveolar size and alveolar volume; reduced alveolar surface area relative to alveolar volume; and increased content of lipids and surfactant proteins A (SP-A) and B (SP-B).[15-17] Lipid deposition also occurs in the diaphragm and intercostal muscles in obese individuals, and the fiber type in diaphragmatic muscle is altered, indicating the direct involvement of these muscles in obesity.[7,11,31]

Biochemical and structural changes in the lung, lipid deposits in respiratory muscles, and adipose tissue accumulation in the chest wall cause alterations in lung function and physiology. The most consistent and characteristic change in lung function is a diminution in the expiratory reserve volume (ERV) (Table 75-2).[18,19,32,33] Other lung volumes, maximal voluntary ventilation (MVV), compliance of the lung (C_L) and chest wall (C_{CW}), expiratory flow rates in small airways, and inspiratory flow rates are also reduced. The respiratory

Table 75-1
Anthropometric, Biochemical, and Structural Alterations in the Lung in Obesity and Malnutrition in the Rat

		Malnutrition		
Measurement	**Obesity**	**Antenatal**	**Birth to Weaning**	**Postweaning**
Body weight	↑	↓	↓	↓
Body length	↑	↓	NA	↓
Lung weight	↑	↓	↓	↓
Lung volume	↑	↓	↓	↓
Lung weight/body weight	↓	↓	Normal	Normal, ↑
Lung weight/body length	Normal	NA	NA	Normal
Lung volume/body weight	↑	↓	NA	↑
Lung DNA content	↑	↓	↓	Normal, ↓
Lung protein content	↑	↓	↓	↓
Lung protein/DNA	Normal	Normal	Normal	Normal, ↓
Alveolar number	Normal	↓	↓	Normal, ↓
Alveolar size	↑	NA	↑	↑
Alveolar volume	↑	NA	↑	↑
Alveolar surface area	↑	↓	↓	↓
Alveolar surface area/alveolar volume	↓	NA	↓	↓
Alveolar septa	Intact	Delayed alveolarization	Disruptions	Disruptions

↑, increased; ↓, decreased; NA, information not available.

Table 75-2
Pulmonary Function Alterations in Obesity and Malnutrition

Pulmonary Function	**Obesity**	**Malnutrition**
Vital capacity (VC)	Normal, ↑, ↓	↓
Functional residual capacity (FRC)	↓	↓
Expiratory reserve volume (ERV)	↓↓	↓
Residual volume (RV)	↑	↑
Total lung capacity (TLC)	Normal, ↑, ↓	Normal
Residual volume/total lung capacity (RV/TLC)	↑	↑
Diffusing capacity (D_{LCO})	Normal, ↑, ↓	Normal, ↓
Maximal voluntary ventilation (MVV)	↓	↓
Airflow rates	↓	Normal
Compliance, lung (C_L)	↓	↓
Compliance, chest wall (C_{CW})	↓	↓
Maximum inspiratory (P_{Imax}) and expiratory (P_{Emax}) pressures	Normal	↓
Minute ventilation ($\dot{V}_E$)	↑	↓
Work of breathing	↑	↑
Oxygen consumption ($\dot{V}O_2$)	↑	↓
Carbon dioxide production ($\dot{V}CO_2$)	↑	↓
Ventilation/perfusion ($\dot{V}/\dot{Q}$) imbalance	Present	Present

↑, increased; ↓, decreased.

rate (RR), minute ventilation ($\dot{V}_E$), work of breathing, O_2 consumption ($\dot{V}O_2$), CO_2 production ($\dot{V}CO_2$), and the residual volume (RV)/total lung capacity (TLC) ratio, which reflects the presence of air-trapping, are elevated, and diffusing capacity (D_{LCO}) measurements are variably altered.[17-28,32-35] Ventilation-perfusion ($\dot{V}/\dot{Q}$) imbalance and hypoxemia are also present.

Airway reactivity and severe cardiorespiratory deconditioning identified clinically and with pulmonary function testing correlate with the elevation in BMI.[26,29,30,36] Although the occurrence and severity of both obesity and asthma are affected by the environment, genetic loci for these disorders are present in similar regions on the same chromosomes and suggest that obesity and asthma may be genetically linked.[36]

CLINICAL FEATURES

Pneumonia and atelectasis occur with increased frequency with obesity and result from alterations in the chest wall, airways, and lung parenchyma. Reduction in thoracic and diaphragmatic motion secondary to adipose tissue in the chest and abdominal walls promotes basilar atelectasis, $\dot{V}/\dot{Q}$ imbalance, hypoventilation, and retention of airway secretions with a predilection for airway and parenchymal infection. Gastroesophageal reflux (GER) can result from gastric overdistention with large meals and relaxation of the gastroesophageal sphincter. Acute or chronic aspiration of gastric contents resulting from GER predisposes to pneumonia and atelectasis, particularly during sleep in the recumbent position.[33,37,38] Airway reactivity can occur with GER from aspiration of gastric contents and/or bronchoconstriction induced by chemical mediators released when acid is in the lower esophagus.[38] Recurrent airway and parenchymal infections also cause airway reactivity.[37,39] In addition, severe obesity, that is, with a BMI ≥ 40 kg/m^2, can be accompanied by pulmonary embolism, pulmonary arterial hypertension, pulmonary edema, acute respiratory distress syndrome (ARDS), respiratory failure, impaired cardiac function, and cor pulmonale.[18,33,40,41]

Obesity itself is associated with eucapnia or hypocapnia.[20] However, severe obesity attenuates the ventilatory response of the brain stem to CO_2 and can cause the obesity-hypoventilation syndrome, which is characterized by central sleep apnea, daytime somnolence, hypercapnia, hypoxemia, polycythemia, pulmonary hypertension, and cor pulmonale.[20,33] Obstructive sleep apnea can result from relaxation of upper airway muscles and infiltration of soft tissues by adipose tissue.[20,33,42,43]

TREATMENT

Therapy includes dietary, pharmacologic, surgical, and mechanical intervention. Weight loss improves pulmonary function with restoration of lung volumes toward normal, diminution of $\dot{V}/\dot{Q}$ imbalance, and reversal of hypercapnia, hypoxemia, and the obesity-hypoventilation syndrome.[20,23,28,43-46] However, the effect of weight loss on the biochemical and structural changes in the lung in obesity is unknown.

Respiratory stimulants, such as progesterone, theophylline, protriptyline, and buspirone, can enhance the central drive to breathe and normalize the arterial tension of CO_2 ($PaCO_2$) in the obesity-hypoventilation syndrome.[20,33,47-49] Theophylline can also increase diaphragmatic contractility and improve pulmonary mechanics and ventilation.[48] However, the side effects and limited efficacy of these medications in these settings curtail their use.[33,49,50]

If not improved with weight loss, upper airway obstruction causing obstructive sleep apnea may be relieved with surgery, such as a tracheostomy, uvulopalatopharyngoplasty, or dental orthoses.[33,49,51] Nocturnal distending airway pressure, including continuous positive airway pressure (CPAP) and bilevel positive airway pressure (BiPAP) ventilation, may also be used.[33,49,52] Gastric bypass, or bariatric, surgery can improve lung function and sleep apnea in selected individuals.[28,33,45,46]

Malnutrition

DEFINITION, RISK FACTORS

Malnutrition is characterized by a caloric intake that is inadequate to meet the metabolic requirements of the body.[53] Unlike starvation, which is acute, malnutrition is chronic and can cause either marasmus, which occurs from a deficiency of total calories (including protein), or kwashiorkor, in which the protein deficit is in excess of the caloric insufficiency.[53,54] An inadequate quantity of food and/or inability to absorb and digest food can cause malnutrition.[53]

PATHOGENESIS

As with obesity, malnutrition alters lung growth, physiology, structure, and function; the respiratory muscles; and control of breathing.[55-60] In addition, humoral and cellular defense mechanisms of the body and the lung itself and the lung's response to injury, barotrauma, and hyperoxia are altered.[54,59,61,62] Malnutrition contributes to the pathogenesis of bronchopulmonary dysplasia, cystic fibrosis, and chronic obstructive pulmonary disease and the respiratory manifestations of certain neuromuscular diseases, such as spinal muscular atrophy and Duchenne muscular dystrophy, chronic infections, malignancies, and eating disorders, including anorexia nervosa and obesity.[54,60,62-65]

Although the severity, timing, and duration of the malnutrition determine its effect on lung growth and structure,[55,56,66-76] some general principles may be applied. Whether antenatal, early postnatal (from birth to weaning), or late postnatal (after weaning), malnutrition in the animal model results in reductions in body weight, lung weight, and lung volume[55-57,66-71,74-76] (see Table 75-1). The lung weight/body weight ratio is diminished during the antenatal and early postnatal periods, indicating that reduced caloric intake during this time has a greater effect on the lung than on the body.[66,67,71,74,75] The lung volume/body weight ratio is increased with late postnatal malnutrition, reflecting alveolar enlargement and reduction in body weight present at this time.[69,70]

Normal tissue growth is initially characterized by cell proliferation without cell hypertrophy. This stage is followed by a slowing of cell division while protein accumulates, resulting in new cells that are larger than during the first stage. Finally, cell hypertrophy without cell hyperplasia occurs.[66,67,71] When compared with controls, animal lungs exposed to antenatal or early postnatal malnutrition have fewer cells as measured by lung DNA content but normal cell size as measured by the protein/DNA and ribonucleic acid (RNA)/DNA ratios and thus have interference only with cell division[55,67] (see Table 75-1). Lungs exposed to late postweaning malnutrition have normal numbers of cells that are small in size, which reflect alterations during the later stages of lung tissue growth.[67,70] As a result, the lungs in malnutrition are hypoplastic at all stages, whether defined by cell number or cell size.[66,67]

The newborn animal lung exposed to antenatal malnutrition has reduced contents of lecithin, phospholipid, disaturated phosphatidylcholine (DSPC), and SP-A mRNA; increased glycogen content; delayed cellular differentiation and alveolarization; and architectural immaturity.[55-57,59,71,74-76] Although alveolar number is reduced in early postnatal malnutrition[71,76] and may be decreased or normal in late postnatal malnutrition,[71,72] diminished alveolar surface area (both absolute and relative to alveolar volume), enlarged alveoli, disruptions in alveolar septa, loss of elastic recoil, and reduced C_L occur during both of these periods and reflect biochemical abnormalities in these lungs[59,68-74,76] (see Tables 75-1 and 75-2). Emphysematous changes identified by computed tomography (CT) scans of the lung in anorexia nervosa indicate alterations in pulmonary architecture later in life.[77]

During early and late postnatal malnutrition, pulmonary levels of collagen and elastin as measured by hydroxyproline and desmosine are diminished.[68,72,78] As a result, lung connective tissue content and structure, which provide the framework for alveolar development and stability, are altered.[72,78]

The respiratory muscles are also affected by malnutrition. Diaphragmatic muscle mass is diminished in malnourished individuals, and diaphragmatic weight, DNA, protein, thickness, mitochondrial activity, and contractile force are reduced in the animal model.[59,79-82] Respiratory muscles in malnourished patients have decreased strength and endurance proportional to the loss in body weight and result in part from atrophy of types I and II muscle fibers.[58,59,82-84] In contrast, acute caloric restriction has little effect on diaphragmatic function and morphology in animals.[84]

CLINICAL FEATURES

Alterations in pulmonary function result from the biochemical and structural changes in the lung and respiratory muscles. Reductions occur in vital capacity (VC), functional residual capacity (FRC), MVV, and forced expiratory volume in 1 second (FEV_1)[58,65,85] (see Tables 75-1 and 75-2).

RV and the RV/TLC ratio are elevated, indicating the presence of air-trapping and perhaps the alveolar enlargement

observed morphologically.[58,65,69,86] Maximal respiratory muscle strength measured by inspiratory (PImax) and expiratory (PEmax) pressures is also reduced.[58,59,85,86] In addition, diminutions in exercise endurance despite normal ventilatory and cardiac responses with exercise occur in individuals with anorexia nervosa and likely result from the reduced mass and contractile force of the skeletal and respiratory muscles.[65] The normal hypoxic and, to a lesser degree, hypercapnic ventilatory drives controlled by the central nervous system are attenuated with malnutrition and, as with respiratory muscle weakness, can cause alterations in ventilation and respiratory failure.[59,85,86]

Pulmonary defense mechanisms, such as the cough reflex, secretory immunoglobulin A (sIgA) levels, pulmonary alveolar macrophage (PAM) number and activity, T-cell–mediated immunity, alveolar fluid mobilization, and lung clearance of certain bacteria and viruses, are diminished with malnutrition.[54,59,61,62,85,87-89] Systemic deficiencies in cellular, humoral, neutrophil, complement, and opsonin activity also occur.[54,59,61,62,85,87,90] These changes predispose the lung to acute and chronic infections.

TREATMENT

Therapy includes caloric and protein supplementation, which may reverse some alterations. For example, decreases in lung weight and contents of DNA and protein normalize with refeeding after late postnatal malnutrition but persist with refeeding after early postnatal malnutrition, suggesting that the earlier in life the caloric restriction, the more severe and permanent are the alterations in the lung.[67] In addition, adult rats who are refed for 7 to 10 days after a period of caloric restriction have increases toward control values of body and lung weights; pulmonary contents of elastin, hydroxyproline, lecithin, DSPC, DNA, RNA, protein, and, in some studies, the protein/DNA and RNA/DNA ratios; alveolar surface area but not the alveolar surface area/alveolar volume ratio; and C_L.[67,78,91,92] Pulmonary elastic recoil pressure remains unchanged, and alveolar enlargement persists although less prominently.[78,91] Thus, some biochemical changes reverse, but the morphologic and functional alterations do not, at least in the refed malnourished adult rat.

In malnourished adults with chronic obstructive pulmonary disease, short-term (16 to 21 days) and longer-term (3 months) caloric supplementation increases $\dot{V}O_2$, $\dot{V}CO_2$, respiratory quotient (RQ), and $\dot{V}E$ and improves gas exchange.[59] Respiratory muscle strength, the hypercapnic ventilatory drive, the ability to wean from assisted ventilation, exercise tolerance, T-lymphocyte number, and delayed cutaneous hypersensitivity responses are augmented.[59,64,93,94] However, improvements do not occur in VC, TLC, FEV_1, MVV, arterial blood gas measurements, humoral immunity, and complement levels.[64,93,94] Similarly, malnourished children with cystic fibrosis have reduced numbers of pulmonary infections and increased MVV and respiratory muscle strength with either short-term (1 month) or longer-term (6 to 34 months) caloric supplementation.[60,63,95,96] Lung volumes and airflow rates either improve or decline less rapidly with up to 3 years of nutritional rehabilitation.[95,96]

These observations in both the animal model and the clinical setting are particularly important in intensive care areas, where nutritional needs may be delayed while more acute problems are addressed. Nutritional supplementation in poorly nourished patients can improve lung and respiratory muscle function, ventilation, and local and systemic immunity.

DISORDERS OF THE PANCREAS

Diabetes Mellitus

PATHOGENESIS

As a metabolic disorder resulting from dysfunction of the endocrine portion of the pancreas, diabetes mellitus affects many organs in the body with varying degrees of complexity.[97-99] Pulmonary involvement results from abnormalities in collagen, elastin, and the microvasculature in the lung and includes alterations in lung growth, structure, function, and physiology, which are manifested clinically in disease.

The immature diabetic animal has reduced body weight and length when compared with controls[100,101] (Table 75-3). The lungs are small in weight and volume but have a high lung weight/body weight ratio and lung volume/body weight ratio.[100] This reflects a greater effect of diabetes on the body than on the lung and is unrelated to the presence of undernutrition, which often accompanies diabetes in the animal model.[99,100] The lungs are polyalveolar; have an increased number of alveoli, which are small in size, volume, and total surface area; and intact alveolar septa.[100-102] However, the alveolar surface area/alveolar volume ratio is elevated and indicates enhanced alveolar complexity with an increased gas-exchange area, which results from the augmented number of alveoli.[100,102] Despite the increase in alveolar number, the lung content of DNA is reduced, indicating a reduction in cell replication.[100] Thus, the diabetic lung is hypoplastic in terms of lung weight, volume, and DNA content but is polyalveolar. These somewhat contradictory observations are explained by the occurrence of alveolar multiplication at the tips, or secondary crests, of newly formed alveoli where DNA and elastin synthesis is high.[100] Thus, despite a total decrease in cell multiplication, there appear to be selective areas, that is, alveolar crests, in the diabetic lung where cell hyperplasia is occurring, resulting in new alveoli.[100] Additional morpho-

Table 75-3
Alterations in the Lung in Diabetes Mellitus in the Immature Rat

Measurement	Alteration
Body weight	↓
Body length	↓
Lung weight	↓
Lung volume	↓
Lung weight/body weight	↑
Lung volume/body weight	↑
Lung DNA content	↓
Lung protein content	↓
Lung protein/DNA	Normal
Alveolar number	↑
Alveolar size	↓
Alveolar volume	↓
Alveolar surface area	↓
Alveolar surface area/alveolar volume	↑
Alveolar septa	Intact, thickened

↑, increased; ↓, decreased.

logic changes in the lung in both experimental and human diabetes mellitus include collagen and elastin deposits in airways, interstitium, and walls of large vessels; interstitial fibrotic nodules; thickening of the basal lamina of the alveolar epithelial and capillary basement membrane; dilation of the endoplasmic reticulum in alveolar epithelial type II cells; and alterations in secretory granules in Clara cells.[102-110]

Pulmonary levels of collagen and elastin are elevated in immature and adult diabetic rats, reflecting both increased synthesis and diminished degradation of these proteins.[99,100,111] The activity of lysyl oxidase, an enzyme associated with normal cross-linking of connective tissue proteins, is augmented in the lungs of diabetic rats and results in tighter cross-linking of collagen and elastin, rendering them resistant to digestion by proteolytic enzymes and increasing their levels in the lung.[99,102,103,111] In addition, hyperglycemia-induced nonenzymatic glycosylation of collagen and elastin causes structurally abnormal cross-linking of these proteins.[97,103,104,112] As a result of both the tighter and structurally abnormal cross-linking, alterations occur in the mechanical properties of the lung. Stiff lungs in the adult diabetic rat and a reduction in pulmonary elastic recoil in humans with diabetes reflect these biochemical and morphologic changes.[103,104,111]

Although lung growth is somewhat enhanced (at least after birth) in diabetes in terms of alveolar number and relative surface area, prenatal lung growth is delayed in the infant of the diabetic mother. The maternal hyperglycemia associated with diabetes crosses the placenta and stimulates the fetal pancreas to secrete insulin.[113] Pulmonary alterations result from the inhibitory effects of the sustained fetal hyperinsulinemia and are observed biochemically with reduced synthesis, availability, and utilization of surfactant precursors and SP-A and increased presence of epidermal growth factor (EGF); morphologically with a decreased number of alveolar epithelial type II cells, increased glycogen content in alveolar epithelial type II cells, and reduced air space relative to the quantity of tissue present; and functionally with diminished lung distensibility.[100,101,113] Immaturity of the lung in the infant predisposes to the development of neonatal respiratory distress syndrome (Box 75-1). Both insulin and insulin-like growth factor (IGF) receptors normally occur in the lung before and after birth, have elevated binding activity in the presence of hyperinsulinemia, and may play a role in the actions of insulin on the lung in the infant of the diabetic mother.[113-115]

Fetal insulin deficiency secondary to a reduced number of pancreatic islet cells occurs with maternal malnutrition and is accompanied by later development of diabetes mellitus and obstructive lung disease even if postnatal nutrition is adequate.[116,117] These observations indicate that maternal nutrition modifies pancreatic development prenatally and postnatally and throughout later life and that fetal alterations in glucose and insulin control have effects on the lung and body decades later.[116,117]

Box 75-1 Respiratory Disorders Associated with Diabetes Mellitus

Neonatal Disorder

Respiratory distress syndrome in infant of diabetic mother

Infectious Disorders

Bacteria: *Staphylococcus aureus, Streptococcus pneumoniae, Escherichia coli, Klebsiella pneumoniae*
Fungi: Zygomycetes (*Mucor, Rhizopus, Absidia* species), *Candida* species, *Aspergillus* species
Mycobacteria: *Mycobacterium tuberculosis*
Viruses

Parenchymal Disorders

ARDS
Pulmonary edema
Aspiration pneumonia
Pneumothorax, pneumomediastinum
Pleural effusion
Cor pulmonale

Airway Disorder

Autonomic neuropathy: reduced bronchial reactivity, mucous plugging

Chest Wall Disorder

Hypokalemic respiratory muscle paralysis

Disorders of Control of Breathing

Diminished responses to hypoxia and hypercapnia
Central hypoventilation
Central apnea
Sleep apnea

CLINICAL FEATURES

Disorders of the lung, chest wall, and control of breathing can complicate diabetes mellitus (see Box 75-1). Individuals with diabetes have an increased incidence of severe acute and chronic infections. Defective cell-mediated immunity, with quantitative and qualitative dysfunction of lymphocytes and monocytes and alterations in the activity of polymorphonuclear leukocytes (PMNs), PAMs, antioxidants, phagocytosis, and chemotaxis in diabetes contribute to the increased frequency and severity of infections.[98,118-120] Diseases caused by gram-positive bacteria (which grow well in a glucose environment), gram-negative rods, Zygomycetes, *Candida* species, influenza virus, and *Mycobacterium tuberculosis* have an increased morbidity and mortality in diabetes.[98,120,121]

Zygomycosis (mucormycosis) is an infection caused by the ubiquitous fungi, *Mucor*, *Rhizopus*, and *Absidia* species, and can result in acute and chronic pulmonary disease in diabetes[98,122] (see Box 75-1). Hyperglycemia and acidemia favor growth of these fungi by inhibiting the phagocytosis of PMNs and PAMs. Although rhinocerebral mucormycosis occurs more frequently in diabetes, pulmonary involvement has also been observed.[98,122,123] Inhalation of spores is the portal of entry to the lung. The fungi invade large airways and blood vessels and cause airway stenosis, thrombosis, ischemic necrosis, and infarction.[98,122] Pulmonary infection occurs as an acute pneumonia. Initially, fever, dyspnea, and cough, which may be dry- or wet-sounding, occur and are followed by pleuritic chest pain and hemoptysis, which can be life-

threatening.[122] Chest radiographs indicate a localized infiltrate or cavity, which then spreads to nearby areas.

The severity of tuberculosis parallels the severity of diabetes.[98] *M. tuberculosis* is more likely to cause cavitary disease, particularly in the lower lobes, in individuals with diabetes than in nondiabetic patients.[98,121]

The direct effect of acidosis in diabetic ketoacidosis can cause increased pulmonary vascular permeability, pulmonary edema, and ARDS[98,124] (see Box 75-1). In addition, crystalloids and fluids used in the therapy of ketoacidosis can contribute to the development of pulmonary edema and ARDS.[98,125] The gastric stasis and impaired gastric emptying occurring with ketoacidosis can cause gastroparesis, emesis, and aspiration pneumonia.[98] Severe vomiting and deep breathing secondary to acidosis can result in a pneumothorax and/or pneumomediastinum.[98] Diabetic autonomic neuropathy resulting in diminished vagal nerve activity can cause sleep-disordered breathing with diminutions in heart rate and ventilatory responses to hypoxia and possibly hypercapnia and may explain the increased incidence of central hypoventilation and apnea in diabetes.[107,126,127] Autonomic neuropathy also causes airway abnormalities, including airway hyporeactivity to inhaled bronchodilators and carbachol and cold air challenge testing.[98,128] Electrolyte imbalance can result in respiratory muscle weakness.[98,107] The lungs can also be affected in diabetic-related diseases of other organs, including heart failure, pulmonary edema, and a transudative pleural effusion with cardiac or renal involvement.[98]

Pulmonary function studies in individuals with diabetes have been performed primarily in adults with type 1 (insulin deficiency, insulin dependency) or type 2 (end-organ insulin resistance, non–insulin dependency) diabetes mellitus and have produced conflicting results. Investigations have included individuals with a history of cigarette smoking, reactive airway disease, and/or obesity and varying degrees of control, duration, and severity of diabetes. Although reductions in VC, forced vital capacity (FVC), TLC, FRC, RV, FEV_1, forced expiratory flow along 25% to 75% of the VC ($FEF_{25-75\%}$), mean maximum expiratory flow rate (MMEF), and MVV are inconsistently observed, diminutions in DLCO corrected for alveolar volume (DLCO/VA), alveolar capillary blood volume, and pulmonary elastic recoil pressure have been frequently noted.[102-104,107,112,127,129-135] Recent studies in children with an early onset of diabetes reveal reductions in FVC, FEV_1, DLCO, and the DLCO/VA ratio; elevations in RV and the RV/TLC ratio; increased airway resistance (Raw); and normal values for ERV, TLC, and the FEV_1/FVC ratio.[108,136] This indicates the presence of narrowed airways, air-trapping, and impaired diffusion of O_2 and CO_2 in the lung.

Reduced pulmonary capillary blood volume, most likely resulting from microangiopathy with thickening of the alveolar epithelial and capillary basal lamina, accounts for the diminished DLCO because the membrane component of DLCO is normal.[103,104,133] Platelet hyperaggregation, which results from reduced synthesis of prostacyclin (an inhibitor of platelet adhesion) and increased synthesis of thromboxane (a stimulant of platelet adhesion), occurs in diabetes and may also contribute to the microangiopathy.[137]

Diminished lung elastic recoil reflects alterations in pulmonary connective tissue.[103,104,107,111] Because immobile joints can result from abnormal connective tissue and are associated with the early development of microangiopathy in diabetes, limited joint mobility may be a clinical marker for abnormal lung connective tissue and altered pulmonary function.[98,128,138] Costosternal and costovertebral joint immobility resulting from connective tissue changes may contribute to the reduced lung volumes.[129] In addition, diaphragmatic and inspiratory muscle strength and respiratory muscle endurance are decreased.[130,131]

Pulmonary function changes correlate directly with the duration of diabetes mellitus in some studies.[103,130,134] Diabetes at its onset may be associated with a faster rate of reduction in lung volumes compared with diabetes of lung duration, that is, the rate of change in lung volumes appears greatest early.[112,135] Investigations of control of hyperglycemia in types 1 and 2 diabetes mellitus suggest the presence of normal pulmonary function, including DLCO/VA measurements, with long-standing near-normal serum glucose levels.[97] However, this may be related to the effects of insulin on the DLCO and not necessarily to normoglycemia.[139] The FVC and FEV_1 are diminished to a lesser extent in type 2 than in type 1 diabetes mellitus, suggesting that the milder the disease, the less severe the reductions in lung volumes and that after good biochemical control of diabetes, the rate of decline in lung volumes may decrease.[112,134,135]

In children who have well-controlled insulin-dependent diabetes and normal lung volumes and airflow rates at rest, exercise testing reveals normal measurements of ventilatory response, anerobic threshold, and maximal heart rate but reduced work capacity, $\dot{V}O_2$, and O_2 pulse measurements.[140] This suggests the presence of inadequate peripheral O_2 use and subclinical microvascular abnormalities with thickening of the capillary basement membrane in skeletal muscles.[140]

DIAGNOSIS

Pulmonary complications of diabetes mellitus are diagnosed by the history, physical examination, radiography, and laboratory studies. The presence of ketoacidosis and/or uncontrolled hyperglycemia in an individual with diabetes and pneumonia should suggest the possibility of a fungal or mycobacterial infection. Pulmonary mucormycosis should be considered in the presence of rhinocerebral disease with a characteristic black eschar.[122] ARDS can develop rapidly in diabetics in the presence of only mild hypoxemia without crackles or radiographic changes initially.[141] Stains and cultures of respiratory secretions and blood for bacteria, fungi, mycobacteria, and viruses; immunologic studies for specific viral antigens and antibodies; anteroposterior and lateral chest radiographs; and when indicated, CT scans are important in the diagnosis of these disorders.

TREATMENT

Therapy includes appropriate antibiotics and antiviral, antifungal, and antimycobacterial agents for the specific etiologic microorganism; thoracentesis for a pleural effusion associated with respiratory distress; supplemental O_2, assisted ventilation, and vasopressors for ARDS; cardiotonic drugs and diuretics for heart failure and pulmonary edema; correction of electrolyte imbalance; and improved serum glucose control. Immunizations with the pneumococcal and influenza vaccines are important in preventing these infections.[98] Studies of the efficacy and safety of inhaled insulin preparations for treat-

ment of diabetes mellitus in children are in progress.[107,136,142,143] However, adequate deposition of the aerosol will be hindered if significant alterations in lung function are already present.[107,136,142,143]

Pancreatitis

RISK FACTORS

The etiologies of pancreatitis in children are listed in Box 75-2, and pulmonary disorders associated with acute and chronic pancreatitis are listed in Box 75-3. Although pleural effusions are recognized in children with pancreatitis, most pleuropulmonary complications of pancreatitis are described in adults, in whom the majority of cases results from alcoholism, trauma, and cholelithiasis.[144-149] Alterations in gene structure and function likely play a role in the development of acute and chronic pancreatitis.[150,151]

PATHOGENESIS, CLINICAL FEATURES

Pleural effusions are usually left-sided but may be right-sided or bilateral.[152-157] They occur shortly after the onset of acute pancreatitis and are characterized by a serous, serosanguinous, or hemorrhagic exudate with a pH of 7.30 to 7.35, a glucose content similar to the level in blood, a predominance of PMNs, and elevations in the pleural/serum ratios of amylase, protein, and lactate dehydrogenase (LDH).[153-155,157-159] Fluid resorption correlates with resolution of acute pancreatitis. However, an effusion persisting greater than 14 days usually indicates chronic pancreatic disease, such as a pseudocyst, abscess, or pancreaticopleural fistula, and represents a chronic effusion.[153] When a pancreaticopleural fistula occurs, a sinus tract develops from the apical aspect of the pseudocyst through the diaphragm to the pleural space.[154-156,159] The resultant pleural effusion may occur after the acute pancreatic symptoms have subsided and characteristically persists despite serial thoracenteses.[154,155,160] A thickened pleura can develop and encase a chronic effusion but usually resolves within 6 months after the onset of disease.[153]

The etiology and pathogenesis of the fluid have not been defined (Box 75-4). Although transdiaphragmatic channels can exist between the pleural cavity and acutely inflamed pancreas, whose tail normally lies just below the diaphragm, they are only infrequently recognized.[152,153,155,158] However, the normally occurring diaphragmatic hiatal openings for the esophagus, aorta, and inferior vena cava can allow passage of pancreatic fluid into the mediastinum and pleural space and cause a right-sided pleural effusion.[154-156,159] Lymph flow across transdiaphragmatic lymphatic vessels between the pancreas and pleural space may also help spread the pancreatic inflammatory exudate.[155,156,158,159] In addition, lymphatic drainage from the pleural space through collecting lymphatics

Box 75-2 Etiology of Pancreatitis in Children

- Cholelithiasis
- Congenital anomalies: pancreatic duct, biliary tract
- Cystic fibrosis
- Diabetes mellitus
- Medications: tetracycline, sulfonamides, chlorothiazide, furosemide, corticosteroids, acetaminophen, oral contraceptive agents, immunosuppressive agents
- Familial pancreatitis
- Hyperparathyroidism
- Hypertriglyceridemia
- Infections
  - Bacteria: *Mycoplasma pneumoniae*
  - Viruses: mumps virus, measles virus, rubella virus, coxsackievirus B, influenza virus type A, hepatitis B virus, Epstein-Barr virus, herpes zoster virus, cytomegalovirus
  - Parasites: *Ascaris lumbricoides*
  - Fungi: *Aspergillus* species
- Malnutrition
- Organic acidemias
- Polyarteritis nodosa
- Porphyria (acute)
- Relapsing pancreatitis (acute, chronic)
- Toxins: alcohol
- Trauma

Box 75-3 Pulmonary Disorders Associated with Pancreatitis

Acute Pancreatitis	Chronic Pancreatitis
Pleural effusion	Pancreaticopleural fistula
Empyema	Pancreaticobronchial fistula
Hemidiaphragm elevation	Pancreaticobronchopleural fistula
Atelectasis: left lower lobe	Recurrent pleural effusion
Pneumonia: left lower lobe	Recurrent lobar pneumonia
Pulmonary embolism (blood, fat)	Secondary α_1-antitrypsin-deficient emphysema
Pulmonary infarction	
ARDS	
Pulmonary edema	

Box 75-4 Possible Etiologies of Pleural Effusions Associated with Pancreatitis

- Passage of inflammatory exudate through the transdiaphragmatic channels between the pancreas and the pleural space
- Passage of inflammatory exudate through the esophageal, aortic, and inferior vena caval openings in the diaphragm
- Passage of inflammatory exudate in lymph flow through the transdiaphragmatic lymphatic vessels, particularly with impaired diaphragmatic mobility
- Passage of inflammatory exudate via retrograde lymph flow into the pleural space, which results from incompetent valves in the lymphatic vessels
- Increased pleural vascular permeability resulting from the release of pancreatic chemical mediators

to hilar lymph nodes is normally aided by diaphragmatic movement.[152,153] Pain and inflammation occurring with pancreatitis can impair diaphragmatic mobility, hinder normal lymph flow, and cause pleural fluid to accumulate.[152,157] Lymphatic valves help promote lymph flow in the collecting lymphatic vessels from both pleural and peritoneal spaces and can become incompetent with inflammatory pancreatic disease.[152] Lymph flow is bidirectional in these vessels, and lymph can then flow back into the pleural space from the peritoneal area.[152,159] Finally, the pancreatic inflammation itself and chemical mediators, such as proteolytic enzymes, prostaglandins, phospholipase A_2, kinins, histamine, and activated complement, released by the inflammatory process can increase permeability of pleural capillaries, disrupt lymphatic vessels, and promote formation of pleural fluid.[152,153,158,161-163]

Empyema occurs if a bacterial infection results in a pleural effusion (see Box 75-3). *Escherichia coli* and *Staphylococcus aureus* have been isolated in this setting.[155,164] The subdiaphragmatic inflammatory process in the pancreas with its associated pain and limited diaphragmatic mobility can cause elevation of the left hemidiaphragm, lower lobe atelectasis, and pneumonia[153,155,164] (Fig. 75-1). If it is severe, $\dot{V}/\dot{Q}$ imbalance, intrapulmonary shunting of blood, and hypoxemia can result. Recurrent pneumonia of the left lower lobe suggests the presence of a pancreaticobronchial fistula, and sputum containing amylase associated with an amylase-rich pleural effusion indicates a pancreaticobronchopleural fistula, both of which occur with chronic pancreatitis.[160,165]

Atelectasis occurs as the inflamed pancreas releases phospholipase A_2 (lecithinase), an enzyme that hydrolyzes dipalmitoyl phosphatidylcholine (DPPC, lecithin), the main component of the phospholipids in surfactant.[166-168] Pulmonary phospholipid synthesis is also reduced.[167] The resultant diminution in surfactant activity increases alveolar surface tension and promotes lung collapse.[166-168]

Pulmonary embolism and infarction result from release of clotting factors, kinin, and activated complement from the inflamed pancreas.[153,164] Fat emboli emanating from bone marrow, increased serum levels of triglycerides secondary to hypertriglyceridemia, and elevated serum levels of free fatty acids resulting from hydrolysis of triglycerides by lung lipoprotein lipase and cleavage of phospholipid by phospholipase A_2 also predispose to pulmonary embolism.[161,169,170]

If the pancreatic inflammatory process is severe, ARDS can occur (see Box 75-3 and Fig. 75-1). The release of multiple chemical mediators, including (in addition to those already mentioned) leukotrienes, pancreatic proteases (trypsin, chymotrypsin, elastase), substance P, chemokines, and cytokines (platelet activating factor, tumor necrosis factor α [TNF-α], interleukins, macrophage migration inhibitory factor [MIF], intercellular adhesion molecule-1 [ICAM-1]), increases vascular permeability and promotes the development of ARDS.[153,157,171-177] The elevated levels of tri-

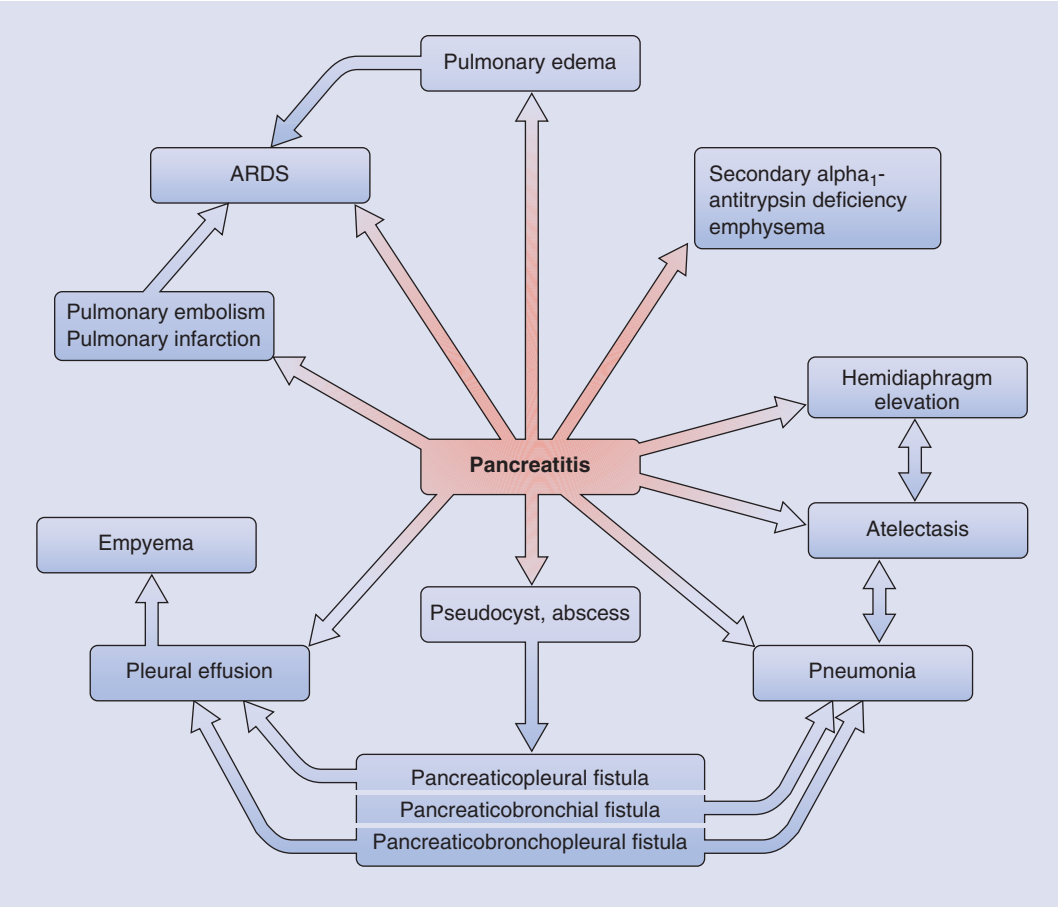

Figure 75-1 Pancreaticopulmonary disorders.

glycerides and free fatty acids also contribute to lung injury by damaging capillary endothelial cell membranes and thereby increasing vascular permeability.[167,170] O_2-free radicals released from activated PMNs and the liver's ability to synthesize, release, and metabolize chemical mediators also aid the inflammatory process in the lung.[163,178,179]

ARDS secondary to acute pancreatitis is accompanied by injury to alveolar epithelial type II cells with destruction of surfactant-containing lamellar bodies, capillary endothelial cell damage, interstitial and alveolar edema, intravascular and interstitial aggregates of PMNs and platelets, intra-alveolar hemorrhage, fibrin deposits, thickening of the alveolar epithelial cell membrane, and distortion of alveolar architecture.[161,163,171-173,180-182] Bronchoalveolar lavage (BAL) fluid contains increased levels of protein and PMNs, and these lungs weigh more and are stiffer than lungs without ARDS.[161,180]

The inflamed pancreas releases trypsin, and as a result, α_1-antitrypsin levels may be decreased and cause an emphysema-like picture in chronic pancreatitis[183] (see Box 75-3 and Fig. 75-1). Elastase released from the pancreas also contributes to the development of emphysema.[183]

Hypoxemia without clinical or radiographic manifestations of lung disease can occur during the early stages of acute pancreatitis and may result from intrapulmonary right-to-left shunting of blood.[146,153,156,157,183-185] Lung function testing reveals reductions in VC, FEV_1, and TLC in acute pancreatitis, but these measurements are normal in chronic disease.[157,183,184] However, the DLCO, both absolute and corrected for lung volume (DLCO/VA), is diminished in acute and chronic pancreatitis.[157,165,183,184] This may reflect a diminution in the effective gas-exchanging surface, thickening of the alveolar epithelial cell membrane, and reduction in capillary blood volume occurring in the lung even without ARDS as a result of the pancreatitis.[183]

DIAGNOSIS

The diagnosis of these pancreaticopulmonary disorders is aided by the history, physical examination, and radiographic and laboratory studies. Pancreatitis is associated with sharp, localized midepigastric abdominal pain that is more severe with eating, vomiting, fever, anorexia, abdominal distention and tenderness, lethargy, and malaise.[144,145,148,149] The signs and symptoms of pleural effusion, atelectasis, and pneumonia are similar with and without pancreatitis.

Pleural effusions are characterized by localized limited chest wall expansion, dullness to percussion, diminished breath sounds, a friction rub, pleuritic pain with splinting, dyspnea, tachypnea, and shallow breathing. Atelectasis is associated with dullness to percussion, localized diminished breath sounds, pectoriloquy, and if large, unilateral tracheal deviation and mediastinal shift. Fever, a wet-sounding cough, crackles, pectoriloquy, and bronchophony indicate pneumonia.

Anteroposterior and lateral chest radiographs reveal the pleural effusion, which if large, may result in contralateral mediastinal shift. Lateral decubitus films are helpful in evaluating the presence of free-moving pleural fluid. Atelectasis on the chest radiograph may be accompanied by unilateral mediastinal shift. Ultrasonography, CT scans, and endoscopic retrograde cholangiopancreatographic (ERCP) studies of the pancreas can help in the diagnosis of an abscess, pseudocyst, or fistula.[148,153,160,165]

Measurements of serum phospholipase A_2 concentrations parallel the severity and course of pancreatitis and atelectasis.[168] Pleural fluid amylase levels are elevated in pancreatitis and remain increased after hyperamylasemia has resolved.[153,157,159] However, unlike chronic pancreatitis, in which pleural fluid amylase levels are characteristically increased, acute pancreatitis may be associated with initially normal levels of pleural fluid amylase that rise later as the disease progresses.[146,154,159] Pleural fluid amylase levels may also be increased in other disorders, including esophageal rupture, pneumonia, pleural fluid metastases, and tuberculosis.[154,159,186] However, in contrast to the pancreatic origin of the amylase in the pleural fluid associated with pancreatitis, the pleural fluid amylase is of salivary origin in these other disorders.[159,186]

TREATMENT

Therapy is directed at the specific pulmonary disorder—antibiotics for pneumonia; thoracentesis for an effusion that causes respiratory distress; chest tube drainage, fibrinolytic agents, and video-assisted thoracoscopic surgery (VATS) for empyema; chest physical therapy for atelectasis; anticoagulants for pulmonary emboli; and assisted ventilation, supplemental O_2, diuretics, vasopressor agents, and extracorporeal membrane oxygenation (ECMO) for ARDS.[187] Nitric oxide (NO) therapy may decrease or even prevent lung damage by prohibiting adherence of PMNs to vascular endothelium and synthesis of O_2-free radicals.[188]

The pleural effusion usually resorbs as the acute pancreatic inflammation resolves.[154] Repeated therapeutic thoracenteses for a pleural effusion may not be helpful if a fistula is present and allows the effusion to recur. Surgery to close the fistulous tract is necessary if the effusion does not resolve with 2 weeks of medical therapy, including parenteral nutrition; therapeutic pharmacologic suppression of pancreatic secretions using somostatin, atropine, acetazolamide, and/or cimetidine; and serial thoracenteses or chest tube drainage.[146,154,159,160] Pseudocysts can be drained percutaneously but are usually removed surgically.[146,148,153,159,160]

DISORDERS OF THE LIVER

Risk Factors, Pathogenesis

Pulmonary disorders can occur with hepatic disease (Table 75-4). Acute hepatic disease associated with lung complications results from infections, medications, and toxins (Box 75-5).[189,190] For example, a pleural effusion can occur with an intrahepatic abscess caused by *Entamoeba histolytica* or a hydatid cyst caused by *Echinococcus granulosus*.[154,159] The pleural effusion associated with *E. histolytica* is composed of blood and liver tissue, has the consistency of chocolate sauce or anchovy paste, and results from direct diaphragmatic irritation by the hepatic lesion causing increased permeability of diaphragmatic pleural capillaries and transudation of fluid into the pleural space.[154] If the hepatic lesion ruptures through the diaphragm, empyema forms, and the communication may remain patent as a hepatopleural fistula.[154,159] Rupture of the lesion into airways can result in hepatobron-

Table 75-4
Pulmonary Disorders Associated with Hepatic Disease

Hepatic Disease	Pulmonary Disorder(s)
Infections	Hilar adenopathy, tracheobronchitis, pneumonia, atelectasis, reactive airway disease, interstitial pneumonitis, interstitial fibrosis, nodules, cysts, pleural effusion, fistulas (hepatopleural, hepatobronchial, biliobronchial)
Primary sclerosing cholangitis	Bronchitis, bronchiectasis
Malignancy	Hilar adenopathy, pneumonitis, nodules, pleural effusion, thromboemboli, lymphangitic carcinomatosis, osteolytic lesions in vertebrae and ribs
α_1-Antitrypsin deficiency	Tracheobronchitis, pneumonia, reactive airway disease, panacinar emphysema, bronchiectasis, bullae, pulmonary angiodysplasia
Chronic granulomatous disease of childhood	Hilar adenopathy, pneumonia, atelectasis, pleural effusion, abscess, honeycomb lung, pulmonary hypertension
Cystic fibrosis	Tracheobronchitis, pneumonia, atelectasis, bronchiectasis, reactive airway disease, cysts, bullae, pneumothorax, pulmonary hemorrhage, pulmonary hypertension
Hereditary hemorrhagic telangiectasia (Osler-Weber-Rendu disease)	Pulmonary angiodysplasia
Langerhans cell histiocytosis	Hilar adenopathy, pneumonitis (lobar, reticulonodular, interstitial), bronchiolitis, noncaseating granulomata, interstitial fibrosis, pleural effusion, pneumothorax, nodules, cysts, bullae, cavitary lesions, honeycomb lung, pulmonary hypertension
Sarcoidosis	Hilar and mediastinal adenopathy, reticulonodular infiltrates, atelectasis, reactive airway disease, bronchial stenosis, noncaseating granulomata, interstitial pneumonitis, interstitial fibrosis, pleural effusion, pneumothorax, nodules, cysts, bullae, honeycomb lung, pulmonary hemorrhage, pulmonary hypertension
Chronic active hepatitis	Pneumonia, atelectasis, interstitial pneumonitis, interstitial fibrosis, fibrosing alveolitis, pleural effusion, pulmonary hypertension, pulmonary hemorrhage, pulmonary angiodysplasia
Cirrhosis (alcoholic, postnecrotic, cryptogenic)	Pneumonia, pleural effusion, pulmonary hypertension, pulmonary angiodysplasia
Primary biliary cirrhosis	Reactive airway disease, interstitial pneumonitis (lymphocytic, usual), interstitial fibrosis, fibrosing alveolitis, noncaseating granulomata, nodules, pleural effusion, bronchiolitis obliterans organizing pneumonia (BOOP), pulmonary hemorrhage, pulmonary hypertension, pulmonary angiodysplasia, rib and vertebral fractures.

chial and biliobronchial fistulae, with sputum that is dark in color with *E. histolytica* or has cystlike structures with *E. granulosus*.[154,159] Viral hepatitis causes an exudative pleural effusion with a predominance of monocytes and without parenchymal disease and may transiently result in the hepatopulmonary syndrome (see later).[154,191] If hepatitis B virus is the etiology, the fluid may have the hepatitis B surface and *e* antigens.[154,159] Hepatitis C virus is associated with lymphocytic alveolitis, interstitial fibrosis, decline in lung function if asthma or chronic obstructive pulmonary disease is present, the hepatopulmonary syndrome, and portopulmonary hypertension.[192-194]

A hepatic hydrothorax forms when ascitic fluid secondary to liver disease passes through normal diaphragmatic openings and/or lymphatics into the pleural space.[154,159,189,195-197] The fluid is usually right-sided but may be bilateral, a transudate with normal protein and glucose levels, and serous or, if a coagulopathy is present, hemorrhagic.[154,159,197] Acute liver failure can cause pulmonary edema, ARDS, and acute respiratory failure.[189,197]

Chronic hepatic disease also causes pulmonary disease (see Table 75-4). Primary sclerosing cholangitis results from cholestasis of intrahepatic and extrahepatic bile ducts, causes cirrhosis and liver failure, frequently accompanies inflammatory bowel disease, and is associated with chronic pulmonary infection.[189,195] Hepatic malignancies metastasize to the diaphragm and lung either directly or hematogenously from the hepatic vein into the inferior vena cava, right heart, and pulmonary artery and cause parenchymal, pleural, vascular, and lymphatic lesions of the lung and bone lesions in the chest wall.[189] Systemic disorders, such as α_1-antitrypsin deficiency, chronic granulomatous disease of childhood, cystic fibrosis, hereditary hemorrhagic telangiectasia, Langerhans cell histiocytosis, and sarcoidosis, can also result in hepatopulmonary disease. For detailed descriptions of these disorders, the reader is referred to other chapters in this book and literature elsewhere.[189,195,198-202]

Clinical Features

The hepatopulmonary syndrome consists of chronic liver disease, pulmonary angiodysplasia with increased pulmonary blood flow, and hypoxemia defined by a partial pressure of arterial oxygen (PaO_2) < 70 mm Hg while breathing room air.[189,194,197,203-212] Portal hypertension may also occur.[205,207,213] Etiologies include chronic active hepatitis, acute viral hepatitis, alcoholic or postnecrotic cirrhosis, primary biliary cirrhosis, congenital liver disease (hepatic fibrosis, biliary atresia, Abernethy malformation), and the Budd-Chiari syndrome (see Table 75-4).[194,205-207,210,213-219] Vasodilating substances that are normally metabolized or detoxified by the liver may bypass the malfunctioning liver, alter the pulmonary vascular endothelium, and cause abnormal vascular dilatations.[189,205,206,220] Possible etiologic agents include NO, glucagon, substance P, vasoactive intestinal peptide, prostacyclin, interleukin (IL)-1, and IL-6, which may have enhanced synthesis in the lung and/or reduced hepatic degradation.[205-207,212,217,221] In addition, levels of endothelin-1, a vasoconstrictor that mediates pulmonary NO activity, may be abnormally reduced.[205,206] Thus, either an excess of vasodilators or deficiency of vasoconstrictors may contribute to the angiodysplasia.[206,212,219]

Pulmonary angiodysplasia results from dilatation of intrapulmonary precapillary and capillary vessels supplying alveoli and anatomic pulmonary arteriovenous communications[189,190,203,206,211,212,220] (Fig. 75-2). An increase in the

Box 75-5 Infections Associated with Hepatopulmonary Disease

Bacteria

Actinomyces israelii
Brucella species
Chlamydia psittacei
Coxiella burnetii
Francisella tularensis
Legionella pneumophila
Leptospira interrogans
Listeria monocytogenes
Mycobacterium tuberculosis, Mycobacterium bovis
Mycoplasma pneumoniae
Rickettsia prowazekii, Rickettsia rickettsii
Treponema pallidum

Viruses

Adenoviruses
Coxsackievirus B
Cytomegalovirus
Hepatitis A, B, and C viruses
Human immunodeficiency virus
Varicella-zoster virus

Fungi

Aspergillus species
Blastomyces dermatitidis
Histoplasma capsulatum
Paracoccidioides brasiliensis

Parasites

Ascaris lumbricoides
Cryptosporidium species
Echinococcus granulosus
Entamoeba histolytica
Leishmania donovani
Plasmodium species
Schistosoma mansoni
Toxocara canis, Toxocara cati
Toxoplasma gondii

Box 75-6 Cardiorespiratory Manifestations of Hepatopulmonary Disorders

Pulmonary Manifestations

Adventitious breath sounds
Clubbing
Cough
Cyanosis
Diaphragmatic impairment
Dyspnea
Exercise intolerance
Hemoptysis
Hyperventilation
Hypoxemia
Orthodeoxia
Orthopnea
Paroxysmal nocturnal dyspnea
Platypnea
Precordial chest pain
Respiratory alkalosis
Tachypnea

Cardiac Manifestations

Accentuation of pulmonic second sound
Systolic ejection murmur in second or third left intercostal space or over left sternal border
Pulmonary bruit increased by inspiration and Müller's maneuver and decreased by Valsalva maneuver

Electrocardiographic Manifestations

Right ventricular hypertrophy
Right axis deviation
Right bundle branch block

Radiographic Manifestations

Prominence of main pulmonary arteries
Paucity of peripheral pulmonary vessels
Cardiomegaly

number of arterioles supplying an alveolus also occurs.[222] The arteriovenous communications, or spiders, occur not only in the lung parenchyma but also in the pleura, are similar to the cutaneous spiders present in liver disease, and contribute to hypoxemia.[189,190,195,203,220,222] In addition, the precapillary vessels, which are normally 8 to 15 μm in diameter, may dilate to 500 μm and diminish the pulmonary vascular resistance and pulmonary artery pressure and cause pulmonary hypotension.[189,197,212] An elevated cardiac output and rapid transit time for blood flow, which results from diminished systemic vascular resistance and increased peripheral blood flow, do not allow adequate oxygenation of venous blood passing through these dilated vessels, and arterial hypoxemia ensues[189,195-197,206] (see Fig. 75-2). As much as 70% of the cardiac output passes through these vessels.[189,195,197,223]

A "diffusion/perfusion" imbalance is present, with inability of O_2 to adequately reach red blood cells (RBCs) because of marked vascular dilatation.[206,212,216,224] This improves following inhalation of 100% O_2 and is in contrast to shunting through arteriovenous communications in which hypoxemia does not significantly diminish after inhalation of 100% O_2.[206,220] With severe liver dysfunction, hypoxemia may not elicit the normal hypoxic pulmonary vasoconstrictive response, which then augments pulmonary hypotension and hypoxemia.[189,195,206,220,225,226]

The dilated vessels and arteriovenous anastomoses are more numerous at the lung bases than at the apices.[189,195,197,206,220,227] As a result of the effect of gravity on augmenting blood flow through these vessels in the upright position, hypoxemia becomes more pronounced after a change from the supine to standing position.[189,191,195,206,210,212,227] Orthodeoxia, defined by a decrease in the Pa_{O_2} by more than 3 mm Hg between these two positions, is characteristic and often associated with an increase in dyspnea, or platypnea[189,191,195,206,217,227] (Box 75-6).

Paradoxically, pulmonary arterial hypertension can result from portopulmonary venous anastomoses, which develop in

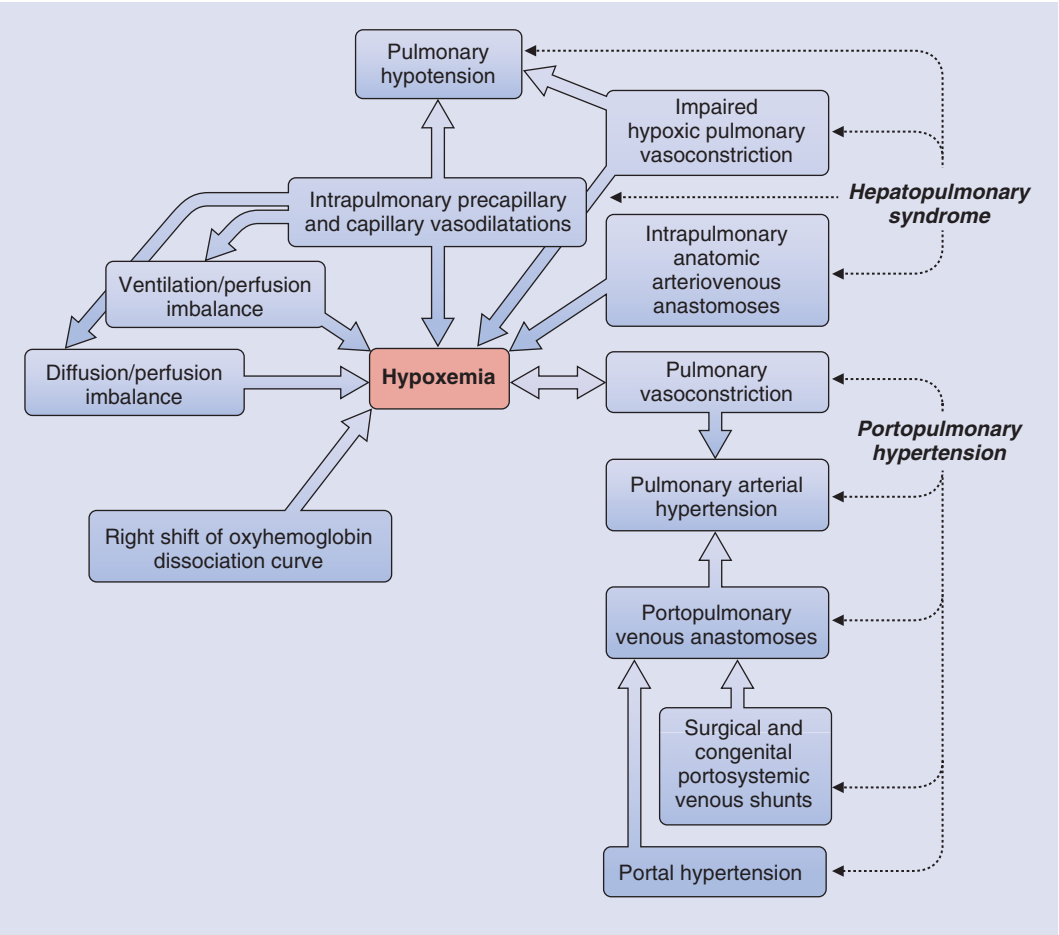

Figure 75-2 Etiology of hypoxemia in hepatopulmonary disorders.

the presence of portal hypertension and surgical or congenital portosystemic venous shunts[207,211,212,220,228-231] (see Fig. 75-2). Portopulmonary hypertension occurs with increases in pulmonary arterial pressure and pulmonary vascular resistance and a normal pulmonary capillary wedge pressure.[194,206,212,230,231] Instead of blood flowing along its normal pathway from the portal vein to the portal triad, where it combines with oxygenated blood from the hepatic artery, and then flowing through the venous system into the inferior vena cava, it is redirected from the portal vein through the periesophageal, mediastinal, and azygous veins, some of which communicate directly with large extrapulmonary and bronchial veins.[195] The contribution of these communications to hypoxemia is negligible because of a relatively high oxyhemoglobin saturation of 70% in portal venous blood and only a small amount of blood flow through these anastomoses.[189,195,196,222] Pulmonary hypertension usually develops after portal hypertension is present but has been identified without it.[189,205,217,220,229,230]

Pulmonary arterial hypertension results from hypoxemia in the presence of moderately severe liver dysfunction; is associated with intravascular platelet aggregation causing endothelial cell injury and vasoconstriction; and has characteristic plexiform lesions of nonfunctional, thin-walled, nonmuscular, saclike dilations of muscular arteries filled with blood, cells, collagen, and elastin.[206,212,217,220,228-231] It may be caused by enhanced activity of a vasoconstrictor, such as hepatocyte growth factor, vascular endothelial growth factor, endothelin-1, and serotonin, or a non-metabolized agent with effects on the pulmonary circulation.[206,212,217,228-230] Right heart failure eventually results from the severe pulmonary vasoconstriction and hypertension.[197,208]

Thus, pulmonary hypotension, which is caused by precapillary and capillary vasodilation and impaired hypoxic pulmonary vasoconstriction in the hepatopulmonary syndrome, and pulmonary hypertension, which is associated with hypoxemia and portal hypertension in portopulmonary hypertension, can occur and may be present simultaneously[206-208,211,212,228,232] (see Fig. 75-2). Although the oxyhemoglobin dissociation curve is shifted to the right with liver disease because of increased RBC 2,3-diphosphoglycerate (2,3-DPG) levels, this does not appear to be an important factor in the development of hypoxemia in hepatopulmonary disorders.[195,216,225,226]

Diagnosis

The history, physical examination, and laboratory and radiographic studies aid in the diagnosis of these disorders. A family history of early onset lung disease may be present with cystic fibrosis and α_1-antitrypsin deficiency. The presence of the signs and symptoms listed in Box 75-6 should signal a possible hepatopulmonary disorder. The occurrence of orthodeoxia and platypnea should alert the examiner to the pres-

ence of pulmonary angiodysplasia and the hepatopulmonary syndrome.[227]

The underlying hepatic disease is diagnosed with appropriate serologic tests for viral hepatitis, serum liver enzyme levels, and stains, cultures, and histologic studies of liver biopsy tissue. Abdominal ultrasonography and CT scans for liver abscesses or cysts; tests for serum α_1-antitrypsin levels and phenotype studies for α_1-antitrypsin deficiency; and cultures of respiratory secretions, a sweat test, and genotype studies for cystic fibrosis are important. Stains and cultures of respiratory secretions, BAL, pleural fluid, and blood are necessary to diagnose pulmonary bacterial infections. Langerhans cell histiocytosis and chronic granulomatous disease are associated with opportunistic infections, including *Pneumocystis jiroveci (P. carinii)*, *S. aureus*, *Enterobacter* species, *Burkholderia cepacia*, and *Proteus*, *Salmonella*, *Aspergillus*, *Serratia*, *Nocardia*, and *Candida* organisms. BAL fluid may be needed for stains and cultures of these organisms. Open lung biopsy aids in the diagnosis of pulmonary angiodysplasia, interstitial lung disease, and pulmonary hypertension.

Anteroposterior and lateral radiographs, ultrasonography, and CT scans of the chest help in the diagnosis of pneumonia, atelectasis, pleural effusion, abscesses, cysts, bullae, nodules, pulmonary hypertension, interstitial fibrosis, and honeycomb lung. Pulmonary angiodysplasia is identified by pulmonary arteriography, which reveals the dilated precapillaries and the arteriovenous anastomoses at the lung bases in a characteristic spongy pattern that correlates radiographically with basilar nodular infiltrates.[189,195,203,206,212,222] Transthoracic contrast-enhanced, two-dimensional echocardiography detects the presence of a shunt by scanning the passage of microbubbles in a contrast material. These particles are normally removed in transit through pulmonary capillaries, but, in the presence of a right-to-left intrapulmonary shunt, bypass the capillaries and appear after several cardiac cycles in the left side of the h eart.[189,191,195,197,203,205,206,210,212,220] Transesophageal contrast echocardiography can identify the contrast in specific veins and if dilatations or arteriovenous communications predominate even when hypoxemia is absent.[205,212,220] Lung perfusion scans using macroaggregated albumin labeled with technetium-99m have particles measuring 20 to 50 μm that wedge into normal capillaries that are 8 to 15 μm wide and do not pass through these vessels. However, these particles travel through arteriovenous fistulas and appear in the systemic circulation of extrapulmonary organs.[189,195,197,203-206,210,212,220,233]

Pulmonary function testing reveals reductions in DLCO, variable decreases in lung volumes and airflow rates, increases in $\dot{V}E$, hypoxemia, and hypocapnia.[196,206,215,216,223,232,233] Diminutions in the transfer factor cause the diminished DLCO, which occurs as a result of an increase in the pathway for gas diffusion from the alveolus through the vasodilated vessel to the RBC and is observed in alveolitis, emphysema, interstitial pneumonitis, and interstitial fibrosis.[206,233] $\dot{V}/\dot{Q}$ imbalance and diffusion/perfusion imbalance result from pulmonary angiodysplasia, pneumonia, atelectasis, bronchiectasis, and emphysema. Adults with the hepatopulmonary syndrome have progressive hypoxemia; reductions in the breathing reserve, $\dot{V}O_2$, and O_2 pulse; and elevations in RR, $\dot{V}E$, and physiologic dead space with exercise.[234]

Measurements of lung volumes and CL may be altered with ascites. Peritoneal fluid can raise intra-abdominal pressure; elevate and fix the diaphragm; reduce lung volumes, CCW, and MVV; and increase the RR.[195,196,232] In addition, oxyhemoglobin saturation, as measured by pulse oximetry, may be underestimated if the serum total bilirubin level is greater than 2.5 mg/dL because of interference of bilirubin pigments in the skin with oximetric readings of light transmission.[189,195]

Treatment

Therapy is directed at the underlying hepatic disorder. However, medications used to treat liver disease can be toxic to the lung. Penicillamine, a drug used in the treatment of Wilson's disease and primary biliary cirrhosis, can cause bronchospasm, bronchiolitis obliterans, bronchitis, hemorrhagic pleural effusion, interstitial pneumonitis, alveolitis, pulmonary fibrosis, hypersensitivity pneumonitis, pulmonary hemorrhage, and a pulmonary-renal syndrome similar to that of Goodpasture's syndrome (Box 75-7).[195,235,236] Methotrexate, an immunosuppressive drug used to treat primary biliary cirrhosis, can result in interstitial pneumonitis and pleural effusions.[154,218,236] Azathioprine, an immunosuppressive agent, can cause pulmonary edema and interstitial pneumonitis and fibrosis, while cyclosporine, another immunosuppressive drug, can cause pulmonary edema and ARDS.[189,195,196] Interferon-α (INF-α) is used in the treatment of chronic hepatitis C viral infection and can result in bronchiolitis obliterans organizing pneumonia (BOOP), interstitial pneumonitis, pleural effusion, pulmonary arterial hypertension, and asthma.[194]

Additional therapy includes treatment of pulmonary infections with appropriate antimicrobial agents and relief of dyspnea caused by pleural effusions or ascites with thoracentesis and paracentesis, respectively. Hypoxemia is treated with supplemental O_2 and positioning to reduce the extent of orthodeoxia and platypnea and can improve with percutaneous embolization of pulmonary angiodysplasia.[237]

Supplemental O_2 and bronchodilators, which improve airflow and minimize Raw and work of breathing, are used to treat pulmonary hypertension. Calcium channel blockers and prostaglandins may also be utilized and include continuous infusion of prostaglandin-I2 (epoprostenol) and inhalation of NO.[206,209,217,228,230,231,238-240] Experimental therapies consist of inhalation of a prostaglandin-I2 (iloprost), subcutaneous infusion of a prostacyclin (treprostinil), an oral prostacyclin (beraprost), oral endothelin receptor antagonists (bosentan, sitaxsentan), and an oral phosphodiesterase inhibitor (sildenafil).[228,238-241] Hypoxemia, clubbing, diffusion/perfusion imbalance, shunts, elevated cardiac output, reduced systemic and pulmonary vascular resistances, abnormal pulmonary function testing, and exercise intolerance may reverse with liver transplantation in selected individuals.[189,205-207,210,216,224,228,231]

DISORDERS OF THE KIDNEY

Renal Failure

DEFINITION

Acute and chronic renal failure can cause disease involving the lung parenchyma, airways, pleural space, blood vessels, chest wall, and control of breathing centers (see Box 75-7).

Box 75-7 Respiratory Disorders Associated with Renal Failure

Parenchymal Disorders

Alveolar hemorrhage
- Goodpasture's syndrome
- Systemic necrotizing vasculitides: Wegener's granulomatosis, Churg-Strauss syndrome, polyarteritis nodosa
- Connective tissue diseases: systemic lupus erythematosus, scleroderma, Behçet's disease
- Henoch-Schönlein purpura, IgA nephropathy
- Medications: penicillamine toxicity, azathioprine toxicity

Bronchiolitis obliterans organizing pneumonia
- Systemic lupus erythematosus, scleroderma, IgA nephropathy, Behçet's disease

Fibrosing alveolitis
- Renal tubular acidosis

Amyloidosis
- Chronic renal failure, end-stage renal disease

Lymphomatoid granulomatosis
- Chronic renal failure, end-stage renal disease

Metastatic pulmonary calcification
- Renal osteodystrophy, chronic hemodialysis, chronic renal failure, end-stage renal disease

Pulmonary edema ("uremic lung")
- Chronic renal failure, end-stage renal disease

Pneumonia: infectious, uremic pneumonitis
- Acute and chronic renal failure, peritoneal dialysis, end-stage renal disease

Rounded atelectasis
- Chronic renal failure, end-stage renal disease

Airway Disorders

Reactive airway disease
- Nephrotic syndrome, peritoneal dialysis, hemodialysis, chronic renal failure, end-stage renal disease

Pleural Disorders

Pleural effusion
- Nephrotic syndrome, peritoneal dialysis, hemodialysis, chronic renal failure, end-stage renal disease
- Wegener's granulomatosis, Churg-Strauss syndrome, systemic lupus erythematosus, scleroderma, Henoch-Schönlein purpura, Behçet's disease

Chylothorax
- Nephrotic syndrome, Behçet's disease

Vascular Disorders

Pulmonary arterial hypertension
- Hemodialysis, chronic renal failure, end-stage renal disease

Chest Wall Disorders

Respiratory muscle myopathy ("uremic myopathy")
- Chronic renal failure, peritoneal dialysis, chronic hemodialysis, end-stage renal disease

Fractures: ribs, vertebrae
- Renal osteodystrophy, chronic renal failure, end-stage renal disease

Disorders of Control of Breathing

Sleep apnea (central, obstructive)
- Chronic renal failure, end-stage renal disease

Pulmonary disease is more likely to be present when the plasma urea concentration is >20 mmol/L, or approximately 60 mg/dL, a level associated with metabolic alterations.[242]

PATHOGENESIS, CLINICAL FEATURES

Alveolar hemorrhage occurs in uremia as a result of vasculitis, alterations in platelet adhesion and aggregation, abnormal coagulation, and hypervolemia.[243] The coexistence of alveolar hemorrhage and glomerulonephritis produces a spectrum of diseases that affect the pulmonary interstitium and vessels, are frequently identified with immune dysfunction, and compose the pulmonary-renal syndrome[244-250] (see Box 75-7 and Table 75-5). For example, antibasement membrane antibody disease, or Goodpasture's syndrome, is associated with linear deposits of IgG, IgA, IgM, and the third component of complement (C_3) in the basement membranes of renal glomerular capillaries and IgG, IgA, and C_3 in the pulmonary alveolar septa; alveolar hemorrhage, inflammation, and fibrosis; PAMs filled with hemosiderin; focal and diffuse interstitial infiltrates; and acute respiratory failure.[244-247,251-253] IgG antibodies combine with basement membrane proteins of type IV collagen in renal tubules and glomeruli and in pulmonary alveoli when factors that increase pulmonary capillary permeability, such as hyperoxia and cigarette smoke, are present.[244,245]

Wegener's granulomatosis is characterized by glomerulonephritis, circulating antineutrophil cytoplasmic IgG antibodies (ANCA), deposits of IgG and complement in alveolar interstitium and small blood vessels, parenchymal cavitary lesions, localized alveolar hemorrhage, alveolitis, and necrotizing granulomatous vasculitis with infiltration by PMNs, T-lymphocytes, monocytes, histiocytes, plasma cells, and giant cells[244,246,252-257] (see Table 75-5). Possible etiologies include genetic susceptibility, chronic exposure to silica, and an association with α_1-antitrypsin deficiency.[258-260]

The pulmonary manifestations of allergic angiitis and granulomatosis, or Churg-Strauss syndrome, include a history of asthma and/or allergies; vasculitis of pulmonary arteries, veins, and capillaries of varying sizes; and eosinophilic infiltrates, granulomata, and necrotizing vasculitis in the lung.[244,248,254,261,262] Although polyarteritis nodosa is infrequently accompanied by respiratory complications, chronic asthma, alveolar hemorrhage, and necrotizing vasculitis of medium and small pulmonary arteries can occur and may represent a variant of Churg-Strauss syndrome.[244,245,254]

Systemic lupus erythematosus is associated with IgG, IgA, IgM, and complement deposition in pulmonary alveolar epithelial and endothelial cells and renal glomerular basement membranes; chronic interstitial pneumonia; pleural effusion; BOOP; hyaline membranes; diffuse alveolar hemorrhage; and

Table 75-5
Pulmonary-Renal Syndrome

Disorder	Signs and Symptoms: Pulmonary	Signs and Symptoms: Systemic	Laboratory Findings	Chest Radiographs
Goodpasture's syndrome	Hemoptysis, cough, dyspnea, hypoxemia	Glomerulonephritis	Anemia, proteinuria, hematuria, RBC casts, ↑ BUN and creatinine, slightly ↑ ESR, serum antiglomerular basement membrane antibodies, antibodies to α3 chain of type IV collagen, association with HLA-DR2 and HLA-B7 antigens	Focal or diffuse, bilateral or unilateral interstitial infiltrates; reticulonodular infiltrates; edema; hemorrhage
Wegener's granulomatosis	Hemoptysis, cough, dyspnea, hypoxemia, pleuritic chest pain, pleural friction rub	Fever, malaise, weight loss, otitis media, hearing loss, uveitis, proptosis, conjunctivitis, arthritis, sinusitis, dermatitis, epistaxis, CNS disease, glomerulonephritis	Anemia; thrombocytosis; ↑ ESR, BUN, and creatinine; RBC casts; hematuria; pyuria; proteinuria; positive RF; circulating immune complexes; ↑ C_3, IgE, and IgA; chemotaxis and cellular dysfunction; hypergammaglobulinemia; association with ANCA IgG antibodies and HLA-DR2 antigen	Bilateral nodular infiltrates with central cavitation; diffuse alveolar, interstitial, or reticulonodular infiltrates; single nodule; platelike atelectasis; pleural effusion; pneumothorax; pyopneumothorax; bronchopleural fistula; hemorrhage
Churg-Strauss syndrome	Wheezing, hemoptysis, dyspnea, hypoxemia, pleuritic chest pain	Allergies, petechiae, purpura, nodular and subcutaneous lesions, seizures, coma, peripheral neuropathy, diarrhea, melena pancreatitis, abdominal pain, myocardial and endocardial lesions, glomerulonephritis	Peripheral eosinophilia; slightly ↑ IgE; ↑ ESR, BUN, and creatinine; circulating immune complexes; hematuria; proteinuria; RBC casts; anemia; ↑ WBC count	Transient diffuse, nodular, or interstitial infiltrates; pleural and pericardial effusions; hemorrhage
Systemic lupus erythematosus	Hemoptysis, cough, dyspnea, hypoxemia, pleuritic chest pain	Fever, malaise, weight loss, CNS disease, alopecia, arthritis, serositis, nephritis, photosensitivity	↓ C_3; positive ANA and anti-DNA titers; circulating immune complexes; positive Coombs test; ↑ ESR, BUN, and creatinine; anemia; ↑ or ↓ WBC count; hypergammaglobulinema; hematuria; proteinuria; RBC and granular casts	Diffuse unilateral or bilateral infiltrates, interstitial infiltrates, atelectasis, pleural effusion, edema, hemorrhage, BOOP, diaphragmatic paresis
Scleroderma	Hemoptysis, cough, dyspnea, hypoxemia, pleuritic chest pain, pleural friction rub, bibasilar crackles	Sclerosis of skin, telangiectasia, myositis, arthritis, cutaneous calcifications, cor pulmonale, Raynaud's phenomenon, hypertension, esophageal hypomotility, gastroesophageal reflux, glomerulonephritis, renal vascular disease and failure	↑ ESR, BUN, and creatinine; positive RF, ANA, and anti-DNA titers; circulating immune complexes; T-cell hyperactivity; hypergammaglobulinemia; proteinuria; hematuria; anemia	Diffuse bilateral interstitial basilar infiltrates, interstitial fibrosis, cystic lesions, honeycomb lung, pleural and pericardial effusions, calcification, hemorrhage, subpleural cysts, pneumothorax, BOOP, prominent pulmonary arteries, cardiomegaly
Henoch-Schönlein purpura	Hemoptysis, cough, dyspnea, hypoxemia	Arthritis, arthralgia, purpura, abdominal pain, melena, glomerulonephritis	↑ ESR, BUN, creatinine, and IgA; hematuria; proteinuria; RBC casts; anemia; ↑ WBC count; normal platelet count	Interstitial pneumonitis, hemorrhage, pleural effusion
IgA nephropathy	Hemoptysis, cough, dyspnea, hypoxemia	Glomerulonephritis	↑ ESR, BUN, creatinine, and LDH; peripheral eosinophilia; ↓ C_3; hematuria; proteinuria; anemia	Interstitial pneumonitis, hemorrhage, BOOP
Behçet's disease	Hemoptysis, cough, dyspnea, hypoxemia, pleuritic chest pain	Uveitis, ulcers (oral, laryngeal, and genital), fever, subcutaneous nodules, thrombophlebitis, glomerulonephritis	↑ ESR, BUN, and creatinine; hematuria; proteinuria; RBC casts; anemia; association with HLA-B51 antigen, herpes simplex virus, hepatitis C virus, and parvovirus B19	Diffuse reticulonodular infiltrates, pleural effusion, chylothorax, infarction, hemorrhage, BOOP, prominent pulmonary arteries, diffuse bilateral perfusion defects on scan

↑, increased; ↓, decreased.; RBC, red blood cell; BUN, blood urea nitrogen; ESR, erythrocyte sedimentation rate; HLA, human leukocyte antigen; RF, rheumatoid factor; C_3, third component of complement; CNS, central nervous system; ANCA, antineutrophil cytoplasmic antibody; WBC, white blood cell; ANA, antinuclear antibodies; BOOP, bronchiolitis obliterans organizing pneumonia; LDH, lactate dehydrogenase.

pulmonary capillary vasculitis.[245-247,252,254,263-265] Progressive systemic sclerosis, or scleroderma, is characterized by fibrous connective tissue deposition in the lung, which may be inflammatory and immunologic in etiology; pulmonary interstitial pneumonitis and fibrosis; alveolitis; BOOP; hemorrhage; and pulmonary hypertension.[250,254,266]

Henoch-Schönlein purpura is associated with alveolar IgA deposition, inflammation, hemorrhage, and widespread pulmonary vasculitis, whereas IgA nephropathy is identified with deposits of IgA-containing immune complexes and C_3 in renal mesangial cells and may be accompanied by IgA deposition in alveolar interstitium and capillaries, pulmonary

hemorrhage, and BOOP.[245,246,248,254,267-269] Behçet's disease is characterized by deposits of IgG, C_3, and C_4 in pulmonary capillaries and venules; vasculitis of different-sized pulmonary vessels; pulmonary thrombosis and infarction; pulmonary arterial aneurysms invading contiguous airways; recurrent pneumonia; hemorrhage; and BOOP.[244-246,254,262,270,271] In most of these disorders, particularly Goodpasture's syndrome and Wegener's granulomatosis, alveolar hemorrhage occurs early in the course of the glomerulonephritis and may be the initial manifestation.[245,247]

The presence and pattern of immunofluorescent staining of ANCA help to identify the type of vasculitis and lung disease present.[244,247,272,273] Two main antigen-staining patterns comprise ANCA—the cytoplasmic pattern (c-ANCA), which has antiproteinase 3 (PR3) antibodies, and the perinuclear pattern (p-ANCA), which has antimyeloperoxidase (MPO) antibodies.[246,247,257,261,272] The c-ANCA, PR3 pattern is specific for Wegener's granulomatosis and is frequently accompanied by acute respiratory failure and bilateral pulmonary nodules radiographically.[246,252,257,272,273] The p-ANCA, MPO pattern is identified with Churg-Strauss syndrome, microscopic polyangiitis, and other types of glomerulonephritis without extrarenal manifestations and is often associated with a ground-glass appearance radiographically.[246,261,272,273] However, exceptions occur, as p-ANCA is recognized in Wegener's granulomatosis, Goodpasture's syndrome, scleroderma, and diabetes mellitus type 2 with glomerulonephritis and pulmonary hemorrhage.[249,250,253,257,274,275] In addition, the activity of PR3 antibody is normally inhibited by α_1-antitrypsin.[260] If α_1-antitrypsin is deficient or absent, the relative increased PR3 antibody activity may enhance synthesis of autoantibodies, including c-ANCA, and promote the development of Wegener's granulomatosis.[260]

Other pulmonary disorders occurring with renal failure include fibrosing alveolitis, which can accompany renal tubular acidosis[276] (see Box 75-7). The presence of both disorders suggests an underlying systemic disease involving the immune system, particularly because autoantibodies and hypergammaglobulinemia may be present with fibrosing alveolitis.[276] Pulmonary airways, alveolar septa, blood vessels, and kidneys are affected by deposits of amyloid, a glycoprotein, with resultant wheezing, dyspnea, pulmonary hemorrhage, pleural effusion, respiratory failure, and diffuse reticulonodular infiltrates and nodular lesions on radiographs.[244,277] Lymphomatoid granulomatosis, a lymphoproliferative vasculitis of medium and small blood vessels injured by atypical lymphocytes and plasma cells, causes lung and renal disease, is associated with T-cell lymphoma formation with a predominance of $CD4^+$ T-lymphocytes, and usually occurs in an already immunocompromised individual.[244,254,278] Bilateral pulmonary nodules, particularly at the bases and occasionally with cavitation, are present on chest radiographs, and pulmonary hemorrhage and pneumonia are frequent causes of death.[244,278] Infections with *Streptococcus pneumoniae*, *Mycoplasma pneumoniae*, *Leptospira*, and Puumala virus and toxic environmental agents can also cause glomerulonephritis, pulmonary hemorrhage, interstitial infiltrates, and acute respiratory failure.[248,259,279]

Metastatic pulmonary calcification occurs in chronic renal failure in the presence of hypercalcemia (see Box 75-7). It can result from primary, secondary, or tertiary hyperparathyroidism; hypervitaminosis D; excessive calcium ingestion (milk-alkali syndrome); and other mechanisms of increased calcium associated with renal insufficiency, including bone infections, bone malignancies, and tumors secreting parathyroid-like hormone.[280-285] Calcium deposits in tissues when the calcium-phosphorus product is larger than the solubility constant of calcium-phosphorus in blood (Table 75-6).[281,283,284] The lung acts as a reservoir for calcium deposition because of its relative alkaline environment resulting from loss of hydrogen ions during ventilation and diminished solubility of calcium salts in areas with a high pH.[281-286] These salts are primarily calcium phosphates.[286] The occurrence and severity of these calcifications are unrelated to the duration of renal failure or dialysis, degree of parathyroid abnormalities, or extent of elevation of the calcium-phosphorus product.[286] Metastatic pulmonary calcification appears as diffuse calcium deposits in walls of alveoli, large and small bronchi, terminal bronchioles, and interstitial blood vessels; may be associated with interstitial thickening, collagen deposition, and fibrosis; can interfere with diffusion across the alveolar-capillary membrane; and can precipitate respiratory failure.[280,284,286,287] Chronic renal failure is the most frequently occurring entity that causes pulmonary calcification in children.[280]

Pulmonary edema results from fluid retention and hypoproteinemia, which occur as the glomerular filtration rate diminishes, and increased pulmonary capillary permeability[242,288,289] (see Box 75-7). This contributes to the increased weight of lungs of individuals dying from uremia.[290] The lung

Table 75-6
Serum Calcium and Phosphorus in Untreated Chronic Renal Failure and Hyperparathyroidism

Disorder	Serum Calcium (mg/dL)	Serum Phosphorus (mg/dL)	Calcium-Phosphorus Product
Chronic renal failure alone	↓	↑	Normal, ↑, or ↓
Chronic renal failure with secondary hyperparathyroidism	Normal or slightly ↓	↑	Normal, ↑↑, or ↓
Primary hyperparathyroidism alone	↑	↓	Normal, ↑, or ↓
Primary hyperparathyroidism with secondary chronic renal failure*	Normal or ↑	↑	↑↑
Tertiary hyperparathyroidism	↑	↓	↑

↑, increased; ↓, decreased.
*Individuals with primary hyperparathyroidism and secondary chronic renal failure often have secondary hyperparathyroidism.

fluid is abundant with protein, including fibrin, and when present radiographically, causes a "uremic lung."[242,290] Uremic pneumonitis is associated with lungs that are heavy and indurated and have protein-rich edema fluid, hyaline membranes, alveolar hemorrhage, and fibrin in inflamed pleura.[159,244,291]

Renal failure alters cellular immunity and predisposes to pulmonary infection with opportunistic organisms[292] (see Box 75-7). Total lymphopenia, reductions in $CD4^+$ and $CD8^+$ T-lymphocytes, reversal of the $CD4^+/CD8^+$ T-lymphocyte ratio, diminished delayed hypersensitivity reactions, enhanced suppression of T-lymphocytes by PAMs, and impaired phagocytosis by PAMs secondary to metabolic acidosis occur, but humoral immunity is intact.[242,285,293-296] Infections caused by *M. tuberculosis*, *Legionella pneumophila*, *S. aureus*, *S. pneumoniae*, *Enterobacter* species, *Klebsiella* organisms, *Serratia* species, *M. pneumoniae*, Epstein-Barr virus, influenza virus type A, echovirus type 9, varicella-zoster virus, herpes simplex virus, cytomegalovirus, human immunodeficiency virus, *P. jiroveci*, *Candida* species, *Mucor* species, *Aspergillus* species, *Coccidioides immitis*, and *Histoplasma capsulatum* are present with increased frequency and can affect both the lungs and kidneys.[244,289,294,297]

Passage of ascitic fluid across diaphragmatic openings and pleural capillaries causes a unilateral or bilateral serous, serosanguinous, or hemorrhagic exudative pleural effusion, which has a predominance of lymphocytes, a normal glucose concentration, high protein and creatinine levels, and a pleural fluid/serum creatinine ratio less than 1.0[154,159,244] (see Box 75-7 and Table 75-7). This "uremic" pleural effusion usually occurs with long-standing renal failure, that is, lasting at least 1 year.[154] It differs from the transudative pleural fluid of nephrotic syndrome and congestive heart failure, which can also occur in uremia, is bilateral and serous, and has predominantly monocytes or lymphocytes with minimal protein and no creatinine.[154,159] In addition, a chylothorax can be present in the nephrotic syndrome when chylous ascitic fluid passes through diaphragmatic openings or across diaphragmatic lymphatic vessels and in Behçet's syndrome secondary to thrombosis of the jugular veins and superior vena cava.[262,271,298] The pleural and ascitic fluid levels of protein, cholesterol, triglyceride, and LDH are elevated with a chylothorax, most likely secondary to selective absorption of water from the pleural space.[298] Approximately 3% of patients with uremia develop a pleural effusion, although half of these individuals are asymptomatic.[159] Complications of a uremic pleural effusion include a fibrothorax and rounded atelectasis, which occurs when a collapsed lung adjacent to the resolving effusion develops parietal pleural adhesions and tries to expand.[154,159,299]

Respiratory muscle weakness occurs in uremia (see Box 75-7), is part of a more generalized myopathy, and is attributed to the presence of large quantities of ascitic fluid, malnutrition, anemia, uremic toxins, elevated parathyroid hormone levels, vitamin D and carnitine deficiencies, aluminum toxicity, and alterations in cellular metabolism affecting protein, fatty acids, and cations.[292,300,301] Although most studies of respiratory muscle strength in uremia have been performed in individuals receiving dialysis, which contributes to altered muscle function, rats with renal failure secondary to surgical removal of 83% of their kidneys have diaphragmatic dysfunction.[301] In addition, chest wall mechanics are altered by rib and vertebral fractures caused by destructive bone lesions in uremia.

Both central and obstructive sleep apnea can be present in renal failure (see Box 75-7). Metabolic acidosis with secondary hyperventilation and hypocapnia, uremic toxins acting on the central nervous system, chemical mediators, diminished airway muscle tone resulting from uremic myopathy, and metabolic cellular alterations may be etiologies.[49,302]

Dialysis

PATHOGENESIS, CLINICAL FEATURES

Complications of peritoneal dialysis include left lower lobe atelectasis and hypoventilation secondary to diaphragmatic immobility and eventration resulting from the large quantities of dialyzing fluid[242,303] (Box 75-8). A weak cough with sputum retention can also occur with diaphragmatic immobilization.[242] Other complications include pneumonia and pleural effusion caused by peritonitis and bacteremia; massive hydrothorax resulting from leakage of dialysate through diaphragmatic openings, which may be present normally, as defects resulting from the pressure of repeated instillation of large amounts of fluid into the abdomen, or from a pleuroperitoneal fistula; and hypoxemia secondary to $\dot{V}/\dot{Q}$ imbalance.[242,285,303-306]

Hemodialysis is associated with intrapulmonary sequestration of PMNs with concomitant peripheral leukopenia; com-

Table 75-7
Pleural Effusion Composition in Uremia

Type	Appearance	Cells	Glucose (mg/dL)	Protein (g/dL)	LDH (IU/L)	Creatinine (mg/dL)	Comments
Uremic	Exudate: serous, serosanguinous, hemorrhagic	Lymphocytes	Normal	↑	↑	↑	Unilateral or bilateral
Nephrotic syndrome, congestive heart failure	Transudate: serous	Monocytes, lymphocytes	Normal	↓↓	Normal	None	Bilateral
Chylous	Transudate: white, opalescent	Lymphocytes	Normal	↑	↑	Normal	Cholesterol and triglyceride present, unilateral
Dialysate	Transudate	Monocytes	↑	↓	↓	↓	Unilateral or bilateral

↑, increased; ↓, decreased.

Box 75-8 Respiratory Manifestations Associated with Renal Dialysis

Peritoneal Dialysis

Atelectasis: left lower lobe
Hypoventilation
Diaphragmatic immobility
Diaphragmatic eventration
Sputum retention
Pneumonia
Pleural effusion
Hydrothorax
Hypoxemia
Ventilation/perfusion imbalance

Hemodialysis

Polymorphonuclear leukocyte sequestration
Complement activation
Anaphylaxis: wheezing
Emboli: air, blood, silicone
Hypoxemia
Ventilation/perfusion imbalance
Hemorrhage: pleural
Pulmonary hypertension
"First-use syndrome"
Abdominal muscle weakness
Metastatic pulmonary calcification

plement activation, particularly C_3 and C_5; anaphylaxis with wheezing secondary to chemical mediator release; silicone emboli in pulmonary capillaries and PAMs originating from blood pump tubing; hypoxemia resulting from $\dot{V}/\dot{Q}$ mismatch and pulmonary embolism caused by blood microemboli; air embolism; pleural hemorrhage induced by anticoagulation; pulmonary hypertension secondary to acidosis and chemical mediator release; and metastatic pulmonary calcification[242,244,284,285,307,308] (see Box 75-8). Hypotension, dyspnea, chest pain, and bronchospasm compose the "first-use syndrome" and result from complement activation and release of inflammatory mediators during an initial hemodialysis with a cuprophane membrane.[242,285,309] Abdominal muscle strength, which is important during expiration, can be reduced after hemodialysis because of diminutions in serum levels of potassium and phosphorus.[310]

DIAGNOSIS

The diagnosis of pulmonary diseases associated with renal failure and dialysis is aided by the history, physical examination, and laboratory and radiographic studies. The presence of pulmonary hemorrhage, particularly bilateral alveolar infiltrates, with renal disease, hematuria, RBC casts, an increased serum creatinine level, anemia, hypocomplementemia, elevated antinuclear and anti-DNA antibody titers, arthritis, and purpura should suggest the parenchymal diseases composing the pulmonary-renal syndrome (see Box 75-7 and Table 75-5). Although most of these diseases have been diagnosed in adults, some have also been identified in children.[248,249,264,267,269,270,278,280,311] With the exceptions of Goodpasture's syndrome and IgA nephropathy, the disorders in this category are accompanied by systemic manifestations.[244,245,251] The identification of hemosiderin-laden PAMs in BAL fluid may aid in the diagnosis of pulmonary hemorrhage, although these cells are also present in other disorders, including congestive heart failure.[245] Serial measurements of serum antiglomerular basement membrane antibodies in Goodpasture's syndrome are useful in evaluating the therapeutic response, but the titers do not parallel the severity or recurrence of pulmonary hemorrhage.[244,245] In addition, the extent of alveolar hemorrhage does not correlate with the quantity of expectorated blood because alveolar hemorrhage is bleeding within the acinus. However, it can be evaluated by chest radiography, oxyhemoglobin saturation, and hemoglobin levels.[245] If serum antiglomerular basement membrane antibody titers are absent in Goodpasture's syndrome, renal and lung biopsy should be considered to identify IgG antibodies on the basement membranes.[247,252] Lung biopsy either with a thoracotomy or VATS helps in the diagnosis of these pulmonary diseases.[244-247,252]

Appropriate stains and cultures of respiratory secretions, pleural fluid, and BAL fluid and serum titers and rapid antigen and antibody studies for viral infections are important in the diagnosis of the etiology of infectious pneumonias. A uremic pleural effusion is frequently associated with cough, chest pain, dyspnea, fever, and a pleural friction rub.[154,159] Evaluation of a pleural effusion by thoracentesis helps determine whether the fluid is a uremic exudate, chylous, or a transudate. A chylothorax occurring in the nephrotic syndrome suggests a peritoneal etiology of the fluid and, if present in Behçet's syndrome, thrombosis of major veins.[262,271,298] An effusion with an elevated glucose level and reduced protein and LDH concentrations reflects the presence of dialysate in the pleural space[304,305] (see Table 75-7). Pleuroperitoneal communications associated with this may be identified by the detection of dialysate stained with methylene blue or by radionuclide scanning of macroaggregated albumin labeled with technetium-99m that passes from peritoneal to pleural spaces.[304-306]

Metastatic pulmonary calcification may not be accompanied by symptoms or visualization on anteroposterior and lateral chest radiographs and may require a CT scan of the chest, lung scan, or lung biopsy for detection.[247,280,284-287,312,313] This diagnosis should be considered in an individual with chronic renal failure; persistent pulmonary infiltrates, which may be diffuse, interstitial, or nodular or appear as pneumonia or edema; hypoxemia; and reduced DLCO measurements.[281,282] Fibrosing alveolitis is associated with a reticulonodular pattern on chest radiographs and decreased DLCO measurements and is more definitively diagnosed by lung biopsy.[276] Alveolar hemorrhage is depicted radiographically as diffuse alveolar and interstitial densities and if chronic, a reticulonodular pattern.[244]

Pulmonary function testing in both acute and chronic uremia reveals reductions in slow vital capacity (SVC), FVC, FEV_1, ERV, TLC, peak expiratory flow rate, DLCO even when corrected for anemia, specific airway conductance, PImax, PEmax, and PaO_2; elevations in RV; and a normal FRC and FEV_1/FVC ratio.[242,290,300,292,309,310] The restrictive ventilatory and gas transfer abnormalities most likely result from interstitial and alveolar edema and fibrin deposits.[290,303] Metastatic pulmonary calcification causes reductions in VC, DLCO,

and PaO_2, which are directly related to the magnitude and extent of the calcium deposits.[287] Wegener's granulomatosis is associated with airflow obstruction and reduced lung volumes and DLCO measurements.[244,254] Decreases in DLCO with normal or reduced lung volumes occur in scleroderma and Henoch-Schönlein purpura.[250,267] An elevated DLCO occurs in pulmonary hemorrhage as a result of carbon monoxide binding to intra-alveolar blood, which may help differentiate hemorrhage from pneumonia and pulmonary edema.[244-246,251,252] The DLCO may be as high as 30% above baseline measurements and return to normal within 48 hours after the acute hemorrhage.[244,245]

Exercise testing in children with renal failure indicates reductions in work capacity, anerobic threshold, $\dot{V}O_2$, and oxygen pulse.[314] These measurements improve after treatment with recombinant human erythropoietin, suggesting that anemia may contribute to the exercise intolerance.[314] In addition, parathyroidectomy improves PImax, FVC, and FEV_1, whereas renal transplantation does not reverse diminished DLCO measurements.[242,300,315]

Peritoneal dialysis results in transient reductions in SVC, FVC, FRC, RV, TLC, and CL, most likely caused by filling the peritoneal cavity with the dialysate and concomitant diaphragmatic elevation.[242,244,303] These measurements return to baseline values with completion of the dialysis.[242,303] Ventilation and perfusion at the lung bases improve after hemodialysis, but elevations in RV, a diminution in the peak expiratory flow rate, respiratory muscle weakness, and hypoxemia become more pronounced, and ERV, $\dot{V}E$, and RQ decrease with this procedure.[242,290,310,316] The DLCO is diminished with chronic hemodialysis, that is, at least 5 years, and may reflect chronic inflammation associated with the membrane used for hemodialysis.[307,309,317]

TREATMENT

Therapy is directed at the underlying renal disease and associated pulmonary disorders. Corticosteroids, immunosuppressive agents, plasmapheresis to remove antibodies, and renal transplantation are used in the treatment of pulmonary-renal disorders.[244,246,253,254,261,271] Azathioprine, an immunosuppressive drug used to treat Goodpasture's syndrome, can cause pulmonary hemorrhage and diffuse alveolar damage.[318] Supplemental O_2, assisted ventilation with positive end-expiratory pressure, and corticosteroids are used in the therapy of pulmonary hemorrhage and concomitant hypoxemia, and factors precipitating the hemorrhage, that is, bleeding disorders, volume overload, and bacterial infection, should be diagnosed and treated.[244,245,253,254] Metastatic pulmonary calcification can be reduced by dialysis to control serum phosphorus levels, parathyroidectomy to reverse hyperparathyroidism, and renal transplantation.[282] VATS with talc pleurodesis may be used to treat persistent pleural effusions secondary to peritoneal dialysis.[306] Although central and obstructive sleep apneas are usually addressed with more conventional modalities of therapy,[49] they have resolved in selected individuals who had kidney transplants for treatment of renal failure.[302]

HEMOGLOBINOPATHIES

Sickle Cell Disease

GENETICS

The sickle cell syndromes comprise three types of anemia—sickle cell disease (hemoglobin SS), sickle cell β-thalassemia (hemoglobin S-thal), and sickle cell hemoglobin C disease (hemoglobin SC)—that cause varying degrees of pulmonary illness.[319-323] Both genes for hemoglobin are altered in these diseases, whereas in sickle cell trait (hemoglobin SA), one gene is abnormal and the other gene encodes the normal hemoglobin A. Homozygosity for hemoglobin S (SS) causes polymerization and sickling of RBCs at a PaO_2 of 50 mm Hg, whereas compound heterozygosity (S-thal, SC, SA) causes variable degrees of sickling at lower reductions in PaO_2 levels.[319,320,322-324]

Human hemoglobin A is composed of two α chains and two β chains, α2β2 or $\alpha^A\alpha^A\beta^A\beta^A$, each of which has amino acids and a heme group that binds with O_2 (Table 75-8).[319-321] The α2 genes are located on chromosome 16, whereas the β2 genes are on chromosome 11.[319,320,325] The genetic mutation causing the synthesis of hemoglobin S occurs at the sixth amino acid position in the β chain, where valine is substituted for glutamic acid.[319-321,323,326,327] Replacement of glutamic acid by lysine at the same position produces hemoglobin C.[319] β-Thalassemia hemoglobin results thalassemia from decreases (β^+-thalassemia) in or absence (β^o-thalassemia) of β chain synthesis and is caused by impaired messenger RNA function or gene transcription or the production of unstable β

Table 75-8
Characteristics of the Sickle Cell Hemoglobinopathies

Disease	Hemoglobin Composition	Genotype	Amino Acid Change	Hemoglobin Level (g/dL)	OxyHb Curve Shift
Sickle cell anemia	SS	$\alpha^A\alpha^A\beta^S\beta^S/\alpha^A\alpha^A\beta^S\beta^S$	S: Glu→Val	6-9 (75-94% S, 2% A_2, 2-23% F)	Yes
Sickle cell β-thalassemia	S-thal	$\alpha^A\alpha^A\beta^S\beta^S/\alpha^A\alpha^A\beta^{thal}\beta^{thal}$	S: Glu→Val	9-11 (75-90% S, <18% A, 5% A_2, 3-7% F)	Yes
Sickle cell hemoglobin C disease	SC	$\alpha^A\alpha^A\beta^S\beta^S/\alpha^A\alpha^A\beta^C\beta^C$	S: Glu→Val C: Glu→Lys	8-10 (49% S, 49% C, 2% F)	Yes
Sickle cell trait	SA	$\alpha^A\alpha^A\beta^S\beta^S/\alpha^A\alpha^A\beta^A\beta^A$	S: Glu→Val	14 (36% S, 60% A, 3% A_2, 1% F)	No
Normal	AA	$\alpha^A\alpha^A\beta^A\beta^A/\alpha^A\alpha^A\beta^A\beta^A$	—	>12 (97% A, 2% A_2, 1% F)	No

OxyHb, oxyhemoglobin; S, hemoglobin S; α, α chain; A, hemoglobin A; β, β chain; Glu, glutamic acid; Val, valine; A_2, hemoglobin A_2; F, hemoglobin F; thal, thalassemia; C, hemoglobin C; Lys, lysine.

chains.[319,325] Both β^+- and β^o-thalassemia hemoglobins can combine with hemoglobin S to form S-thal.[319,322]

PATHOGENESIS

RBC sickling, hemolysis, and anemia occur when hemoglobin S is deoxygenated and its molecules are packed closely together.[319,321-323,328-330] Hemoglobin S has diminished O_2 affinity, and RBCs with hemoglobin S have increased levels of 2,3-DPG.[323,331-333] As a result, the oxyhemoglobin dissociation curve is shifted to the right, causing arterial O_2 desaturation, promoting RBC sickling, and generating the pathophysiologic, clinical, and radiographic manifestations of the sickle cell syndromes (Boxes 75-9 and 75-10).[319,323,332-335] These occur, in decreasing order of severity, in SS, S-thal, SC, and SA hemoglobinopathies.[319,320,332,336,337] Individuals with SA do not have alterations in the oxyhemoglobin dissociation curve[334] (see Table 75-8).

Hypercoagulability, as evidenced by increased production of thrombin and fibrin and increased activation and utilization of platelets, also occurs with hemoglobin SS and contributes to the pathophysiology of events occurring during sickling[323,338] (see Box 75-9). In addition, RBCs with hemoglobin S, as well as with hemoglobin C, are more rigid and less deformable than those with hemoglobin A even when they have a normal shape and oxygenation.[319,323] This results in increased viscosity of blood, which contributes to plugging of blood vessels.[319,320,322,323] RBCs with hemoglobin S also interact with and adhere to the capillary endothelium, a process that is enhanced by hypoxemia and causes the release of vasoactive mediators that promote the sequence of events leading to vaso-occlusive crises.[319,320,323,329,335,339]

CLINICAL FEATURES

The pulmonary disorders occurring most frequently in sickle cell disease are pneumonia, pulmonary vascular injury, pulmonary infarction, acute chest syndrome (ACS), and sickle cell chronic lung disease (SCLD) (see Box 75-10 and Table 75-9). Most hospitalizations of children with sickle cell disease result from bacterial pneumonia.[332] Functional and anatomic asplenia causes deficient phagocytosis associated with opsonin, PMNs, and PAMs; altered chemotaxis; and impaired alternate pathway of complement.[321,323,340-346] Individuals with sickle cell disease are predisposed to lung infections with encapsulated bacteria (*Haemophilus influenzae*, *S. pneumoniae*), *Salmonella typhimurium*, *S. aureus*, *E. coli*, *M. pneumoniae*, *P. jiroveci*, and *Klebsiella*, *Acinetobacter*, and *Plasmodium* species.[321,332,336,340,342,343,345,347-351] Pneumonia caused by *L. pneumophila*, *Cryptococcus neoformans*, respiratory syncytial virus (RSV), adenovirus, influenza virus, parainfluenza virus, and cytomegalovirus has also been identified.[344,345,352,353]

Pulmonary vascular injury results from RBC sickling, pulmonary thrombosis, and pulmonary embolism and can cause sudden death if a large vessel is occluded[321,332] (see Table 75-9). RBC sickling, increased blood viscosity, vascular stasis, and thrombus formation predispose to pulmonary thromboembolism and infarction.[332,347,354] In addition, fat from necrotic bone marrow can enter and occlude the pulmonary circulation and cause pulmonary infarction, particularly during an aplastic crisis.[323,332,347,355,356]

The ACS is characterized by a new pulmonary infiltrate affecting at least one segment of lung, chest pain, fever greater than 38.5°C, wheezing, tachypnea, and cough[321,323,326,328,338,339,355,357-359] (see Box 75-10 and Table 75-9). Hypoxemia ($PaO_2 < 70$ mm Hg) and leukocytosis also occur.[360] It is an acute injury to the lung that can cause pulmonary edema, acute respiratory failure, ARDS, and 25% of deaths in sickle cell disease.[326,339,355,360-363] It can result from pneumonia, particularly with *S. pneumoniae*, *M. pneumoniae*, *Mycoplasma hominis*, *Chlamydia pneumoniae*, *L. pneumophila*, and parvovirus B19.[321,349,353,355,358,362-366] Other etiologies include atelectasis associated with hypoventilation and regional hypoxemia accompanying pain resulting from chest wall infarction or a vaso-occlusive crisis; fat embolism with augmented activity of secretory phospholipase A_2; and pulmonary vascular injury with thrombosis, infarction, and necrosis.[321,323,326,335,349,353,355,357,358,360,367,368]

Plastic bronchitis can occur in the ACS and is identified by the presence of branching mucoid bronchial casts that obstruct airways.[357,369] Possible etiologies include increased

Box 75-9 Characteristics of Sickle Cell Disease That Predispose to Pulmonary Disorders

- Abnormal hemoglobin levels: right shift of the oxyhemoglobin dissociation curve
- Hypoxemia
- Sickling crises: sequestration, vaso-occlusive, aplastic, hyperhemolytic
- Hypercoagulability of blood
- Hyperviscosity of blood
- Arteriolar vasculopathy: adherence of RBCs to endothelium, production of vasoactive mediators
- Lung parenchymal injury: synthesis of free oxygen radicals
- Chest wall: small and narrow thorax
- Immune dysfunction: phagocytosis, chemotaxis, opsonin, alternate complement pathway

Box 75-10 Pulmonary Disorders Occurring in the Sickle Cell Syndromes

Acute Disorders	Chronic Disorders
Pneumonia	Chronic lung disease
Pulmonary thromboembolism	Pulmonary arterial hypertension
Pulmonary infarction	Recurrent acute chest syndrome
Bone marrow and fat embolism	Restrictive lung disease
Acute chest syndrome	Cardiac: cardiomegaly, right ventricular strain, cor pulmonale
ARDS	
Pulmonary edema	
Asthma	
Plastic bronchitis	

Table 75-9
Characteristics of Pneumonia, Pulmonary Vascular Injury, Pulmonary Infarction, Acute Chest Syndrome, and Sickle Cell Chronic Lung Disease (SCLD) in Sickle Cell Disease

Pneumonia	Pulmonary Vascular Injury	Pulmonary Infarction	Acute Chest Syndrome	SCLD
Age				
<4 yr	All ages	>12 yr	All ages	Teenage years, adults
Predisposing Factors				
Defective phagocytic complement, opsonin, PMN leukocytic, and chemotactic function; preceding upper respiratory tract infection	Bone marrow necrosis with bone marrow and fat embolism, RBC sickling, ↑ blood viscosity, hypoxemia, ? pregnancy	Bone marrow necrosis with bone marrow and fat embolism, RBC sickling, pulmonary thrombosis, hypoxemia, pregnancy, preceding upper respiratory tract infection	Presence of hemoglobin S levels >20%, ? lung infection with *Chlamydia pneumoniae* and human parvovirus B19, bone marrow necrosis with bone marrow and fat embolism, lung vascular injury, atelectasis, hypoventilation, infarction of ribs and sternum	Recurrent episodes of acute chest syndrome
Signs and Symptoms				
Fever, chills, cough, malaise, tachypnea, chest wall retractions, flaring of nasal alae, crackles, purulent sputum, pleuritic chest pain, dyspnea	Fever, dyspnea, tachypnea, chest and bone pain, petechiae, funduscopic changes (including refractile bodies), mental status changes	Fever, tachypnea, crackles, jaundice, pleuritic chest pain, dyspnea	Fever; cough; tachypnea; dyspnea; rib and sternal tenderness; local soft tissue swelling; pleuritic or chest wall pain; chest wall retractions; flaring of nasal alae; ↓ breath sounds; crackles; wheezes; hemoptysis; pain in back, abdomen, and extremities	Progressive dyspnea, exercise intolerance, pleuritic chest pain, hypoxemia, syncope, proliferative retinopathy, fatigue
Laboratory Findings				
↑ WBC count, pathogens in cultures of blood and respiratory secretions	Fat globules in sputum, urine, and blood; lipid-laden PAMs in BAL; ↑ fibrin-degradation products	↑ WBC count; fat globules in sputum, urine, and blood; lipid-laden PAMs in BAL; bilirubin level >5 mg/dL; negative cultures; atypical RBCs ("blister" cells) peripherally	↑ WBC count; fat globules in sputum, urine and blood; lipid-laden PAMs in BAL; positive bone scan; negative cultures; ↓ Pa_{O_2}; ↓ O_2 saturation; ↑ fibrin-degradation products; thrombocytopenia; serosanguinous pleural fluid	ECG abnormalities
Chest Radiographs				
Multilobar, frequently in upper or middle lobes, pleural effusion	Infiltrate, edema, ARDS, occluded small blood vessels in CT scan	May be normal initially, unilateral density, may be wedge-shaped, frequently in lower lobes, pleural effusion, filling defects in lung perfusion scan, occluded small blood vessels in CT scan	May be normal initially, unilateral or multilobar infiltrates, frequently in middle and lower lobes, atelectasis, pleural effusion, edema, ARDS, occluded small blood vessels in CT scan	Diffuse interstitial markings, interstitial edema, prominent pulmonary arteries, defects in lung perfusion scan, cardiomegaly
Pulmonary Function Testing				
↓ Lung volumes, hypoxemia	Hypoxemia	↓ Lung volumes, hypoxemia	↓ Lung volumes, ↓ D_{LCO}, hypoxemia	↓ Lung volumes, ↓ D_{LCO}, hypoxemia

PMN, polymorphonuclear; RBC, red blood cell; ↑, increased; ↓, decreased; WBC, white blood cell; ECG, electrocardiogram; PAM, pulmonary alveolar macrophage; BAL, bronchoalveolar lavage; Pa_{O_2}, arterial O_2 tension; ARDS, acute respiratory distress syndrome; CT, computed tomography, D_{LCO}, diffusing capacity.

quantity and viscosity of airway secretions associated with asthma and inflammation, hypoxemia of airways secondary to vaso-occlusion and altered mucociliary clearance, and/or increased amount of lymph in airways resulting from pulmonary hypertension or fat embolism.[357] The impacted airway mucus can potentiate hypoxemia, $\dot{V}/\dot{Q}$ imbalance, and RBC sickling.[357] In addition, airway reactivity and asthma occur with increased frequency with recurrent ACS and may reflect injury to the lung.[370-372]

The ACS is associated with increased activity of secretory endothelial vascular cell adhesion molecule-1 (VCAM-1), which promotes adhesion of RBCs to the pulmonary vascular endothelium; enhanced activity of endothelin-1, a pulmonary vasoconstrictor; and reduced activity of NO, a pulmonary vasodilator, inhibitor of VCAM-1, and modulator of platelet aggregation, thrombus formation, and adhesion to vascular endothelium.[326,329,330,339,366,373,374] Hypoxemia and RBC sickling inhibit NO synthesis.[339] In addition, phospholipase A_2 releases free fatty acids, leukotrienes, thromboxanes, and prostaglandins, which cause bronchospasm and increased airway secretions, vascular permeability, and PMN chemotaxis.[323,326,355,358,367]

Multiple episodes of the ACS may promote the development of SCLD, although SCLD can occur without a previous episode of ACS.[321,323,355,359,361,375,376] Abnormal lung function with restrictive and obstructive lung disease, diminished DLCO, and hypoxemia occurs, and pulmonary arterial hypertension, myocardial ischemia, cardiomegaly, cor pulmonale, respiratory failure, and sudden death can ensue[323,338,347,360,370,375,377,378] (see Box 75-10 and Table 75-9). Pulmonary hypertension may result from chronic hemolysis, persistent hypoxemia, thrombosis, infection, fat emboli, and vascular injury, while hypoxemia occurs with defects in pulmonary perfusion, reductions in diffusion, pulmonary fibrosis, and restrictive lung disease.[338,358,375,378] $\dot{V}/\dot{Q}$ imbalance and intrapulmonary shunts may be present, particularly since the resting PaO_2 and oxyhemoglobin saturation are often 70 to 90 mm Hg and 80% to 90%, respectively.[332,341] $\dot{V}/\dot{Q}$ imbalance results from RBC sickling, potentiates hypoxemia, and promotes further sickling.[347] Chronic lung parenchymal injury occurs with the presence of free O_2 radicals, and elevated pulmonary vascular resistance results from endothelial hyperplasia of small arterioles caused by sickled RBCs.[375] The increased blood flow associated with chronic anemia and myocardial microinfarcts and anoxia occurring with RBC sickling in myocardial blood vessels cause cardiomegaly.[347]

S-thal disease, SC disease, and SA trait are also associated with these pulmonary disorders but to different degrees, depending on the amount of hemoglobin S present and the magnitude of increased blood viscosity[320,321,336,337,346,354-356] (see Tables 75-8 and 75-10). The likelihood of RBC sickling rises as the level of hemoglobin S increases.[319] The course of the anemia and splenic dysfunction in S-thal disease, SC disease, and SA trait is milder and has a later onset than with sickle cell disease, and the risk of pulmonary disorders and their severity are, in general, less than with sickle cell disease.[321,342] Pneumonia occurs in S-thal disease, SC disease, and SA trait with similar organisms as in sickle cell disease and may be unusually severe.[342,343,345,346,379-381]

The early onset of splenomegaly in SC disease is accompanied by an increased incidence of infection.[380] SC disease is frequently associated with bone marrow and fat embolism, pulmonary vascular injury, pulmonary arterial hypertension, and cor pulmonale, particularly during the third trimester of pregnancy.[332,365,377,382,383] This may be a result of a relatively increased hematocrit level with reduced circulatory transit time and elevated blood viscosity in SC disease compared with sickle cell disease.[332,365] SA trait has been identified with pulmonary infarction, ACS, and ARDS caused by hypoxic-induced sickling.[354,384] Unlike S-thal disease and SC disease, SA trait is not associated with immune dysfunction.[321,325,342,343]

Table 75-10
Pulmonary Disorders With Hemoglobin S

	S-Thal	SC	SA
Acute Disorders			
Acute chest syndrome	X	X	X
ARDS	X	X	X
Bone marrow and fat embolism	X	X	—
Pneumonia	X	X	X
Pulmonary infarction	X	X	X
Chronic Disorders			
Chronic lung disease	X	X	—
Pulmonary arterial hypertension	X	X	—
Cardiac: cardiomegaly, right ventricular strain, cor pulmonale	—	X	—

S-thal, sickle cell β-thalassemia; SC, sickle cell hemoglobin C disease; SA, sickle cell trait; ARDS, acute respiratory distress syndrome.

DIAGNOSIS

These pulmonary disorders are diagnosed by a history, physical examination, and laboratory and radiographic studies. Pneumonia and pulmonary infarction are often difficult to differentiate, but age, the presence of pathogens in cultures of respiratory secretions and blood, and chest radiographic findings may help[323,332,347] (see Table 75-9). Parvovirus B19 can be identified with the polymerase chain reaction.[356,365] Although a preceding upper respiratory tract infection suggests pneumonia, it can also precipitate a sickle cell crisis with a nonpneumonic pulmonary process.[385] Fever and chills also suggest pneumonia rather than pulmonary infarction, but children with hemoglobin SS can have high fever and appear quite ill despite lack of objective or laboratory findings of pneumonia.[385] Pneumonia in sickle cell disease is usually severe, is associated with fever lasting up to 12 days, and may resolve slowly despite appropriate antibiotic therapy.[319,332,354]

Pulmonary infarction in the sickle cell syndromes is typically not accompanied by hemoptysis, may have a prolonged course, and is suggested by the presence of acute pulmonary symptoms and an initially normal chest radiograph followed by a radiographic density[332,347] (see Table 75-9). The occurrence of extensive jaundice and atypical "blister" RBCs in the peripheral blood also suggests infarction, whereas the white blood cell (WBC) count is of little diagnostic value because it is elevated in pneumonia and pulmonary infarction and during crises.[332] Pneumonia and pulmonary infarction can occur simultaneously since necrotic tissue secondary to infarction can promote a milieu for bacterial growth.[347] Conversely, hypoxemia resulting from a slowly resolving pneumonia can promote RBC sickling, vascular occlusion, and pulmonary infarction.[354] In addition, pulmonary arterial hypertension may be present if unexplained syncope or dyspnea occurs.[377]

The distinguishing extrapulmonary features of the ACS include tenderness along the ribs and sternum with localized soft tissue swelling and pain in the abdomen, extremities, and back[361,362] (see Table 75-9). The presence of fat globules in sputum, urine, and blood and lipid-laden PAMs in BAL during a sickle cell crisis is diagnostic of fat embolism.[321,323,324,355,383] It occurs in ACS, pulmonary vascular injury, and pulmonary infarction and is associated with hypoxemia and disseminated intravascular coagulation.[324]

Bone marrow infarction can be detected by technetium-99m bone scanning, which reveals initially diminished radioactivity in areas of infarction associated with reduced vascularity and later increased tracer uptake secondary to augmented bone activity.[324,361,362] Reversible occlusion in small blood vessels can be identified with thin-section CT scans of the chest, and perfusion defects secondary to throm-

boemboli are revealed with $\dot{V}/\dot{Q}$ lung scans even when chest radiographs are normal.[360,386] Thin-section CT scans can indicate the presence of interstitial lung disease associated with lung injury, and these findings may be present despite normal pulmonary function testing.[376]

Pulmonary function testing in asymptomatic individuals with sickle cell disease reveals reductions in SVC, FVC, FEV_1, FRC, ERV, TLC, $FEF_{25-75\%}$, peak expiratory flow rate, dynamic and specific CL, work capacity, and anerobic threshold; elevations in $\dot{V}E$ and RQ; and a variable FEV_1/FVC ratio.[332,375,387-392] Airway reactivity, particularly of the small airways, also occurs.[391] In addition, infants with sickle cell disease have narrowing in small airways even prior to the occurrence of vaso-occlusive crises and the ACS.[393] As SCLD develops, decreases in the FEV_1/FVC ratio occur.[375] The DLCO is usually normal before the teenage years and subsequently increases when corrected for anemia and lung volume (DLCO/VA), perhaps secondary to an augmented pulmonary capillary blood volume.[388,394] However, the DLCO/VA ratio is diminished when compared with control values as a result of a low membrane diffusing capacity.[387,394]

The reductions in lung volumes, which are unlikely to occur during the first decade of life, reflect the presence of a short and narrow chest wall in relation to standing height and recurrent episodes of pulmonary disease with subsequent pulmonary fibrosis[387,388] (see Box 75-9). When these changes occur during the teenage years before the symptoms of SCLD, they can predict later development of SCLD.[375] S-thal disease and SC disease are also associated with decreased lung volumes, whereas lung volumes, DLCO, and exercise tolerance in settings of ambient O_2 as low as 18% are normal in SA trait.[389,395,396]

O_2 desaturation during sleep without evidence of central or obstructive apnea can occur in sickle cell disease and SA trait and may precipitate RBC sickling and crises.[333] In addition, obstructive sleep apnea secondary to enlarged tonsils can contribute to nocturnal O_2 desaturation.[397]

TREATMENT

Therapy includes appropriate antimicrobial agents for pulmonary infections and should provide coverage for penicillin-resistant *S. pneumoniae*, methicillin-resistant *S. aureus*, ampicillin-resistant *H. influenzae*, *C. pneumoniae*, *M. pneumoniae*, and *L. pneumophila*.[321,398,399]

Antibiotics should be instituted prior to identification of the specific etiologic agent because infections, particularly pneumococcal pneumonia, can be fulminant and life-threatening with hemoglobin SS.[321] Adequate hydration, analgesics, supplemental O_2 administration, correction of acidosis, bronchodilators, and folic acid supplementation are important therapeutic adjuncts.[319,323,326,349,353,355,377] However, vigorous administration of hypotonic saline for hydration, which may alter hydrostatic and oncotic pressures, and narcotics, which may augment vascular permeability, can precipitate pulmonary edema.[321,341,355,400] Corticosteroids can inhibit release of inflammatory mediators associated with hypoxemia and diminish the manifestations of the ACS.[323,355,358,359]

RBC transfusions to maintain a hemoglobin level of 11 to 12 g/dL, a hemoglobin A level of at least 30%, and/or a hemoglobin S level of less than 20% prevent RBC sickling, improve the O_2-carrying capacity of hemoglobin, and reduce the incidence and severity of ACS, myocardial ischemia, and endothelial hyperplasia leading to SCLD.[326,355,359,373,375,377] In addition, exchange transfusion with hemoglobin A improves the O_2-carrying capacity of hemoglobin and thus exercise performance.[389] Chronic transfusion therapy enhances growth and can prevent crises and ACS.[321,323,359,373,401] However, it can cause alloimmunization and iron overload, which can be prevented with chelation with deferoxamine.[321,323,359,371]

Bronchoscopy to relieve airway mucoid impaction associated with plastic bronchitis aids in reducing hypoxemia.[357,369] Use of CPAP or BiPAP can help reduce splinting, hypoventilation, atelectasis, regional hypoxemia, and RBC sickling.[326] Frequent use of incentive spirometry may diminish chest pain and prevent atelectasis and hypoxemia.[326,355,402]

Additional therapeutic modalities for sickle cell disease include splenectomy after 2 years of age to prevent sequestration crises; oral penicillin administered prophylactically starting in infancy to reduce the morbidity and mortality of pneumococcal infections; administration of pneumococcal, influenza, *H. influenzae* type b, and meningococcal vaccines with subsequent boosters when appropriate to confer immunologic protection against *S. pneumoniae*, influenza virus, *H. influenzae* type b, and *Neisseria meningitidis;* and administration of hepatitis B vaccine because of the necessity for multiple blood transfusions.[319,321,323,341,346,350,353,371,399] Pneumococcal infections may occur despite the use of penicillin prophylaxis and pneumococcal vaccine if penicillinase-producing organisms are present or if antibody production is insufficient.[350,398] Administration of palivizumab to prevent RSV infection should be considered for young children with sickle cell disease meeting selective criteria for increased severity of RSV bronchiolitis and pneumonia.[403]

Oral hydroxyurea increases synthesis of fetal hemoglobin (hemoglobin F) in RBCs, reduces the level of hemoglobin S, decreases the activity of VCAM-1, and is oxidized by heme to form NO.[323,326,328,359,404-407] It decreases the incidence of RBC sickling and vaso-occlusive crises, reduces RBC adhesion to vascular endothelium, and can prevent the ACS.

Because serum magnesium levels are reduced in sickle cell disease and diminish further with hydroxyurea, administration of supplemental magnesium may be necessary with hydroxyurea therapy.[405]

Experimental therapy includes inhalation of NO for as long as four hours, which can depress VCAM-1 activity, increase oxyhemoglobin levels, enhance NO transport on hemoglobin S, improve $\dot{V}/\dot{Q}$ imbalance, and reduce RBC sickling, vaso-occlusive crises, and pulmonary hypertension.[326,329,335,371,408] Other modalities consist of the use of chemotherapeutic agents, such as 5-azacytidine and decitabine, which elevate hemoglobin F levels and reduce the incidence and severity of vaso-occlusive crises and RBC sickling; butyrate compounds, which increase hemoglobin F levels by stimulating fetal globin genes; oral L-arginine, which is a substrate for NO synthesis, is reduced in sickle cell disease, and can reduce pulmonary hypertension; and the combination of oral hydroxyurea and L-arginine.[330,371,407,409-411] Transplantation with allogeneic bone marrow and hematopoietic stem cells using cord blood is curative for sickle cell disease.[407,412-417] The incidence of ACS diminishes, lung function plateaus, and functional asplenia improves.[321,414] Gene

replacement therapy with lentiviral and retroviral vectors has also been investigated.[323,327,407,412,418]

Thalassemia

GENETICS, PATHOGENESIS

The more frequently occurring types of thalassemia are caused by an absence of or reduction in the synthesis of α or β chains.[325,419-422] Mutations on chromosomes 16 (for α chains) and 11 (for β chains) are responsible for these alterations.[325,419,421,422] The resultant RBCs have clumps of the unaffected, normally produced chains, which occur in excess, form inclusions, and injure cell membrane integrity.[419] Reduced RBC survival time and intramedullary RBC destruction contribute to the resulting hemolytic anemia, and ineffective erythropoiesis is present.[325,419,423] Hypercoagulability, tissue anoxia, increased blood volume, high-output cardiac failure, and infections are characteristic.[325,419,423] In addition, excessive iron deposits from chronic hemolysis and repeated blood transfusions cause cardiac and liver failure and pancreatic dysfunction with insulin-dependent diabetes mellitus, which can also contribute to lung disease.[325,419,422,423] Iron accumulation in PAMs and airway epithelium enhances free O_2 and hydroxy radical formation, with resultant airway and interstitial injury in the lung.[424-431]

The homozygous β-thalassemias (thalassemia major, thalassemia intermedia) are associated with severe microcytic, hypochromic anemia; extramedullary hematopoiesis; hypersplenism; hepatosplenomegaly; lymphadenopathy; growth retardation; bony changes, including frontal and parietal bossing and mandibular and malar prominence; and shortened survival span.[325,419,421-423]

The heterozygous β-thalassemias (thalassemia minor, thalassemia minima) produce mild, if any, anemia and clinical manifestations.[325,419,421,422]

The α-thalassemias include a homozygous form associated with absence of all four α chains, hydrops fetalis, and perinatal death.[419] The heterozygous forms of α-thalassemia consist of hemoglobin H disease with absence of three α chains and moderately severe anemia; α-thalassemia trait with two missing α chains and mild chronic anemia; and a silent carrier type with only one α chain and no anemia or symptoms.[419,420] However, genetic heterogeneity, that is, different combinations of these genes, can cause variable phenotypic expression.[432]

CLINICAL FEATURES

Pulmonary disorders occurring in thalassemia are primarily described in β-thalassemia (Box 75-11). Severe pulmonary infections occur in β-thalassemia, particularly because the presence of excess iron enhances microbial growth and impairs cytotoxicity, cellular immunity, and activity of PAMs.[325,420,426,433] Hemolytic, sequestration, and aplastic crises often secondary to parvovirus B19 infection occur.[325,434] A hemothorax can result from extramedullary hematopoiesis in the chest wall.[435] Recurrent chest pains and pulmonary thromboembolism are associated with thrombocytosis postsplenectomy.[420] Pulmonary arterial hypertension, cor pulmonale, cardiomyopathy, congestive heart failure, and dysrhythmias resulting from iron deposits are the usual causes of death.[325,422,436,437]

Box 75-11 Pulmonary Disorders Associated with Thalassemia Major

Pneumonia
Chronic pneumonitis
Hemothorax
Pulmonary edema
Pulmonary thromboembolism
Pulmonary arterial hypertension
Cardiac: cor pulmonale, right and left ventricular hypertrophy, dysrhythmias, cardiomyopathy, congestive heart failure

Other pulmonary disorders relate to therapy for β-thalassemia, with serial blood transfusions to maintain a hemoglobin level of at least 9 to 10 g/dL and use of the iron-chelating agent, deferoxamine.[423,424,430,431,438-444] Although children with thalassemia intermedia who never receive blood transfusions have elevations in FRC, RV, and the RV/TLC ratio, which indicate the presence of abnormal lung function secondary to the disease,[438] multiple blood transfusions in thalassemia major are associated with restrictive lung disease, small airway obstruction, air-trapping, alterations in DLCO, and hypoxemia. These are observed as reductions in FVC, FEV_1, FRC, ERV, TLC, MMEF, maximal expiratory flow rates at 60% TLC, $FEF_{25-75\%}$, static and dynamic CL, and PaO_2; elevations in RV, the RV/TLC ratio, lung elastic recoil pressure, Raw, and $\dot{V}E$; and variable measurements of DLCO corrected for hemoglobin concentration[424-429,438-442,445,446] (Table 75-11). These findings are unchanged with diuresis; improve somewhat after splenectomy, that is, VC and ERV increase and RV decreases; and, when measured before and after a blood transfusion, indicate further reductions in FVC and PaO_2 after the transfusion.[441,442] The presence of massive hepatosplenomegaly can impair chest wall mobility and contribute to these reductions in lung volumes.[439]

Exercise testing of individuals with thalassemia major reveals reduced exercise tolerance and hypoventilation, with reductions in anerobic threshold, $\dot{V}E$, $\dot{V}O_2$, O_2 pulse, and ventilatory equivalents for O_2 ($\dot{V}E/\dot{V}O_2$) and CO_2 ($\dot{V}E/\dot{V}CO_2$) and elevations in end-tidal CO_2, cardiac output, and heart rate.[447-449] Only the anerobic threshold, $\dot{V}O_2$, O_2 pulse, and $\dot{V}E/\dot{V}CO_2$ increase somewhat after a blood transfusion, most likely resulting from improved arterial oxygenation and enhanced availability of O_2 to exercising muscles.[447-449]

Histologic observations of the lungs in thalassemia major indicate interstitial fibrosis; subpleural emphysema; vascular congestion and fibrosis; pulmonary angiodysplasia; emboli from bone marrow and thrombi; and hemosiderin, iron, and lipofuscin deposits in PAMs, epithelial cells, smooth muscle, blood vessels, and interstitial connective tissue[439,450] (see Table 75-11). This helps explain the occurrence of restrictive lung disease, reduced DLCO, and hypoxemia.[439,450] CT scans of the chest reveal air-trapping and interstitial fibrosis.[425,427] Elevated numbers of lymphocytes and iron-containing PAMs are identified in BAL, indicating a lymphocytic alveolitis.[427]

Intravenous infusions of deferoxamine to prevent iron accumulation and hemosiderosis are associated with an acute pulmonary disorder characterized by fever, tachypnea, a dry

Table 75-11
Correlation of Histologic Features and Functional Abnormalities of the Lung in Thalassemia Major

Histologic Features	Pulmonary Function Testing
Parenchymal	
Interstitial fibrosis	↓ Lung volumes, ↓ D_{LCO}, ↓ C_L, hypoxemia, ↑ $\dot{V}_E$
Subpleural emphysema	air-trapping (↑ RV, ↑ RV/TLC), ↑ elastic recoil, hypoxemia, $\dot{V}/\dot{Q}$ imbalance
Hemosiderin, iron, and lipofuscin deposits	↓ D_{LCO}, ↓ C_L
Ferrugination of interstitial and airway connective tissue	↓ D_{LCO}, ↓ C_L, ↓ airflow rates in small airways, ↑ Raw
Chronic interstitial pneumonitis	↓ Lung volumes, ↓ D_{LCO}, hypoxemia, $\dot{V}/\dot{Q}$ imbalance
Pulmonary edema	↓ Lung volumes, ↓ D_{LCO}, ↓ C_L, ↓ airflow rates in small airways, ↑ Raw, hypoxemia, $\dot{V}/\dot{Q}$ imbalance
Vascular	
Pulmonary angiodysplasia	Hypoxemia, $\dot{V}/\dot{Q}$ imbalance
Vascular fibrosis	↓ D_{LCO}, hypoxemia, $\dot{V}/\dot{Q}$ imbalance
Ferrugination of vascular connective tissue	↓ D_{LCO}, ↓ C_L
Thromboemboli	Hypoxemia, $\dot{V}/\dot{Q}$ imbalance
Bone marrow emboli	Hypoxemia, $\dot{V}/\dot{Q}$ imbalance

↑, increased; ↓, decreased; D_{LCO}, diffusing capacity; C_L, lung compliance; $\dot{V}_E$, minute ventilation; RV, residual volume; TLC, total lung capacity; $\dot{V}/\dot{Q}$, ventilation/perfusion; Raw, airway resistance.

cough, hypoxemia, and bilateral interstitial pneumonitis radiographically.[430,434,441,442] Diffuse alveolar damage, interstitial inflammation and fibrosis, and mast cell proliferation with fixation of IgE antibody observed with immunofluorescence are also present.[443] Pulmonary function testing reveals restrictive lung disease with reductions in FVC, FEV_1, and TLC and air-trapping with elevations in the RV/TLC ratio.[429,430,443] Resolution may be slow even with discontinuation of the drug and corticosteroid therapy.[443]

TREATMENT

In addition to serial blood transfusions and deferoxamine administration, therapy of thalassemia includes splenectomy to relieve abdominal pressure resulting from massive splenic enlargement and to control hypersplenism, which is evidenced by an increasing requirement for blood transfusions; oral penicillin prophylaxis postsplenectomy; immunizations with the pneumococcal, *H. influenzae* type b, influenza, meningococcal, and hepatitis B vaccines; and daily folic acid supplementation.[325,419,421,423,424] Experimental procedures include gene therapy and administration of hydroxyurea, butyrate, and 5-azacytidine, which enhance fetal hemoglobin synthesis and decrease the percentage of abnormal hemoglobin and the frequency and severity of hemolysis.[325,327,419,421-423,451] Transplantation with hematopoietic stem cells from peripheral blood, bone marrow, or umbilical cord is curative.[412,419,421,423,444]

Familial Dysautonomia

GENETICS, RISK FACTORS

Familial dysautonomia (Riley-Day syndrome, hereditary sensory neuropathy type III) is an autosomal recessive neurologic disease characterized by abnormalities of the autonomic, sensory, and central nervous systems and specific clinical features[452-456] (Box 75-12). It occurs in 1 of 3600 live births of Ashkenazi Jewish ancestry, is associated with mutations of the *IKAP* (1κB kinase complex-associated protein) gene on chromosome 9 at the q31-33 locus, and can be diagnosed prenatally.[456-459] An enzyme involved with dopamine catabolism appears to be deficient, as reflected by reduced urinary vanillylmandelic acid levels.[453,460] Histopathology reveals loss of neurons and atrophied nerve fibers in the reticular formation of the pons and medulla; cerebellum; nucleus of the vagus nerve; sympathetic, parasympathetic, and dorsal root ganglia; and along the spinal cord in the spinothalamic tract and posterior columns.[453,454,461]

Box 75-12 Characteristic Features of Familial Dysautonomia

- Dysautonomic crises
  - Episodic vomiting
  - Diaphoresis
  - Hypertension
  - Tachycardia
  - Skin blotching
- Typical facies
- Feeding disturbances
  - Swallowing difficulties with excessive salivation and drooling
  - Absent gag reflex
  - Esophageal dysmotility
  - Alterations in taste perception, particularly to bitter or sweet substances
- Growth retardation
- Hyporesponsiveness to temperature
- Recurrent fevers
- Absent lacrimation
- Corneal ulcers
- Insensitivity to pain
- Postural hypotension
- Ataxia
- Seizures
- Psychomotor retardation
- Nasal speech

PATHOGENESIS, CLINICAL FEATURES

Individuals with familial dysautonomia have recurrent wheezing and pneumonia secondary to aspiration from GER and oropharyngeal secretions and bronchiectasis resulting from repeated pulmonary infections[452,453,456,462-464] (Box 75-13). GER may be overshadowed clinically by autonomic dysfunction and can cause autonomic symptoms, that is, syncope, hypotension, and bradycardia, without emesis.[462] Insensitivity to pain and inadequate cough and gag reflexes contribute to an inability to mobilize aspirated material.[452,454,457,464] Atelectasis, air-trapping, and pneumothoraces can occur.[452] Kyphoscoliosis contributes to reactive airway disease and alterations in pulmonary function.[452,453,464,465] Neonatal respiratory difficulties include delayed initiation of breathing, difficulty in coordination of sucking with swallowing resulting

Box 75-13 Respiratory Disorders Associated with Familial Dysautonomia

Pulmonary Disorders

Reactive airway disease
Pneumonia: infectious, aspiration
Tracheobronchitis
Bronchiectasis
Atelectasis
Pneumothorax

Chest Wall Disorders

Kyphosis
Scoliosis

Disorders of Control of Breathing

Delayed initiation of breathing in neonate
Diminished responses to hypoxia and hypercapnia
Breath-holding with syncope
Sleep apnea

in aspiration of feedings, and meconium aspiration pneumonitis.[452,466]

Diminished responses to hypoxia and hypercapnia cause abnormalities in control of breathing, including breath-holding with syncope and nonresponsiveness to hypoxia while swimming underwater, resulting in drowning[452-454,465] (see Box 75-13). Irregular breathing patterns and apnea can occur during sleep.[452,464,465]

DIAGNOSIS

The history, physical examination, and laboratory and radiographic studies help in the diagnosis. The presence of repeated pneumonias, episodes of cyclic vomiting, temperature instability with recurrent fevers, and mottling of the skin in a child whose family is of Ashkenazi Jewish descent suggests the diagnosis.[452,453,460,466] Familial dysautonomia can be diagnosed in the neonate who is likely to be born full-term in a breech presentation, small for gestational age, meconium-stained, and hypotonic and has respiratory distress, incoordination of suck and swallow, feeding difficulties, lack of weight gain, temperature instability, and mottling of the skin.[452,459,466] Three clinical tests that can be used as early as 3 days of life are helpful in confirming the diagnosis[452,453] (Table 75-12). Pulmonary function studies reveal reduced lung volumes, airflow rates, and DLCO measurements and hypoxemia at rest and with exercise, which correlate with the repeated episodes of lung infections.[465] Pneumonia, atelectasis, air-trapping, and pneumothoraces occurring during acute episodes of respiratory distress are observed on chest radiographs. Residual markings from repeated episodes of pneumonia may be present radiographically. Fluoroscopic examination of ingested barium may reveal GER and oropharyngeal aspiration of the barium. A salivogram with a radioactively labeled contrast material can diagnose aspiration of oropharyngeal secretions.

TREATMENT

Therapy includes the use of appropriate antibiotics for lung infections; bronchodilators, anti-inflammatory agents, and leukotriene inhibitors for wheezing; chest physical therapy and airway clearance devices for mobilization of respiratory secretions; and supplemental O_2 for hyoxemia. Daily use of high-frequency chest wall oscillation can prevent pneumonia, increase O_2 saturation, and improve lung function.[464] β-Adrenergic bronchodilators are used with caution because familial dysautonomia is associated with reduced sympathetic neuronal innervation and augmented sensitivity to sympathomimetic agents.[452,463,464] Feeding difficulties are addressed with enteral nutrition, such as a gastrostomy or jejunostomy tube, and a fundoplication if GER is present.[462] Maintenance of a patent airway, often with a tracheostomy and laryngotracheal separation, is helpful for preventing aspiration of saliva and for suctioning and removing secretions. Adequate hydration, appropriate temperature control, and aggressive airway care, including endotracheal intubation, assisted ventilation, BiPAP or CPAP, antibiotics, and chest physical therapy, during

Table 75-12
Clinical Tests Used in the Diagnosis of Familial Dysautonomia

	Histamine Test	Methacholine or Pilocarpine Test	Observation of Tongue
Procedure	Intradermal injection of 1 : 1000 dilution of histamine phosphate, use 1 : 10,000 dilution in infant	Instillation of 2.5% methacholine or 0.0625% pilocarpine into conjunctival sac of one eye, comparison of both eyes every 5 minutes for 20 minutes	Examination of tip and sides of tongue for red, vascularized papillae
Normal response	Pain and erythema, development of central wheal with surrounding axon, flare of erythema measuring 1-3 cm in radius, wheal and axon flare occur within 10 minutes	No effect	Red, vascularized papillae at tip and sides of tongue
Response in familial dysautonomia	↓↓ Pain, absence of axon flare	Meiosis in eye with methacholine or pilocarpine	Absent fungiform papillae with smooth and pale sides and tip of tongue, lack of vascularization
False-negative results	None	None	None
False-positive results	Congenital sensory neuropathy, atopic dermatitis	Disorders with parasympathetic denervation	Present

↓, decreased.

the perioperative period help reduce the incidence and severity of post-operative lung infections and atelectasis.[463] Because responses to hypoxia and hypercapnia are diminished, administration of drugs less likely to cause respiratory depression, that is, non-narcotic agents, can help prevent post-operative respiratory difficulties.[463] Gastric decompression and sedation aid in the treatment of dysautonomic crises after surgery.[463] Although individuals with familial dysautonomia are surviving into adulthood, pulmonary infections, sepsis, cor pulmonale, and respiratory arrest while asleep or precipitated by hypotension remain frequent causes of death.[452,465,467]

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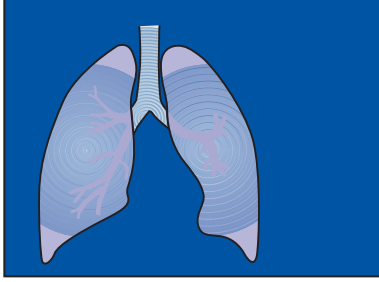

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