Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

SECTION D: Lower Respiratory Tract Infections

33 Bronchiolitis

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Bronchiolitis is a syndrome of inflammation and obstruction of the lower respiratory tract that usually is caused by a viral infection occurring in the first 12 months of life.[1] Between 2% and 3% of infants younger than 1 year of age are hospitalized with bronchiolitis annually, accounting for 57,000 to 175,000 hospitalizations in the United States.[2–4]

Yearly hospital admissions attributable to bronchiolitis increased more than twofold between 1980 and 1996, likely reflecting the increased use of childcare centers and changes in criteria for hospital admission for children with bronchiolitis.[5] However, during the first 16 years of the 21st century, bronchiolitis hospitalization rates have fallen by 20% to approximately 20 to 30 admissions per 1000 children younger than 12 months of age.[6] One explanation for lower rates of bronchiolitis hospitalization is the improved health of neonates at the time of discharge compared with several years earlier. This can be attributed to the use of antenatal glucocorticoids, surfactant replacement, improvements in methods for ventilatory support, corrective cardiac surgery performed earlier in life, and a better understanding of neonatal nutrition.

ETIOLOGIC AGENTS

During seasonal outbreaks of bronchiolitis from November through March in North America, respiratory syncytial virus (RSV) is identified as the etiologic agent in up to 80% of hospitalized children[7] (Table 33.1). Other respiratory viruses that cause a largely indistinguishable syndrome include human rhinoviruses, parainfluenza viruses, human metapneumoviruses, coronaviruses, adenoviruses, influenza viruses, enteroviruses, and human bocaviruses.[8–11] The yearly cycles of respiratory virus circulation are depicted in Fig. 33.1.

No evidence has been found for a primary role for bacteria as a cause of bronchiolitis. However, *Bordetella pertussis, Chlamydia trachomatis,* and *Mycoplasma pneumoniae* should be included in the differential diagnosis of a young child with lower respiratory tract infection.

EPIDEMIOLOGY

The peak incidence of severe disease occurs before 6 months of age, and the highest rates of hospitalization occur among infants between 60 and 90 days of age.[1] Most of those hospitalized for bronchiolitis are term infants with no known risk factors. Chronologic age is the single most important determinant for severe bronchiolitis; about two thirds of hospitalizations occur before 6 months of age.[1,2] Several reasons may account for this age distribution. Birth shortly before or soon after the onset of the RSV season results in a longer period of exposure to RSV earlier in life. Maternal antibody concentrations to RSV also show seasonal variation, and infants born early in the RSV season

are more likely to be born to mothers with low neutralizing antibody concentrations.[12–14]

Certain comorbidities, including prematurity (<29 weeks' gestation), chronic lung disease of prematurity, and hemodynamically significant congenital heart disease, may result in more severe disease compared with children without these comorbities.[15,16] Worldwide, 65,000 to 200,000 deaths due to bronchiolitis were estimated to occur in 2005 among children younger than 5 years of age.[17,18] Fewer than 100 US pediatric deaths occur annually as a complication of RSV-associated bronchiolitis.[19]

TABLE 33.1 Infectious Causes of Bronchiolitis

Infectious Agent	Occurrence[a]
Respiratory syncytial virus	++++
Rhinovirus	++
Human metapneumovirus	++
Parainfluenza virus 3	++
Parainfluenza virus 1	+
Parainfluenza virus 2	+
Coronaviruses	+
Adenovirus	+
Influenza virus (A or B)	+
Mycoplasma pneumoniae	+
Enterovirus	+

[a]Relative importance varies with season and epidemic disease.
++++, Most common cause; ++, causes substantial percentage of cases in some studies; +, occasional cause.
Data from references 7, 8, 39–41.

Occurrence of the respiratory virus season is predictable even though the severity of the season, the date of onset, the peak of activity, and the end of the season cannot be predicted with precision.[20] There can be variation in timing of community outbreaks of disease due to RSV from year to year in the same community and among neighboring communities, even in the same season. Southern US communities tend to experience the earliest onset of RSV activity, and those in the Midwest tend to experience the latest onset. The duration of the season in western and northeastern areas is typically between that in the South and the Midwest. Nevertheless, these variations occur within the overall pattern of RSV outbreaks, usually beginning in November or December, peaking in January or February, and ending by the end of March or April.[20–23]

Limited numbers of cases of bronchiolitis may occur during late spring, summer, and early fall, and they often are caused by viruses other than RSV, such as rhinoviruses or parainfluenza viruses. These cases often are milder than RSV-related cases. In tropical countries, the annual epidemic of RSV coincides with the rainy season, although cases can occur throughout the year.

Household crowding is a risk factor for severe viral lower respiratory tract illness due to RSV and other respiratory viruses.[24–27] As the number of household members increases, the likelihood of close exposure to infectious respiratory secretions also increases. Childcare attendance has been correlated with an increased risk of bronchiolitis in some studies.

Unlike other respiratory viral infections, exposure to passive household tobacco smoke has not been associated with an increased risk of RSV hospitalization on a consistent basis. Exposure to secondhand smoke has been associated with an increased risk of respiratory infections

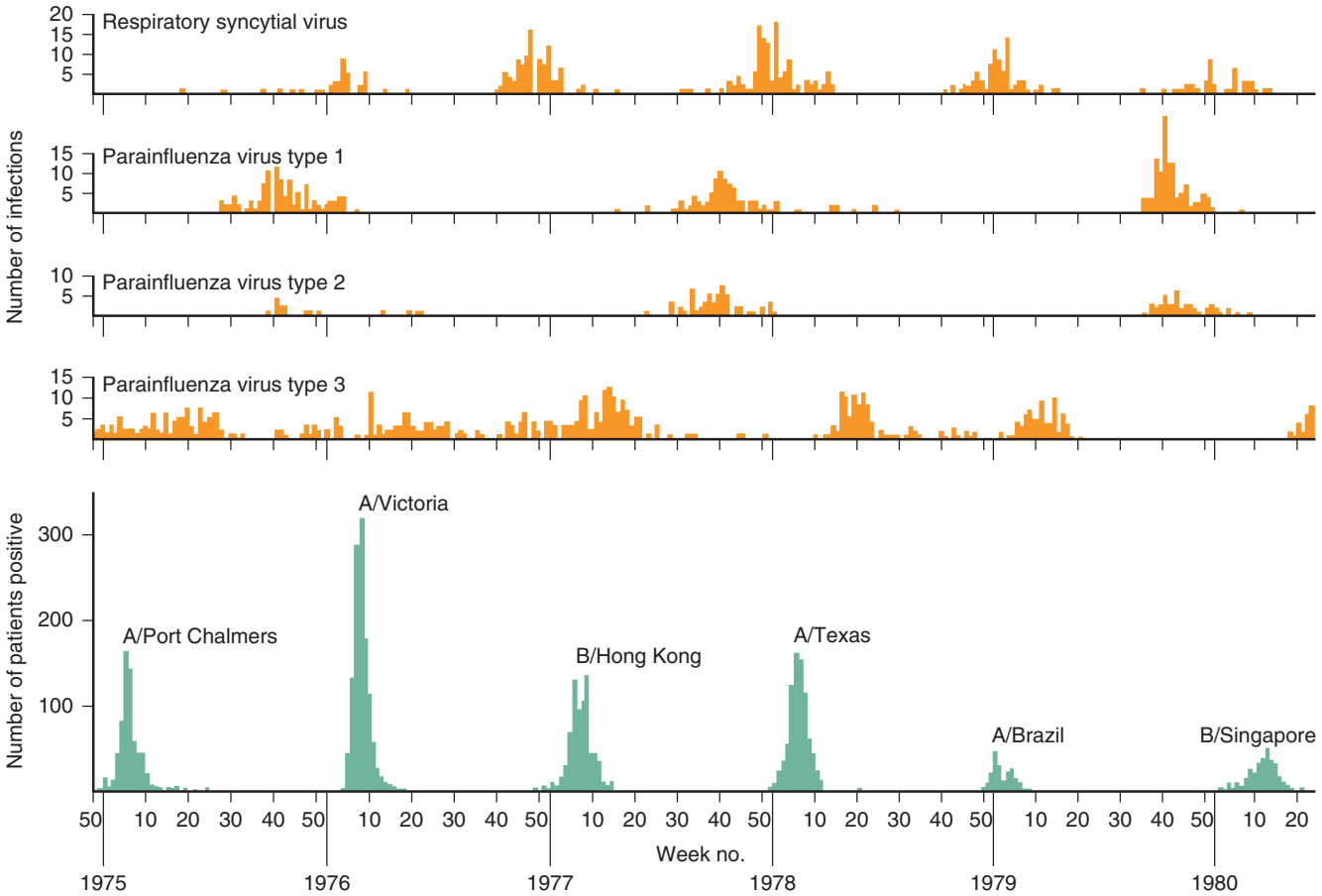

FIGURE 33.1 Patterns of occurrence of respiratory syncytial virus and parainfluenza virus in Houston, Texas. (From Couch RB. Viral respiratory diseases. In: Stringfellow DA [ed]. Virology. Kalamazoo, MI: Scope; 1983, p. 65.)

due to other viruses. In contrast to the well-documented benefit of breastfeeding against some viral illnesses, existing data are conflicting regarding the specific protective effect of breastfeeding against RSV infection.

Other reported risk factors for bronchiolitis include poverty, malnutrition, maternal smoking during pregnancy, congenital malformation of the airways, neuromuscular impairment, household crowding, childcare attendance, size of the childcare facility, lower level of maternal education, and living at an increased altitude. However, most of these risk factors are inconsistent from study to study, and in most instances, the impact on increased hospitalization is small.[15]

PATHOGENESIS AND PATHOLOGIC FINDINGS

Acute bronchiolitis is caused by an infectious agent, usually a respiratory virus with specific tropism for bronchiolar epithelium. Because most infants experience mild illness and recover from bronchiolitis, information regarding the pathologic changes caused by infection is not available.

Largely based on results from animal studies, RSV infection of the epithelial cells of the human respiratory tract mucosa results in a lymphocytic infiltration of the bronchiolar walls and edema of the surrounding tissue. Disease progression is associated with proliferation and necrosis of the bronchiolar epithelium. The sloughed necrotic epithelium and the increased mucus production lead to obstruction of the lumen of the infant's small airways. Air movement is restricted during inspiration and expiration but is more restricted during expiration, when the lumen is further compromised by positive expiratory pressure, resulting in expiratory wheezing. Obstruction results in air trapping and the characteristic appearance of hyperinflation on chest radiographs. As this air is absorbed, the radiographic pattern evolves to show atelectasis.[23,27–29] Chapter 225 discusses the pathophysiology of RSV bronchiolitis.

CLINICAL MANIFESTATIONS

Upper respiratory tract symptoms consisting of nasal congestion and discharge and a low-grade fever begin about 3 to 5 days after the onset of infection. Bronchiolitis represents the later stage of a respiratory viral infection that develops after 2 to 4 days of illness. Approximately 30% to 40% of RSV-infected infants experience progression of disease to the lower respiratory tract. Spread to the lower airway occurs by aspiration of sloughed RSV-infected epithelial cells from the upper airway or by cell-to-cell spread of the virus.

Lower airway involvement is marked by an increase in the work of breathing, cough, tachypnea, wheezing, crackles, use of accessory muscles, and nasal flaring.[1] The respiratory rate often exceeds 60 to 70 breaths/min in young infants. Intercostal, supracostal, and subcostal retractions are evident. Initially, wheezing occurs during the expiratory phase only and is audible only through a stethoscope. As wheezing progresses, it can be heard without a stethoscope. The chest becomes hyperexpanded and hyperresonant, respirations become more labored, and retractions become more severe. Mild hypoxemia occurs in most infants with bronchiolitis. Respiratory failure can occur due to progressive hypercapnia and respiratory muscle fatigue.[1]

Disease severity may be recognized by the absence of audible air exchange on auscultation; flaring of the alae nasi; expiratory grunting; severe subcostal, supraclavicular, and intercostal retractions; and hypoxemia. A child with these findings may require intubation and ventilatory support. Apnea can be an early manifestation of RSV infection, sometimes resulting in respiratory failure.[30–32] Because the severity of bronchiolitis often waxes and wanes before consistent improvement, serial assessment of respiratory status should be performed. The ability of a young infant to breastfeed or bottle-feed without distress over time often provides a practical guide to disease severity and management. An infant who has substantial difficulty feeding as a result of respiratory distress has moderate or severe illness and usually requires hospitalization.

Otherwise healthy infants younger than 2 months of age, infants born prematurely (<29 weeks' gestation), and infants with chronic lung disease of prematurity or infants born with congenital heart disease are most likely to experience severe RSV disease.[1] Infants born with hemodynamically significant congenital heart disease are at increased risk of more severe bronchiolitis.[15,16,33,34] Infants with hemodynamically insignificant heart disease, including secundum atrial septal defect, small ventricular septal defect, pulmonic stenosis, uncomplicated aortic stenosis, mild coarctation of the aorta, and patent ductus arteriosus, and infants with lesions adequately corrected by surgery (unless they continue to require medication for management of congestive heart failure) are not considered to be at increased risk for hospitalization.[35] Severe respiratory distress with bronchiolitis can be the presenting manifestation of previously unrecognized congenital heart disease.

RSV-infected infants have various courses after hospitalization.[22] Among otherwise healthy infants, intensive care unit admission because of respiratory deterioration is uncommon (approximately 2% of patients). The decision to admit to the intensive care unit is based on the possible need for intubation because of progressive hypercapnia, increasing hypoxemia despite supplemental oxygen, or episodes of apnea.

The typical course for a previously healthy infant older than 6 months of age is one of improvement over 2 to 3 days, as evidenced by a lower respiratory rate and fewer retractions. Pulmonary function abnormalities and evidence of mild desaturation may persist for several weeks. The differential diagnosis of bronchiolitis includes airway hypersensitivity to environmental irritants, anatomic abnormality of the airway, cardiac disease with pulmonary edema, cystic fibrosis, foreign-body aspiration, and gastroesophageal reflux.

DIAGNOSIS

A diagnosis of bronchiolitis should be based on the history and physical examination. Serial examinations may reveal fluctuations in disease acuity over a short period, reflecting rapid changes in blockage of the lumens of the small airways.[1] Specific signs and symptoms at the time of presentation have a limited ability to predict disease severity. Assessment of the likelihood of progressive disease should consider the risk factors, including: age younger than 12 weeks, a history of prematurity, underlying cardiopulmonary disease, or immunodeficiency.[1]

Routine radiographic studies are not recommended. Infants with bronchiolitis may have abnormalities (e.g., atelectasis) on chest radiography, but the changes have little correlation with disease severity.[36,37] Radiography should be reserved for infants who require intensive care management and for those who do not improve as expected.

Routine virologic testing is not recommended because the result is unlikely to influence management.[1] Respiratory isolation recommendations are similar for most viral infections and are based largely on the symptoms, not the specific cause. The positive predictive value of an antigen detection assay decreases as disease incidence goes down. Specificity of antigen detection assays is lowest during the off-season and at the onset and the end of the respiratory virus season.

Polymerase chain reaction (PCR) assays have improved sensitivity and specificity compared with antigen detection, but they are expensive, and results are unlikely to influence management. Using PCR assays, coinfections with more than one virus have been identified in as many as one third of hospitalized patients with bronchiolitis. The significance of coinfections is incompletely understood.[38–42] PCR assays should be interpreted with caution because positive results can be found in more than 30% of asymptomatic young children.[43] Whether this reflects prolonged shedding from a previous infection, the incubation period for a pending infection, infection by a strain with limited ability to cause disease, or a low-grade infection producing small amounts of virus is unknown.

MANAGEMENT

General Measures

Most infants with bronchiolitis can be managed at home with supportive care, but concerns regarding increasing respiratory effort, apnea, or inability to feed adequately may precipitate hospitalization of a young child.[1] Disease severity may be estimated by respiratory rate, use of accessory muscles, and degree of hypoxemia. However, the course of bronchiolitis varies, ranging from mild dyspnea to progressive respiratory distress. Certain underlying conditions such as prematurity, immunodeficiency, chronic lung disease of prematurity, and congenital

heart disease are associated with an increased risk of progression to severe disease.

Despite the high burden of disease from bronchiolitis, no available treatment shortens the course or hastens the resolution of symptoms. Therapy is supportive, and most children with bronchiolitis do well regardless of management.[1]

Therapies

Bronchodilator Therapy. Most randomized, controlled trials have failed to demonstrate a consistent benefit from α- or β-adrenergic agents. Although transient improvement in respiratory status has been reported, most infants treated with bronchodilators do not benefit from their use.[44–47] The potential adverse effects (i.e., tachycardia and tremors) and cost of these agents outweigh the potential benefits. Recommendations from the American Academy of Pediatrics state, "Clinicians should not administer albuterol to infants and children with a diagnosis of bronchiolitis."[1]

Epinephrine. Epinephrine is an adrenergic agent with α- and β-receptor agonist activity. It has been evaluated in children with bronchiolitis after systemic administration and when delivered directly into the respiratory tract. Large, multicenter trials comparing nebulized epinephrine with albuterol or placebo in hospitalized children with bronchiolitis found no improvement in outcomes.[48–50] Available evidence does not support a role for epinephrine use among hospitalized patients or outpatients with bronchiolitis.

Corticosteroid Therapy. Although corticosteroids may benefit selected patients with asthma or croup, no evidence supports the use of corticosteroid therapy in the general population of children with bronchiolitis. Numerous studies have documented a lack of benefit.[51–53]

Oxygen Therapy. Various degrees of hypoxia are commonly seen in infants and young children with bronchiolitis. Intermittent periods of hypoxemia (≥90% oxyhemoglobin saturation) as measured by pulse oximetry should not be interpreted as a need for supplemental oxygen. Transient desaturation is common in healthy infants. Oxygen saturation has much less impact on respiratory drive than carbon dioxide concentration in the blood. Oxygen saturation and respiratory distress have poor correlation among infants with lower respiratory tract infections. Continuous monitoring with pulse oximetry of children with mild degrees of oxygen desaturation has been associated with prolonged length of stay compared with children who do undergo continuous monitoring.[54,55]

Chest Physiotherapy. Suctioning of the nasopharynx to remove secretions and temporarily improve airflow is a common practice for children with bronchiolitis. Chest physiotherapy using vibration or percussion or deep suctioning is not recommended.[56,57]

Hydration. As many as one third of patients admitted to the hospital with a diagnosis of bronchiolitis require fluid replacement therapy. The ability to swallow may be compromised when the respiratory rate exceeds 60 breaths/min, especially if the child has nasal congestion. For infants who are unable to maintain hydration orally, fluid may be administered intravenously or through a nasogastric tube.[58,59]

Antibiotic Therapy. Antibacterial therapy should not be administered to an infant or young child with bronchiolitis unless there is a strong suspicion of a concomitant bacterial infection.[1]

Nebulized Hypertonic Saline. Data suggest that nebulized hypertonic saline may have a modest benefit in infants with RSV bronchiolitis.[60–62] Hypertonic saline may facilitate mucociliary clearance of the bronchioles that results from the inflammatory response to infection. Some evidence suggests that 3% inhaled saline may be safe and may reduce length of hospital stay when a hospitalization lasts longer than 3 days.

Antiviral Therapy. Ribavirin is a nucleoside analogue with in vitro activity against RSV, adenovirus, influenza A and B viruses, and parainfluenza viruses. Early trials indicated that ribavirin therapy was associated with a modest improvement in clinical scores, oxygenation, and duration of mechanical ventilation for infants with severe bronchiolitis due to RSV infection. These studies were challenged on the basis that control groups received water aerosols, which can produce bronchospasm in individuals with hyperreactive airways. Clinical trials with ribavirin have not demonstrated a consistent decrease in the need for mechanical ventilation, decrease in length of stay in the intensive care unit, or reduction in days of hospitalization. Conflicting results from efficacy trials, concern about the potential toxic effects among exposed healthcare professionals, aerosol route of administration, and high cost have resulted in the limited use of ribavirin.[63]

Chapter 225 discusses ribavirin. Options for the treatment of bronchiolitis if caused by influenza A or B viruses are discussed in Chapter 229.

PROGNOSIS, COMPLICATIONS, AND SEQUELAE

Most infants recover completely from acute bronchiolitis. Severe bronchiolitis early in life is associated with an increased risk of asthma, especially after RSV or rhinovirus bronchiolitis, and the risk can persist into early adulthood. It is not understood whether bronchiolitis injures the lung such that normal lung development does not occur and predisposes to subsequent episodes of wheezing or whether certain infants have a pre-existing aberration of the immune response or airway function that predisposes to severe bronchiolitis and recurrent wheezing.[64–69]

PREVENTION

Strategies that reduce exposure of vulnerable infants to contagious individuals with respiratory tract infections offer opportunities to reduce bronchiolitis morbidity. Encouraging breastfeeding and avoiding passive exposure to cigarette smoke are critical aspects of proper healthcare for all children. The role of monoclonal antibodies in reducing the risk of RSV infection in certain high-risk infants and young children is discussed in Chapter 225.

No safe and effective vaccine is available to prevent infection with RSV or most other viral causes of bronchiolitis. The influenza vaccine is the only exception, and this vaccine should be administered annually to all infants starting at 6 months of age. Because influenza vaccine is not approved for use in infants younger than 6 months of age, annual influenza vaccination is important for the family members and caregivers of young patients.

All references are available online at www.expertconsult.com.

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