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27 BRONCHIOLITIS

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Acute viral bronchiolitis is a clinically diagnosed condition characterized by a wheezing illness associated with an upper respiratory tract infection (URTI). It typically presents with coryza and low-grade fever that progresses to cough; tachypnea; hyperinflation; intercostal chest wall retractions; grunting; nasal flaring; and diffuse crackles, wheezes, or both.[1] Most definitions of bronchiolitis limit the affected age group to younger than 2 years of age, with some limiting it even further, to 12 months of age. Bronchiolitis is characterized by acute inflammation, edema, necrosis of small airway epithelial cells, increased mucus production, and bronchospasm.[2] Worldwide, it is one of the most common respiratory tract infections of infants.

INCIDENCE

Respiratory syncytial virus (RSV) is the most common etiology for bronchiolitis, with the highest incidence of infections in North America from December to April of each year.[3] In warmer climates, the first presentations of RSV tend to occur earlier, during the fall or summer months.[4]

In North America, bronchiolitis is the leading cause of hospitalization for infants younger than 1 year of age.[5,6] An estimated 75,000 to 125,000 American infants are hospitalized each year with this illness, representing approximately 2% to 3% of all children affected with bronchiolitis.[7,8] In both Canada and the United States, admissions for this illness have increased 1.4- to 2.4-fold over the last decade, and it has been associated with increasing morbidity and cost.[7,9] It is estimated that annual health costs associated with bronchiolitis reach $1 billion in the United States.[8]

CLINICAL PRESENTATION

Bronchiolitis is virally induced bronchiolar inflammation. As such, its clinical manifestations closely resemble those of an older child with asthma. There has been much debate about a definition for bronchiolitis as it is a clinical diagnosis and, as such, relies upon clinician judgment of presenting signs and symptoms. The American Academy of Pediatrics Clinical Practice Guideline defines bronchiolitis as "a constellation of clinical symptoms and signs including a viral upper respiratory prodrome followed by increased respiratory effort and wheezing in children less than two years of age."[2] Infants with bronchiolitis often have abnormal vital signs. For children with bronchiolitis, respiratory rate is often higher than 50 to 60 breaths per minute, and often heart rate is increased as well. Elevated body temperature may or may not be present; when present, fever may reach as high as 41° C. Oxygen saturation measurements by pulse oximeter are commonly used to assess children with bronchiolitis. Although ubiquitous in most health care settings, pulse oximeters are not without their limitations; they can misread the oxygen saturation due to normal monitor variations (+/–2%), motion artifact, or poor placement.[10] Clinicians must take care to confirm a hypoxemic reading on a pulse oximeter, prior to initiating oxygen therapy. While there is no one clinical sign or symptom that accurately diagnoses hypoxemia, studies suggest that cyanosis, grunting, difficulty feeding, and level of mental alertness are predictive.[11] Manifestations of URTI, including mild conjunctivitis, otitis media, and pharyngitis, are present in many of the patients.

The clinical presentation of bronchiolitis can be quite variable, both over time and between patients. A child's manifestations may range from mild signs of respiratory distress with transient events such as mucous plugging, all the way to apnea and respiratory failure. Excessive nasal secretions may lead to upper airway obstruction, with both inspiratory and expiratory noise on auscultation. Increased work of breathing is manifested as nasal flaring, intercostal retractions, subcostal retractions, and use of accessory muscles. Upon auscultation, diffuse bilateral wheezes and crackles are often present; the expiratory phase of respiration also can be prolonged. Due to hyperinflation of the lungs secondary to air trapping, it is not uncommon to find the liver and spleen to be palpable in the abdominal exam of an infant with bronchiolitis.

As with any illness of early childhood, it is key to assess the hydration and feeding status of a child with bronchiolitis. This can be done through inquiry regarding total volume of fluid intake, number of wet diapers, presence of tears, and the child's activity level. If care is not taken to address fluid intake early in the child's course of illness, increased work of breathing combined with decreased intake can rapidly lead to dehydration.

Certain underlying conditions can predispose a child to a more turbulent course of illness with bronchiolitis. When inquiring about a child's medical history, care should be taken to inquire about prematurity, chronic lung disease, cardiac disease, immunodeficiency, and neuromuscular disorders.[12]

The utility of radiographs in the diagnosis of bronchiolitis is limited. When available, the radiographic findings tend to be nonspecific and include hyperinflation and patchy atelectasis. Occasionally, peribronchial infiltrates, consolidation, pleural fluid, or pneumonia may be seen.

ETIOLOGIC AGENTS

Respiratory syncytial virus (RSV) is the predominant etiologic agent for acute viral bronchiolitis, and 50% to 80% of cases are attributed to this virus.[13] Ninety percent of children will have been infected with RSV by

2 years of age.[14] Unfortunately, RSV infection does not result in long-term immunity, and re-infections are commonly experienced throughout childhood and into the adult years.

Recently, there has been a notable increase in the number of other viruses recognized as etiologic agents for bronchiolitis. This is due, in great part, to the availability of highly sensitive, molecular amplification-based diagnostic testing. These other viruses include rhinovirus, adenovirus, coronavirus, enterovirus, parainfluenza virus type 3, influenza, and the recently identified human metapneumovirus (HMPV).[12] HMPV is a new paramyxovirus that was first isolated in 2001 from young children with respiratory tract disease.[15] It is now thought to be responsible for up to 19% of cases of bronchiolitis and is considered the second most common cause of bronchiolitis, after RSV.[16] As with most respiratory viruses, there is seasonal variation in occurrence. Peak occurrence is in the late winter/early spring in North America and Europe, which is slightly after RSV's peak activity.[17]

PATHOLOGY

Acute viral bronchiolitis is characterized by extensive inflammation of the airways, increased mucus production, airway cell necrosis, and some bronchoconstriction.[18] RSV, the most common infecting virus in bronchiolitis, binds to toll-like receptor-4 (TLR-4) on epithelial cells, fuses its membrane with the cell membrane, and causes both direct cellular and ciliary damage and an indirect inflammatory effect on the respiratory tract.[19] The infecting virus (usually RSV) then replicates, causing epithelial cell necrosis and ciliary destruction.[16] This cell destruction triggers an inflammatory response, and infiltration of the submucosa with both neutrophils and lymphocytes (Fig. 27-1). Thick mucus plugs are created by increased mucus secretion from goblet cells combining with desquamated epithelial cells. These mucus plugs result in bronchiolar obstruction, leading to air-trapping and varying degrees of lobular collapse. These mechanisms cause ventilation-perfusion mismatch, and ultimately hypoxemia.[20]

The immunopathogenesis of RSV bronchiolitis is still poorly understood. There is seemingly contradictory evidence regarding the role of T cells in the development of RSV bronchiolitis. Some studies show that specific T cells are required for pathology and actually enhance the severity of disease.[21,22] In contrast, recent studies have demonstrated that CD8+ T cells can protect against RSV-induced disease.[23,24] There is little doubt that T cells have an important role in RSV bronchiolitis. This is witnessed by the RSV vaccine trial in the 1960s in which the inactivated viral vaccine did not protect immunized children from natural infections.[25] In fact, it paradoxically led to more severe cases and two deaths in those who were immunized. Considering this historical issue and newer emerging evidence, it is likely that there are coexisting protective and disease-promoting adaptive immune mechanisms at play.[26] Future research should clarify this apparent conundrum.

DIAGNOSIS

The diagnosis of bronchiolitis is essentially based upon clinical presentation. The constellation of presenting signs and symptoms combined with the patient's age and the presence of a bronchiolitis-related virus in the community (usually RSV) make the diagnosis likely.

Laboratory testing of nasopharyngeal aspirates for bronchiolitis-related viruses can support patient diagnosis, aid with syndromic surveillance, and help inpatient bed assignment (see Chapter 24). For most cases of bronchiolitis, a clinical diagnosis is adequate, and viral testing adds little to routine management.[2] A blood gas (capillary, venous, or arterial) can aid with assessment of gas exchange and acidosis in a child with moderate to severe respiratory distress. If a child has poor oral intake and signs of dehydration, one can assess electrolyte

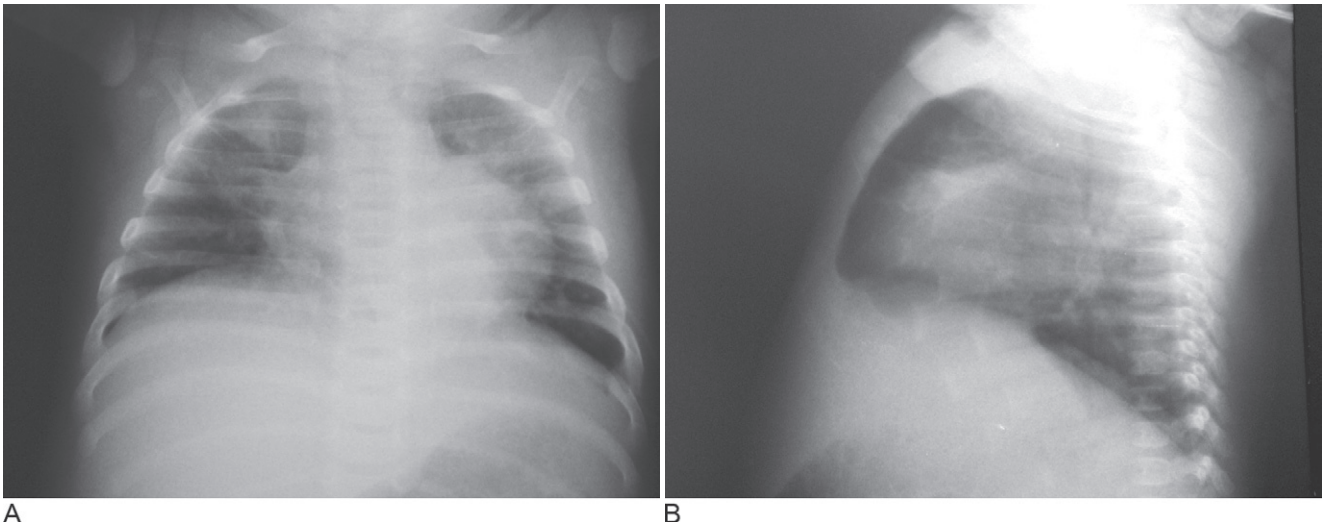

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FIGURE 27-1. Histologic section of a bronchiole from an infant who died from acute severe RSV bronchiolitis. Peribronchiolar lymphoid infiltration and plugging of the lumen with exudate and cellular debris is shown. The surrounding alveoli are essentially spared. (Courtesy of Dr. W. Aherne.)

abnormalities and extent of dehydration can by measuring the plasma BUN, creatine, and electrolytes. If performed, the white blood cell count can range from low to normal to high, with counts as low as 5000 cells/mm^3 or as high as 24,000 cells/mm^3. [27] However, there are no laboratory tests that are specific to bronchiolitis, and as such, no single laboratory test can confirm or rule out the diagnosis of acute viral bronchiolitis.

Radiologic testing, mainly in the form of chest radiography, is commonly performed in children with suspected bronchiolitis. It is estimated that up to 60% of children presenting to the emergency department or admitted to an inpatient ward receive a chest radiograph.[28–30] Despite its high frequency of use, there is little evidence to support the effectiveness of this practice. In a large survey of 30 children's hospitals in the Unites States, performing chest radiographs for infants with bronchiolitis was associated with increased likelihood to prescribe antimicrobials and increased length of stay. This is likely due to the fact that bronchiolitis-related atelectasis is difficult to distinguish from consolidation on a radiograph.[1] A study of the utility of chest radiographs in acute bronchiolitis included 265 children who underwent radiography after a clinical diagnosis of bronchiolitis. [31] Ninety-three percent of the patients had "simple bronchiolitis" evident on imaging. The authors also concluded that risk of airspace disease was particularly low in children with hemoglobin oxygen saturations greater than 92% with mild-moderate distress.[31] If performed, a typical radiograph for a child with bronchiolitis will demonstrate hyperinflation, flattening of the diaphragms, peribronchial infiltrates, airway wall thickening, and (occasionally) patchy atelectasis (Fig. 27-2).[32] Currently, there is no evidence to support the routine use of radiographs in a child with typical bronchiolitis; further, there is no benefit evident, even if the child is to be admitted.

When considering the clinical diagnosis of bronchiolitis, it is important to also consider reasonable differential diagnoses. Other causes of respiratory distress to consider include upper airway obstruction (e.g., adenoidal hypertrophy, retropharyngeal abscess), laryngeal obstruction (e.g., croup, foreign body), asthma, pneumonia, and metabolic disorders that mimick respiratory disease (e.g., salicylate poisoning, diabetic ketoacidosis, inborn errors of metabolism). Congestive heart failure (e.g., pre-existing congenital heart conditions, new-onset viral myocarditis) and parenchymal lung disease (e.g., exacerbation of cystic fibrosis, congenital lung disease) may also present in a fashion that is similar to bronchiolitis, or may be exacerbated by bronchiolitis.

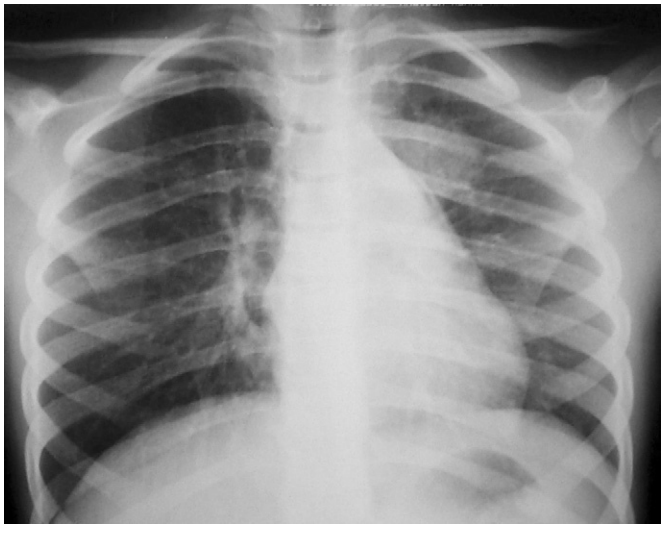


FIGURE 27-2. Chest radiograph of an infant with acute bronchiolitis. (Courtesy of Dr. ME Wohl.)

MANAGEMENT PRINCIPLES

There have been two recent comprehensive evidence-based guidelines for the diagnosis, management, and prevention of bronchiolitis. It is reassuring to note that both the American Academy of Pediatrics (AAP) and the Scottish Intercollegiate Guideline Network (SIGN) performed comprehensive reviews of the literature that led to the same conclusions.[2,33] The cornerstone of bronchiolitis treatment remains supportive care. Most infants with mild bronchiolitis require no specific treatment and can be successfully treated at home. Infants with moderate to severe respiratory distress are often hospitalized; this is approximately 1% to 3% of all children with bronchiolitis. There is great variability in the clinical approach to treatment of bronchiolitis.[30,34–36] Despite four decades of research, there is much confusion and controversy regarding the treatment of this common life-threatening condition.[37] The following sections will attempt to summarize the currently available medical literature in order to support evidence-based decision making.

Fluid and Hydration Therapy

As previously stated, monitoring of fluid intake and hydration status is key in the assessment of an infant with bronchiolitis. If an infant can breastfeed, this should be highly encouraged, as it contributes to hydration and confers immunologic advantages. Breast milk has been shown to have neutralizing activity against RSV,[38] containing RSV immunoglobulins A and G as well as interferon-α.[39] It is estimated that approximately 30% of children admitted with bronchiolitis require fluid replacement therapy.[40] However, there is a lack of agreement on which method of fluid replacement should be used. Nasogastric feedings may be considered for a child who has decreased oral intake, with mild to moderate respiratory distress. When the respiratory rate exceeds 60 to 70 breaths per minute, there can be an increased risk of food aspiration into the lungs.[41] At this point, intravenous fluids should be considered for maintaining hydration. The evidence to determine the optimal route for fluid replacement in infants with bronchiolitis is currently inadequate. A large randomized multicenter trial is planned by an Australian pediatric emergency research collaborative, which may provide a definitive answer.[42]

Supplemental Oxygen

In the clinical setting, measurement of reduced oxygen saturations and the resultant use of supplemental oxygen is one of the major determinants of both hospital

admission and length of stay.[43,44] Interestingly, there are no studies that examine the effect of oxygen on clinical recovery from bronchiolitis. A recent Cochrane Collaboration review of oxygen therapy for lower respiratory tract infections in children did not identify a single trial comparing oxygen therapy versus no oxygen supplementation.[11] To date, there is no clear direction as to what constitutes a safe admission or discharge hemoglobin oxygen saturation level.[45] The AAP recommends supplemental oxygen if the hemoglobin oxygen saturation is persistently below 90%.[2] Their suggested point of discontinuation of oxygen therapy is when the child's oxygen saturation can be maintained at or above 90% with room air *and* the child is feeding well, with minimal respiratory distress. Premature or low birth weight infants, as well as those with chronic lung disease or congenital heart disease may require further consideration when administering or discontinuing oxygen, as these children are likely to have lower tolerance for hypoxemia and a higher likelihood of severe disease.

Nasal Suctioning

Children with bronchiolitis often suffer from copious, thick nasal secretions. Their young age precludes effective self-clearing of the nasal passages, so nasal suctioning is commonly used both at home and in the hospital setting.[46] While it makes intuitive sense to continue with this practice, to our knowledge there is not a single trial that assesses the effectiveness of nasal suctioning for bronchiolitis.

Chest Physiotherapy

It might be thought that chest physiotherapy would improve the clearance of secretions associated with bronchiolitis and decrease ventilatory effort. However, a recent Cochrane review of three clinical trials of percussion and vibration (techniques used for chest physiotherapy in infants) versus no intervention does not support its routine use. This review concluded that for nonventilated infants with bronchiolitis, chest physiotherapy did not reduce the length of hospital stay or oxygen requirements or improve clinical severity scores.[47]

Albuterol/Salbutamol

Bronchodilators are commonly used in the management of bronchiolitis in North America. However, the evidence to support this practice is not very strong, and the practice remains controversial. A Cochrane review of 22 trials comparing bronchodilator (other than epinephrine) use with placebo for bronchiolitis included data from 1428 infants. Studies of both oral and inhalational short-acting β-2 agonists were included. There was a statistically significant but clinically modest improvement in the overall average clinical score of patients treated with bronchodilators.[48] Of note, there was no improvement in oxygenation. It appeared that bronchodilators have a greater effect in the outpatient setting rather than in the hospital setting. However, patients receiving bronchodilators showed no improvement in hospitalization rates or duration of hospitalization. The authors of this review noted that the effectiveness of bronchodilators for bronchiolitis may have been overestimated, as many of the reviewed studies included patients with recurrent wheezing, a group thought to be clinically different from those with acute bronchiolitis. Overall, it would appear that short-acting β-2 agonists provide, at best, modest transient relief with no clear benefit to hospitalization rates or duration of hospitalization. As such, the AAP has recommended that bronchodilators should not be routinely used in the management of bronchiolitis. They do concede that a carefully monitored trial of an inhaled short-acting β-2 agonist can be considered, and its use can be continued if a beneficial clinical response is documented.[2]

Nebulized Epinephrine

Another commonly used bronchodilator for the treatment of bronchiolitis is nebulized epinephrine, or adrenaline. Just as with short-acting β-2 agonists, the AAP has recommended that nebulized epinephrine should not be routinely used in the management of bronchiolitis.[2] A Cochrane review of nebulized epinephrine for bronchiolitis reviewed 14 trials and included both inpatients and outpatients. For inpatient trials (n = 5), clinical score was improved in the epinephrine group, but oxygen saturation and admission rates did not differ.[49] Outpatient studies (n = 3) demonstrated short-term improvement in clinical scores, oxygenation, respiratory rate, and overall improvement of the patient. Of seven trials comparing epinephrine to salbutamol in both the inpatient and outpatient setting, it appeared that epinephrine might be the preferred drug for outpatients.[49] However, there was insufficient evidence to recommend epinephrine use in the inpatient setting. A carefully monitored trial of epinephrine can be performed for an individual patient, and its use should be continued only if a documented positive clinical response is noted. If the decision is made to test an inhaled bronchodilator, the current state of the evidence would seem to support a trial with epinephrine, first, as it appears to have a slightly greater effect than β-2 agonists. However, given the fact that epinephrine is not available for use in the home setting, the AAP suggests that a β-2 agonist trial might be appropriate in the clinic or nonhospital setting.[2]

Corticosteroids

Corticosteroids can be administered via inhalation or systemically (via oral, intramuscular, or intravenous route). Up to 60% of infants admitted to the hospital receive corticosteroid therapy.[50,51] As with many therapies for bronchiolitis, the use of corticosteroids is controversial.

Systemic corticosteroid use in bronchiolitis is a long and hotly debated topic. A recently completed Cochrane review conducted in 2010 included 17 trials with a total of 2596 infants.[52] Overall, the use of systemic corticosteroids did not demonstrate a benefit. The review concluded that glucocorticoids did not significantly reduce outpatient

visits or length of stay for inpatients. Interestingly, a recent large multicenter, randomized 4-armed trial (n = 800 infants) examined the emergency department use of both oral corticosteroids and nebulized epinephrine in preventing hospital admission.[53] This study demonstrated a possible synergistic effect when combining the two medications in the treatment of bronchiolitis as demonstrated by reduced hospital admissions, as well as shortening both the time to discharge and the duration of some clinical symptoms. Bronchodilator and glucocorticoid synergy is a phenomenon that is well documented with β agonist/steroid use in asthma,[54–56] and it has also recently been seen in other smaller bronchiolitis studies.[57,58] In considering the synergy of epinephrine and oral glucocorticoids, this study should be considered exploratory, as the results were unexpected. Further studies will be required to confirm the finding.

The role of inhaled glucocorticoid use in infants with bronchiolitis has been examined in a systematic review to determine if there was any effect on the prevention of post-bronchiolitis wheezing. Five studies, including 374 infants, were included in the analyses and failed to demonstrate any effect on such wheezing, hospital re-admission rates, or use of bronchodilators.[59] The authors noted that the strength of their recommendations was negatively affected by the small number of participants and the clinical diversity of the studies. Of the two known studies that investigated the role of inhaled glucocorticoids for the treatment of the acute symptoms of the disease, neither has demonstrated any benefit.[60,61] Currently, there is no evidence to support the use of inhaled corticosteroids for acute or long-term benefit in bronchiolitis.

Mucolytics

Since it is known that mucous plugging plays a significant role in the small airway obstruction of bronchiolitis, it would seem reasonable that interventions that might thin airway secretions could improve clinical outcomes. Inhaled hypertonic saline and deoxyribonuclease (DNase) are two such interventions that have been successfully used in cystic fibrosis and are now being considered for bronchiolitis therapy.

While the exact mechanism of action remains unclear, nebulized hypertonic saline is thought to improve mucociliary clearance by causing osmotic movement of water into the airway. A recent Cochrane review of the effects of hypertonic saline reviewed four trials, with a total of 254 infants (189 inpatients and 65 outpatients). Three trials used 3% hypertonic saline combined with either nebulized epinephrine (two studies) or terbutaline (1 study); the remaining trial used nebulized hypertonic saline alone. Overall, patients treated with nebulized 3% hypertonic saline had a significantly shorter mean length of hospital stay (of almost 1 full day) and improved clinical severity scores compared to those who received nebulized normal saline.[62] They also demonstrated no adverse effects with its use. A recent emergency department–based randomized trial of hypertonic saline for bronchiolitis (which is not included in this review) would suggest that the effects of hypertonic saline are not seen immediately, as this trial demonstrated no effect on clinical severity in the first 2 hours posttreatment.[63] While the safety and efficacy evidence for the use of hypertonic saline is compelling, the trials in the review were small and few. Given the lack of adverse events and the possibility of improved outcomes, it seems reasonable to suggest the use of hypertonic saline in acute bronchiolitis. If one plans to use hypertonic saline, the current best recommendation would be to begin its use early, with the expectation that its beneficial effects would not be seen immediately post-use. DNase enhances mobilization of mucus by liquefying mucous plugs, which contain large amounts of lysed inflammatory cell DNA, in the airways.[8] There have been two trials of DNase for bronchiolitis reported in the current literature. To date, DNase has not been found to have any effect on length of stay, clinical severity scores, or duration of oxygen therapy.[64,65]

Leukotriene Modifiers

Leukotrienes are thought to contribute to the airway inflammatory response in bronchiolitis, thus the role of leukotriene modifiers has been explored for this illness. One small trial (n = 53) of daily oral montelukast (versus placebo) failed to demonstrate any difference in length of stay, clinical severity scores, or cytokine levels.[66] In a very large trial of 979 infants, RSV-positive infants were randomized to receive either oral montelukast or placebo.[67] In this study, montelukast did not improve the respiratory symptoms of post-RSV bronchiolitis in children. Currently, there is insufficient evidence to recommend leukotriene modifier use for bronchiolitis.

Heliox Inhalational Therapy

Heliox, a mixture of oxygen and helium, has been used for the treatment of acute asthma exacerbations since 1935.[68] A limited number of studies of heliox use in bronchiolitis have emerged over the last two decades. The mechanism of action for heliox inhalational therapy is not clearly understood. It is proposed that the decreased work of breathing and wheezing that occurs during heliox use might be due to increased flow rate or less turbulent flow, ultimately resulting in better ventilation of distal alveoli.[69] Heliox therapy has been traditionally reserved for the sickest patients. A recent Cochrane review of heliox therapy in bronchiolitis identified four intensive care unit (ICU) trials with a modest total number of patients (n = 84). While the patients benefited from a significantly lower mean clinical score in the first hour post–heliox therapy (versus air or oxygen therapy), there was no clinically significant reduction in rate of intubation, need for mechanical ventilation, or length of stay in the ICU.[70] At present, there is not enough evidence to routinely recommend the use of heliox therapy for severely ill children with bronchiolitis, and there is no evidence for its use in mild to moderately ill infants.

Antivirals

Ribavirin is an inhaled broad-spectrum antiviral agent that is sometimes, albeit controversially, used in the treatment of severely ill or high-risk infants with bronchiolitis.

It is the only antiviral agent licensed for use with RSV bronchiolitis, and it has been shown to provide limited clinical benefit.[16] A Cochrane review of twelve ribavirin trials for infants with RSV lower respiratory tract infections determined that its use may decrease the number of days of hospitalization and mechanical ventilation.[71] However, ribavirin did not reduce respiratory deterioration or mortality. Routine use of ribavirin is not recommended for children with bronchiolitis, as studies are limited, the drug is difficult to administer, and it is potentially toxic.

Antimicrobials

Despite bronchiolitis being recognized as a viral illness, antimicrobials are commonly prescribed. Reasons cited for antimicrobial use include high fever, young age, and concerns of bacterial superinfection.[72,73] A Cochrane review of the use of antimicrobials in bronchiolitis identified only one trial of ampicillin versus placebo, which demonstrated no difference in duration of illness or deaths between the two groups.[74] A recent moderate-sized study (n = 295) of antimicrobial use in infants with bronchiolitis demonstrated that there was no clinical advantage to using antimicrobials in the care of such children. The authors concluded that supportive measures without antimicrobials remained the standard of care in the hospital setting.[75] Given the results of this study and the low rates of serious bacterial co-infections in children with bronchiolitis, the routine use of antimicrobials cannot be recommended.

There has been some recent exploration of the effect of macrolide antimicrobials in lower respiratory tract disease. Macrolide therapy is thought to exert its effect through three potential mechanisms: antimicrobial (through direct bacterial killing action and indirect bacterial modulation), anti-gastroesophageal reflux (via its pro-motility effects), and anti-inflammatory (by altering the release and action of pro-inflammatory cytokines).[76] Currently, studies exist for the use of macrolides in bronchiolitis obliterans, cystic fibrosis, and bronchiectasis.[76] A recent small study (n = 21) of clarithromycin use in acute bronchiolitis suggests that this macrolide had a statistically significant effect on length of stay, use of β-2 agonists, and plasma levels of inflammatory markers.[77] While there is currently no role for the routine use of macrolide therapy in acute viral bronchiolitis, its role remains to be clarified by future research.

Ventilatory Support

When supportive care fails to lead to improvement in the clinical status of a child with moderate to severe respiratory distress, and respiratory exhaustion or failure is imminent, assisted ventilation is the next step. Endotracheal intubation and mechanical ventilation is the time-honored intervention. However, mechanical ventilation is not without risks and complications. As such, clinicians and researchers have considered nasal continuous positive airway pressure (nCPAP) as a less invasive alternative to ventilation. The proposed mechanisms of action for nCPAP in bronchiolitis include a pneumatic splinting effect, which then expands the airway diameter; improved air flow during exhalation; and a decrease in work of breathing.[78] Evidence is quite limited for the use of CPAP with only one trial identified.[79] A recent review of the topic found that there is no evidence that the use of nCPAP in bronchiolitis leads to lower rates of mechanical ventilation.[80] It is possible, however, that early use of nCPAP for moderate to severe bronchiolitis may lead to some modest improvements in cardiorespiratory parameters.[81]

Clinical Pathways

In reviewing the evidence for the treatment of bronchiolitis, it quickly becomes clear that there are many modalities of treatment available and many possible approaches to therapy. The near-exponential increase in evidence, opinions, and advice regarding the treatment of bronchiolitis, coupled with the demands of everyday clinical practice make it very challenging for the average health care professional to keep abreast of the latest approach. Clinical pathways aim to link evidence to practice in a condition-specific manner, thereby optimizing patient outcomes and clinical efficacy.[82] Studies specific to bronchiolitis show that implementation of evidence-based guidelines results in a decrease in the use of unnecessary nasopharyngeal virus testing (52%),[83,84] chest radiographs (14%),[83,84] and bronchodilators (10% to 17%).[83–85] In the reported studies, rate of admission decreased 30%, mean length of stay decreased 17%, and mean costs of respiratory care services decreased 72% to 77%.[83,84]

While clinical guidelines provide generic recommendations, clinical pathways outline the *specific* steps and timeframes in which to realize these said recommendations. A recent elaborate Cochrane review of 27 studies involving 11,398 patients suggests that the use of clinical pathways in general is associated with reduced in-hospital complications and improved documentation, without negatively impacting length of stay or hospital-based costs.[82]

Admission Criteria

There are no clear criteria for determining when to hospitalize children with bronchiolitis. Hospitalization can be considered for infants who have a respiratory rate greater than 60 to 70 breaths per minute or a hemoglobin oxygen saturation less than 90%; those with a history of apnea; and those who are lethargic or dehydrated. Factors that may influence disposition determination include prematurity, very young age, pre-existing cardiopulmonary disease, immunodeficiency, or neuromuscular disorder. An infant's social situation and caregiver exhaustion also play a role in decision making. A recently published abstract has identified that gestational age, heart rate, respiratory rate, respiratory distress assessment instrument score, and oxygen saturation on room air were significantly associated with the development of severe bronchiolitis in a cohort of Canadian infants with bronchiolitis.[86] The utility of such variables for predicting need for admission have yet to be determined.

PREVENTION

Frequent, thorough, and consistent hand hygiene has been shown to reduce the nosocomial spread of RSV.[87] This is a key infection-control principle both in the health care setting and in the home. RSV and other viruses can be spread through secretions, hand contact, and fomites. Viruses, including RSV, have been found on secretion-contaminated beds, toys, crib rails, and tabletops; such organisms can remain viable for many hours.[88,89] The Centers for Disease Control and Prevention has published detailed evidence-based recommendations regarding hand hygiene and antisepsis in the health care setting.[90] Of note, they recommend that hands should be decontaminated prior to and after direct contact with a patient, after contact with inanimate objects in the direct vicinity of a patient, and after removing gloves. Hand hygiene with antimicrobial soap is recommended for visibly dirty hands; otherwise, an alcohol-based rub is preferred.[91]

Currently, no vaccine exists for the prevention of RSV infection, which is the predominant etiologic agent for bronchiolitis. The development of a successful vaccine has been challenging, as immunity to multiple strains of the virus would be required. One would expect that a series of boosters would be necessary for the vaccine to be effective, as natural infection with the virus does not confer long-term immunity.[16]

Passive immunization to RSV has been accomplished through the development of two different products. Their use is currently recommended for infants who are considered at high risk for developing severe RSV bronchiolitis. The American Academy of Pediatrics' Subcommittee of Management and Treatment of Bronchiolitis has outlined groups of infants whom they consider to be high risk for severe RSV and its complications, and for whom they recommend Palivizumab (Table 27-1).[2]

RSV immune globulin (RSV-IG) was the first form of immunoprophylaxis to become available. It was an expensive therapy that required administration of a large volume (15 mL/kg) of fluid over a long period of time (2 to 4 hours). In a moderate sized (n = 249 subjects) randomized, blinded, multicenter trial of RSV-IG, there was an increased incidence of adverse events in the subgroup of infants with congenital heart disease, thus RSV-IG is not recommended for this group.[92]

Palivizumab is a humanized monoclonal antibody, and it has become the passive immunization agent of choice. It is administered as a monthly intramuscular injection over the 5 peak months of RSV season. In a large (n = 1502 subjects) randomized, double-blind, multicenter trial, palivizumab was associated with a 55% reduction in RSV-related hospitalizations, fewer overall days in the hospital, and a lower rate of ICU admissions.[93] These findings were further confirmed through similar results for a study of children with significant congenital heart disease.[94] Ease of administration and lack of interference with routine immunizations are the main considerations in choosing palivizumab over RSV-IG. Unfortunately, palivizumab is quite expensive, and it is estimated to cost $5000 to $6000 per season. Most of the economic analyses of RSV immunoprophylaxis have failed to demonstrate any overall savings in health care expenditure because of the large financial costs of immunizing all at-risk infants.[95–97] While the main advantage of palivizumab is related to its decrease in RSV-related *hospitalizations,* to date none of the five clinical randomized controlled trials have demonstrated a significant decrease in the rate of *mortality* attributable to receiving RSV immune prophylaxis.

DISEASE COURSE AND COMPLICATIONS

The majority of infants infected with RSV and other bronchiolitis-causing viruses develop a mild URTI during the first few days of illness. While some will only have URTI manifestations, up to 40% will then progress to

TABLE 27-1 RECOMMENDED HIGH-RISK GROUPS FOR RSV IMMUNOPROPHYLAXIS WITH PALIVIZUMAB

		IMMUNOPROPHYLAXIS	
Risk Factor	**Details of Risk Factor**	**First RSV Season**	**Second RSV Season**
Chronic lung disease (CLD)	Required medical therapy for CLD within 6 months before onset of RSV season	Y	
	More severe CLD requiring ongoing medical therapy	Y	Y*
History of prematurity	32-35 weeks gestation with 2 or more risk factors† (most benefit in first 6 months of life)	Y	
	Younger than 32 weeks gestation, with or without CLD	Y	
	29-32 weeks gestation (most benefit in first 6 months of life)	Y	
Congenital heart disease	Younger than 28 weeks gestation (most benefit in first 12 months of life)	Y	
Congenital heart disease	Cyanotic heart disease	Y	
	Taking medications for congestive heart failure	Y	
	Infants with moderate to severe pulmonary hypertension	Y	

From American Academy of Pediatrics Subcommittee on Diagnosis and Management of Bronchiolitis. Diagnosis and management of bronchiolitis. *Pediatrics.* 2006;118:1774-1793.

*Please note that data are limited for the use of immunoprophylaxis in the second year of life.

†Risk factors include child care attendance, school-aged siblings, exposure to environmental air pollutants, congenital abnormalities of the airway, and severe neuromuscular disease.

lower respiratory tract involvement (or bronchiolitis), with wheezing, crackles, and varying degrees of respiratory distress.[98] The mean duration of illness is 15 days, and the majority of these infections resolve uneventfully within 3 to 4 weeks.[30,99] Of note, up to 25% of infants with bronchiolitis remained symptomatic after 21 days of illness, in a recent prospective cohort study highlighting the prolonged disease course of this acute illness.[99]

Epidemiologic studies indicate that, while there is a very high degree of morbidity with bronchiolitis, there is low mortality. Over the last decades, it appears that mortality has remained stable for bronchiolitis. Of all children who are hospitalized with bronchiolitis, mortality rate estimates around 1%,[16,100,101] but rates are as high as 3.5% for children with underlying cardiac or chronic lung conditions.[102] Overall, rates of hospitalization have increased up to 2.4-fold.[7,9]

With bronchiolitis, apnea, or risk of apnea, is a cause for concern for caregivers and health care professionals alike and can often lead to hospitalization. Rates of apnea with RSV bronchiolitis range from 1.2% to 23.8%.[103,104] In a recent systematic review, it would appear that the rates of apnea in previously healthy term infants is less than 1%, while infants with risk factors (e.g., prematurity and congenital heart disease) carry a greater risk of occurrence.[105] Occurrence of prolonged or recurrent apnea is a consideration with regard to intubation of a patient; the risk of requiring intubation for hospitalized children with bronchiolitis is estimated at approximately 5%.[100]

Some studies have identified that up to 50% to 60% of children with bronchiolitis may have concomitant acute otitis media.[106,107] Unfortunately, there is no clinical feature that can reliably distinguish viral from bacterial ear infections. While tympanocentesis can reliably accomplish this differentiation, it is considered impractical for the average clinician to engage in this practice. When identified, acute otitis media is best treated as per the well-recognized AAP/American Academy of Family Physicians' guidelines.[108]

Serious bacterial infections, including bacteremia, urinary tract infection, and meningitis are a concern when evaluating febrile infants, including those with bronchiolitis. A number of studies have shown that febrile infants diagnosed with RSV infections are at significantly lower risk of serious bacterial infection when compared to children without RSV infection.[1,109–111] If a child has a bacterial infection, it is likely to be a urinary tract infection.[109] Vey young febrile infants (younger than 3 months of age) with bronchiolitis require careful assessment for the source of their fever. For any febrile infant younger than 4 to 6 weeks of age, most clinicians would perform a full septic workup (including blood culture, blood count, catheter urine sample, chest radiograph, and lumbar puncture), and many would consider at least a partial if not full septic workup for infants between 6 weeks and 3 months of age.[112]

There have been reports of children with inappropriate secretion of antidiuretic hormone associated with bronchiolitis.[113,114] This should be kept in mind, and monitoring of fluid status and measurement of serum sodium levels should be performed, when appropriate, for infants receiving intravenous fluids.

A variety of cardiac manifestations of RSV have been noted, including myocarditis, arrhythmias, and complete heart block.[115–118] Sepsis-like syndrome, in the absence of a secondary bacterial infection, has also been known to occur in children with RSV infection.[104,119] Other extrapulmonary manifestations of severe RSV infection include focal and generalized seizures, focal neurologic findings, and hepatitis.[120]

LONG-TERM SEQUELAE

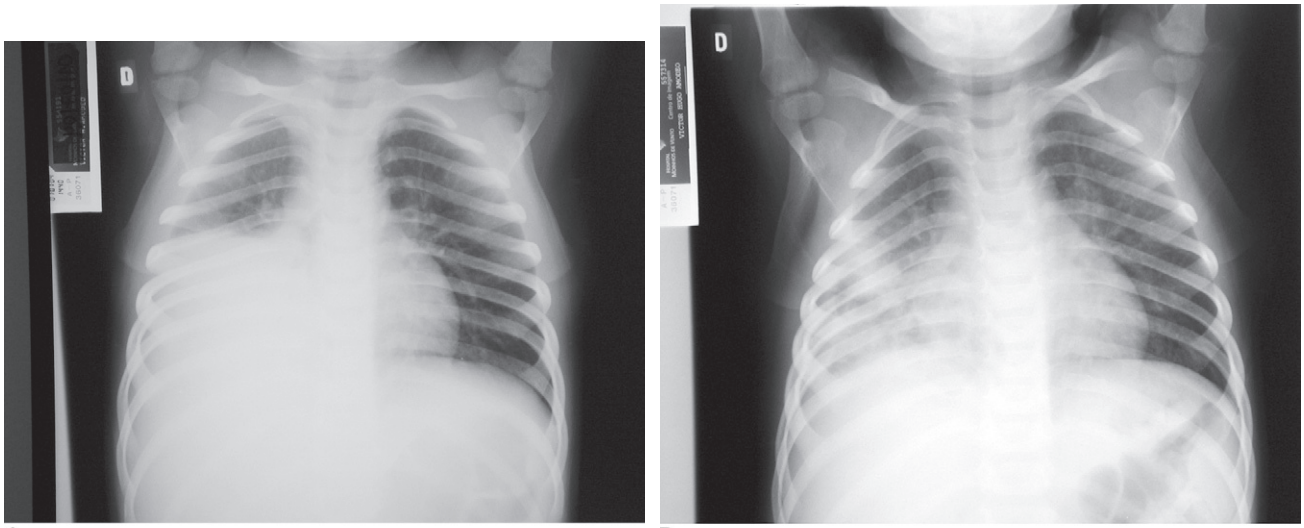
While hospitalization is a major notable outcome of severe bronchiolitis, it is not the only outcome. There are also longer-term complications including bronchiolitis obliterans, allergic sensitization, and the development of wheezing or (arguably) asthma later in life. Studies that attempt to link bronchiolitis in infancy with allergic sensitization and atopic illness have yet to produce clear answers. While some studies have demonstrated an association between the two entities,[121] others have not.[122,123]

BRONCHIOLITIS OBLITERANS

Bronchiolitis obliterans is a rare fibrosing form of chronic obstructive lung disease that follows a severe insult to the lower respiratory tract (see Chapter 59). It was first described by Lange in 1901.[124] Bronchiolitis obliterans results in partial or complete obliteration of the small airways (Fig. 27-3).[125] The exact incidence of childhood bronchiolitis obliterans is not known. The etiology of adult forms of bronchiolitis obliterans includes inhalational injuries, hypersensitivity pneumonitis, post-transplant, and autoimmune disorders.[126] In contrast, childhood bronchiolitis obliterans is most often seen after a severe lower respiratory tract infection. The most common associated viral etiology is adenovirus, especially serotypes 1, 3, 7 and 21,[127,128] however it has been suggested that RSV may cause it as well.[1] Table 27-2 outlines the varied possible etiologies for pediatric bronchiolitis obliterans.

The chain of events leading to bronchiolitis obliterans likely begins with an injury to the epithelial cells of the airways, causing transient derangements in cell function and necrosis. Local necrosis leads to intraluminal accumulation of fibrinopurulent exudate, inducing an overgrowth of the exposed myofibroblasts of the denuded submucosa.[124] The myofibroblast hyperproliferation leads to collagen and acid mucopolysaccharide deposition, with resultant narrowing of the bronchioles. Occasionally, a large intraluminal polyp known as a *Masson body* may develop secondary to histiocyte and capillary proliferation.

The clinical presentation of bronchiolitis obliterans may mimic acute viral bronchiolitis, but often without fever and rhinorrhea. Older patients may complain of dyspnea, cough, or decreased exercise tolerance. Physical findings are quite nonspecific, but expiratory wheezes or crackles may be heard on occasion. In the postinfectious setting, the infant may appear to partially recover from the acute illness, only to have persistent respiratory symptoms. Typically, the respiratory findings persist for more than 60 days.[129] Chest radiographs demonstrate dramatic hyperinflation and bilateral increase in interstitial markings. Bronchiolitis obliterans is most accurately diagnosed by microscopic examination of adequate biopsy material. Transthoracic



A B

FIGURE 27-3. Histologic representation of bronchiolitis obliterans in an 18-month-old child who had severe adenovirus bronchiolitis one year before. The obliterated lumen of the bronchiole is filled with vascularized connective tissue. (From Wohl ME, Chernick V. State of the art: bronchiolitis. *Am Rev Respir Dis.* 1978;118:759.)

biopsy with two tissue site sampling is currently recommended for definitive diagnosis.[124] Because of the invasive nature of this type of diagnostic testing, criteria were created in the 1990s to reflect *bronchiolitis obliterans syndrome,* and they take into account pulmonary function testing as a surrogate for graft dysfunction in lung transplant recipients.[130] High-resolution CT has become an important test in the diagnosis of bronchiolitis obliterans, with mosaic perfusion, vascular attenuation, and central bronchiectasis as key features.[131]

TABLE 27-2 POSSIBLE ETIOLOGIES FOR PEDIATRIC BRONCHIOLITIS OBLITERANS

Post-infectious	Adenovirus types 3, 7, and 21 Influenza Parainfluenza Measles Respiratory syncytial virus (RSV) Varicella Mycoplasma pneumoniae
Post-transplant	Chronic rejection of lung or heart/lung transplantation Graft-versus-host disease associated with bone marrow transplantation
Connective tissue disease	Rheumatoid arthritis Sjögren's syndrome Systemic lupus erythematosus
Toxic fume inhalation	NO_2 NH_3
Chronic hypersensitivity pneumonitis	Avian antigens Mold
Aspiration	Stomach contents: gastroesophageal reflux Foreign bodies
Drugs	Penicillamine Cocaine
Stevens-Johnson syndrome	Idiopathic Drug-induced Infection-related

From Moonnumakal SP, Fan LL. Bronchiolitis obliterans in children. *Curr Opin Pediatr.* 2008;20:272-278.

The morbidity and mortality for bronchiolitis obliterans remains uncertain. Post-adenovirus bronchiolitis obliterans seems to have low mortality, but high chronicity.[132,133] On occasion, gradual resorption of the fibrovascular connective tissue occurs, with a restoration of normal airway caliber and epithelium. The treatment for bronchiolitis obliterans in children is often difficult and unsuccessful. Azithromycin, a macrolide antimicrobial, appears to have been effective in the treatment of bronchiolitis obliterans, presumably acting via its postulated anti-inflammatory effects. Corticosteroids have not been shown to improve outcome, and experimental therapies include immunomodulators, monoclonal antibodies directed at the interleukin-2 receptor, and aerosolized cyclosporine.[124] The ultimate option for children with severe bronchiolitis obliterans is lung transplantation.

Up to one third of children with postinfectious bronchiolitis obliterans will develop Swyer-James syndrome[131] (or Macleod syndrome when diagnosed in adulthood). It is a long-term complication of postinfectious constrictive bronchiolitis of childhood. It also is associated with adenovirus pneumonia or bronchiolitis.[134] This syndrome describes the development of a unilateral hyperlucent lung with decreased vascularity and increased air trapping evident on plain radiographs. It develops due to postinfectious fibrotic healing of the immature lung, which leads to a decrease in the number of alveoli and pulmonary vessels. Imaging of Swyer-James syndrome demonstrates diffuse, asymmetric, patchy lobar or lobular air trapping that is almost often bilateral (Fig. 27-4).[135] Before the routine use of CT scan, it was believed that this syndrome was a unilateral phenomenon; this has since been disproved.[136]

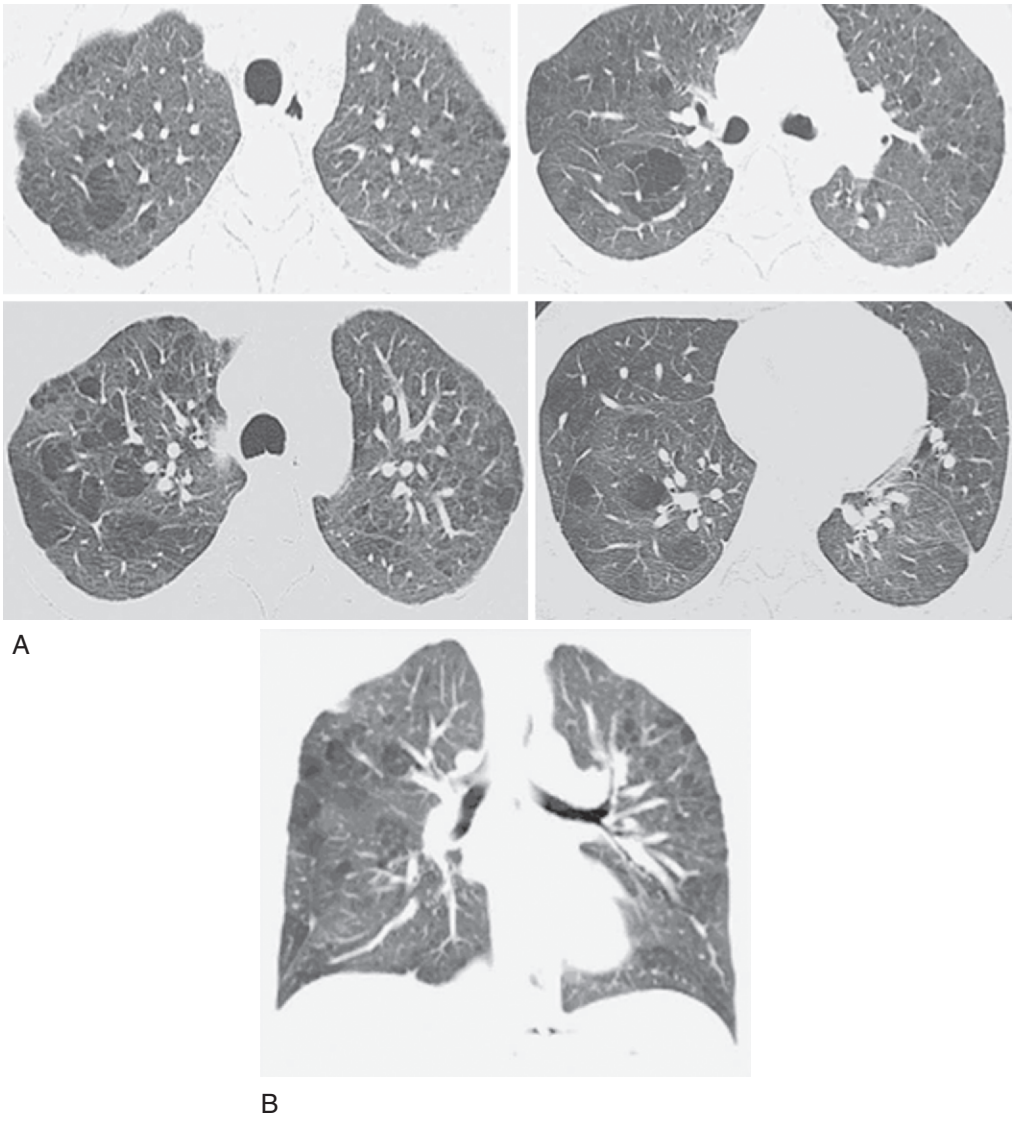


FIGURE 27-4. **(A)** High-resolution CT of the chest demonstrates asymmetric lobular air trapping with diminished vascularity shown in the lungs bilaterally from Swyer-James-Macleod syndrome. **(B)** Distribution of abnormality is better appreciated on the coronal reformatted image. (From Pipavath SN, Stern EJ. Imaging of small airway disease (SAD). *Radiol Clin North Am.* 2009;47:313.)

RELATIONSHIP TO ASTHMA

A relation between bronchiolitis in infancy and subsequent wheezing has been repeatedly demonstrated in the medical literature.[26] There is even some evidence to suggest that early RSV infection may affect pulmonary function in adulthood.[137,138] This association has led to much speculation and research into the mechanism behind this finding. The association may be causal (and RSV bronchiolitis actually leads to long-term changes in the lungs), or RSV infection simply may serve as a marker for a genetic or physiologic/ anatomic predisposition to future wheezing.[1] At present, it is clear that there is an association between infant bronchiolitis and subsequent development of asthma; however the exact nature of this relationship remains to be determined.

Suggested Reading

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The complete reference list is available online at www.expertconsult.com