SECTION D: Lower Respiratory Tract Infections

33 Bronchiolitis

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Bronchiolitis, a disease primarily of the first 2 years of life characterized by signs and symptoms of obstructive airway disease, is caused most commonly by viruses.[1] Approximately 2% to 3% of infants in the first 12 months of life are hospitalized with bronchiolitis, accounting for approximately 125,000 hospitalizations and 200 to 500 deaths annually in the United States.[2] Data from the Centers for Disease Control and Prevention (CDC) indicate that the number of yearly hospital admissions attributable to bronchiolitis increased more than twofold between 1980 and 1996.[3] Increasing survival rates for premature infants as well as infants with compromised cardiac, pulmonary, and immune status increase the number of children at risk for severe bronchiolitis.

ETIOLOGIC AGENTS

Many viruses can cause bronchiolitis, although respiratory syncytial virus (RSV), human metapneumovirus, and parainfluenza virus type 3 are the most common etiologic agents.[1–7] Other viruses are implicated less frequently (Table 33-1).[8–10] During the winter months, RSV is identified as the etiologic agent by cell culture or antigen detection assays in up to 80% of children hospitalized with bronchiolitis or pneumonia. Epidemics of bronchiolitis in early spring and fall often are caused by parainfluenza virus type 3.[11–14] The yearly cycles of these respiratory viruses are depicted in Figure 33-1. Other viral causes of bronchiolitis include rhinoviruses and coronaviruses.

Bordetella pertussis, Mycoplasma pneumoniae, measles, influenza, and adenovirus have been associated with a severe form of bronchiolitis, bronchiolitis obliterans.[15–18] This uncommon obstructive pulmonary disease is characterized histologically by the progression of acute airway inflammation to necrosis of the cells lining the lumen with severe obliterative fibrosis in the final stages. The pathogenesis of bronchiolitis obliterans probably differs from that of simple viral bronchiolitis.

EPIDEMIOLOGY

Bronchiolitis may be defined as an episode of obstructive lower airway disease precipitated by a viral infection in infants younger than 24 months of age. The peak incidence of severe disease occurs between 2 and 6 months of age.[1,19,20] Rates of hospitalization are higher in boys and among infants living in industrialized urban settings rather than in rural settings.[21] Hospitalization rates are about 5 times higher among infants and children in high-risk groups than among non-high-risk infants. High-risk groups include premature infants (<35 weeks' gestation), infants born with hemodynamically significant congenital heart disease, as well as infants with chronic lung disease of prematurity (previously called bronchopulmonary dysplasia).[22–27] Although mortality has been reduced in recent years, morbidity among high-risk patients can be high, with average hospital length of stay and intensity of care several times that of previously healthy infants.[2,28]

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. 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. In the U.S., communities in the south tend to experience the earliest

onset of RSV activity and the midwest tends to experience the latest onset.[29] The duration of the season for the west and the northeast 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.

TABLE 33-1. Infectious Causes of Bronchiolitis

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

++++, most common cause; ++, causes substantial percentage of cases in some studies; +, occasional cause. Relative importance varies with season and epidemic disease (see text).

Data from references 7, 8, 11, 13, 15.

Limited numbers of cases of bronchiolitis occur during summer and early fall, and they are likely to be caused by viruses other than RSV, such as rhinovirus and parainfluenza viruses. These cases are generally milder than RSV-related cases. In tropical countries, the annual epidemic of RSV coincides with the rainy season or "winter," although sporadic cases can occur throughout the year.[10]

RSV can be divided into A and B strains, each with numerous subtypes or genotypes. Type A strains may be associated more commonly with epidemics, severe disease, and a higher hospitalization rate than type B strains, although not all studies are consistent with regard to differences in severity.[30–33] Both strains may circulate during the same season, and infants may be reinfected within the same year.

A progressive increase in hospitalization rates for bronchiolitis in the U.S. has occurred since the late 1980s.[3,22] This increase may be related to a greater ability to identify hypoxic infants through the use of pulse oximetry. Alternatively, the increase in hospitalization may reflect increased use of daycare centers or changes in criteria for admission.[3] Household crowding is an important risk factor for severe viral lower respiratory tract illness due to RSV as well as other respiratory viruses.[34,35] Generally it is recognized that as the number of household members increases, the risk of exposure to infectious respiratory secretions also increases. Childcare attendance has been correlated with an increased risk of bronchiolitis in some studies. Unlike other respiratory virus infections, exposure to passive household tobacco smoke has not been associated with an increased risk of RSV hospitalization on a consistent basis. In contrast to the well-documented beneficial effect of breastfeeding against some viral illnesses, existing data are conflicting regarding the specific protective effect of breastfeeding against RSV infection.[35–39] Parental history of bronchiolitis or

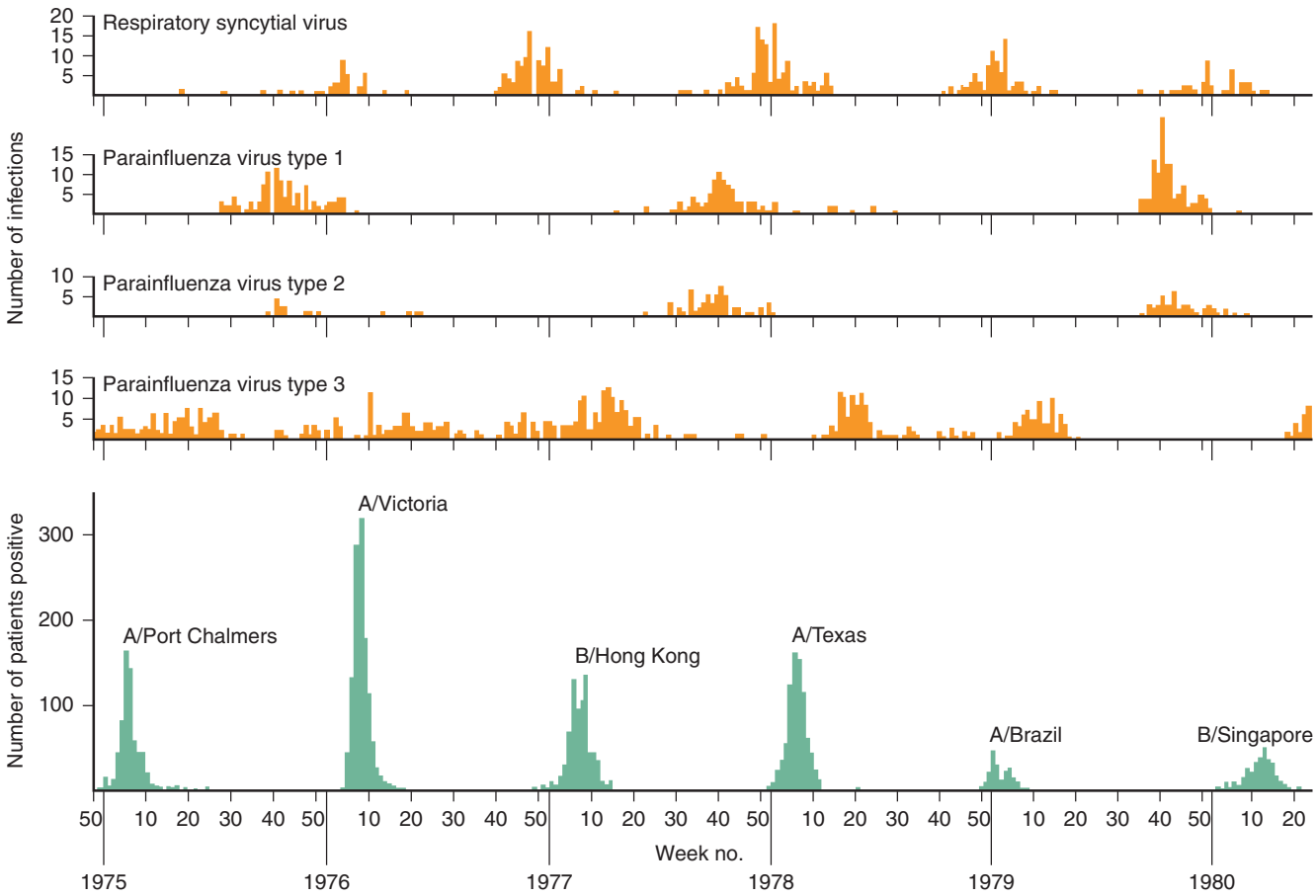

Figure 33-1. Patterns of occurrence of respiratory syncytial virus and parainfluenza virus in Houston, Texas. (From Couch RB. Viral respiratory diseases. In: Stringfellow DA (ed) Virology. Kalamazoo, MI, Scope, 1983, p 65.)

asthma is associated with a higher risk for the development of lower respiratory illness in offspring.[40,41]

Young chronologic age at the beginning of the RSV season is a consistent risk factor for RSV hospitalization. Several reasons may account for this increase in risk. Most severe RSV disease occurs in the first 6 months of life so that birth shortly before or early after the onset of the RSV season will result in a longer period of exposure to RSV earlier in life. Second, maternal antibody concentrations to RSV show seasonal variation and infants born early in the RSV season are more likely to be born to mothers with low serum antibody concentrations to the F (fusion) protein of RSV.[42,43] Low concentrations of RSV antibody correlate with susceptibility to severe RSV disease in infants.

PATHOGENESIS AND PATHOLOGIC FINDINGS

Acute bronchiolitis generally implies disease of infectious etiology, usually due to viruses with specific tropism for bronchiolar epithelium. Because most healthy infants recover from bronchiolitis without incident, information regarding the pathologic changes caused by infection is inferred from animal studies and from biopsy or autopsy materials in severe cases. Viral infection causes profound alterations in the epithelial cell and mucosal surfaces of the human respiratory tract. The characteristic histopathology in bronchiolitis is 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. The 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.[44–49]

The presence of high serum concentrations of immunoglobulin IgG antibodies to RSV (whether transplacentally acquired or administered intramuscularly) ameliorates RSV illness.[50–54] Severe obstructive illness may be related to stimulation of virus-specific IgE-mediated hypersensitivity responses or altered cell-mediated immune responses.[55–60]

CLINICAL MANIFESTATIONS

Bronchiolitis represents the late stage of a respiratory disease that progresses over several days. Upper respiratory tract symptoms consisting of nasal discharge and mild cough begin about 3 to 5 days after onset of infection. Approximately 30% to 40% of RSV-infected infants have progression of disease to involve the lower respiratory tract. Spread to the lower airway occurs either by aspiration of RSV-infected epithelial cells or by cell-to-cell spread of the virus. Lower-airway involvement is marked by a sudden increase in the work of breathing, cough, tachypnea, wheezing, crackles, use of accessory muscles, and nasal flaring.[61,62] The respiratory rate often exceeds 60 to 70 breaths/minute in young infants, and expiration is prolonged. Intercostal and subcostal retractions with wheezing are evident. Initially, wheezing occurs during the expiratory phase only and is only audible through a stethoscope. As wheezing progresses, it can be heard without a stethoscope. The chest becomes hyperexpanded and hyperresonant, respirations more labored, and retractions more severe. Hypoxemia out of proportion to clinical distress is typical of RSV infection. Mild hypoxemia occurs even in otherwise well-appearing infants, the so-called happy wheezers. Respiratory failure can be due to hypoxemia (an early and sometimes sudden occurrence) or progressive hypercapnia due to fatigue. The small airways of young infants can become so narrowed that wheezing is inaudible. In this setting disease severity is recognized by the absence of audible air exchange, flaring of the alae nasae, expiratory grunting, severe subcostal, supraclavicular, and intercostal retractions, and hypoxemia. Progressive illness often is accompanied by a rapid fall in oxygen saturation after minimal manipulation. A child with these findings usually requires intubation and ventilatory support. Apnea can be an early manifestation of RSV infection, at times resulting in respiratory failure.[63] RSV-related apnea is mediated by the central nervous system, occurring in young, often prematurely born infants.[64] Because the severity of bronchiolitis often waxes and wanes prior to consistent improvement, assessment of respiratory status can vary markedly over a short period. The ability of the young infant to breast- 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 (less than 35 weeks' gestation), and infants with chronic lung disease of prematurity (previously called bronchopulmonary dysplasia) or infants born with congenital heart disease have the highest morbidity and mortality rates due to bronchiolitis.[65,66] Infants born with congenital heart disease at greatest risk of hospitalization due to bronchiolitis include those with moderate to severe pulmonary hypertension and infants with cyanotic heart disease. RSV-infected infants and children with the following hemodynamically insignificant heart disease are generally not considered to be at increased risk of hospitalization: secundum atrial septal defect, small ventricular septal defect, pulmonic stenosis, uncomplicated aortic stenosis, mild coarctation of the aorta, and patent ductus arteriosus, as well as infants with lesions adequately corrected by surgery (unless they continue to require medication for management of congestive heart failure).[67,68] Severe respiratory distress with bronchiolitis can be the presenting manifestation of previously unrecognized congenital heart disease.

Once hospitalized, the RSV-infected infant may have a highly variable course of illness.[69–73] Among otherwise healthy infants, intensive care unit admission because of respiratory deterioration is uncommon.[74] A 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 apnea. The typical course for a previously healthy infant older than 6 months is one of improvement over 2 to 5 days, as evidenced by decreases in respiratory rate, retractions, duration of expiration, and oxygen requirement. The median duration of symptoms in 95 infants with first-time bronchiolitis who came to medical attention at an emergency department in Wisconsin was 15 days and one-quarter of the infants remained symptomatic after 3 weeks.[75] Pulmonary function abnormalities and evidence of mild desaturation (oxygen saturations in the range of 93% to 95%) can persist for several weeks.[76] 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

The diagnosis of bronchiolitis is based on clinical criteria with supporting radiographic findings. Typical chest radiographic findings are hyperinflation, with flattening of the diaphragms and hyperlucency of the lungs, and patchy atelectasis, especially involving the right upper lobe (Figures 33-2 and 33-3).[74,76] Atelectasis is due to airway narrowing or mucous plugging and is associated with volume loss; it may be confused with lobar consolidation or aspiration pneumonia, both of which are generally volume-expanding lesions. Bacterial pneumonia infrequently occurs as a complication of bronchiolitis but should be suspected in the infant with fever persisting for more than 2 to 3 days and lack of response to supportive management.

Establishing a specific etiologic diagnosis is helpful in predicting the clinical course, in cohorting in the hospital, and may become increasingly useful as more antiviral agents effective against respiratory viruses become available. Although viral culture of respiratory secretions has been the "gold standard" for

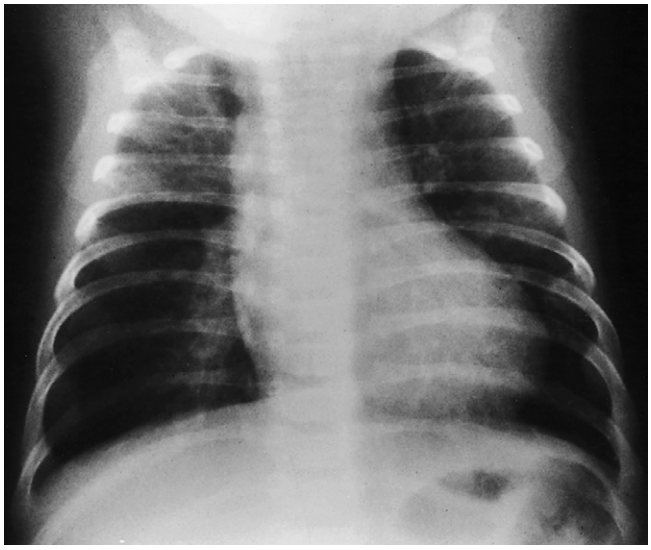

Figure 33-2. Typical radiographic appearance of bronchiolitis. Hyperinflation, hyperlucency, and flattened diaphragms are most characteristic. Peribronchiolar infiltrates are common, and parenchymal infiltrates are less common. (Courtesy of Richard Heller, MD, Vanderbilt University Children's Hospital, Nashville, TN.)

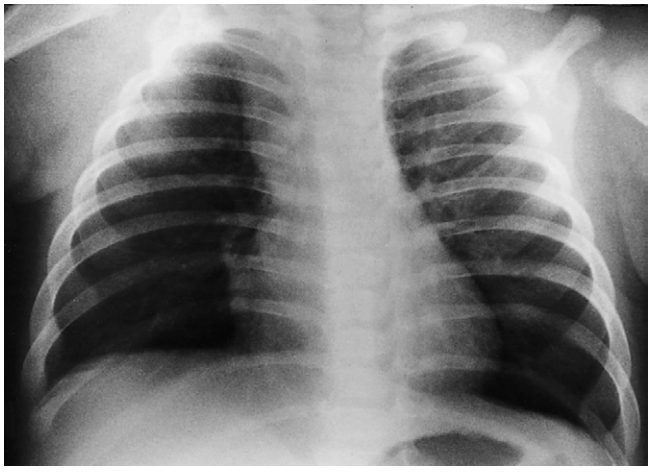

Figure 33-3. Atelectasis, particularly of the right upper lobe, is a not uncommon feature of bronchiolitis. This should not be confused with pneumonia, which manifests as volume expansion, not volume loss. (Courtesy of Richard Heller, MD, Vanderbilt University Children's Hospital, Nashville, TN.)

diagnosis of RSV infection, it often is too slow a method to be clinically useful. Enzyme immunoassays and direct fluorescent antibody (DFA) techniques for the identification of RSV, influenza virus, parainfluenza viruses, and adenoviruses permit rapid and accurate diagnoses.[77–81] Nasal wash is the preferred method of specimen collection. The DFA test permits evaluation of adequacy of the specimen's number of epithelial cells for antigen detection. A respiratory screening of nasal secretions using pooled monoclonal antibodies to the common agents of bronchiolitis, followed by specific identification for a positive reaction, is a cost- and time-saving procedure compared with standard tissue culture isolation. Amplification of virus using the shell vial method, followed by use of specific monoclonal agents, and amplification of viral genome by the polymerase chain reaction offer the promise of improved sensitivity for rapid detection but are not as widely available nor as rapid as enzyme immunoassay and fluorescent antibody techniques.[82,83] A multitest system for quantitative reverse transcription–polymerase chain reaction–enzyme hybridization assay (Hexaplex) is available to test a single nasopharyngeal sample for RSV, influenza A and B viruses, parainfluenza virus, and adenoviruses.[84]

Antigen detection tests are useful in diagnosing certain viral infections, but, as with all tests, the positive predictive value decreases as disease incidence goes down. Specificity of antigen detection assays are lowest during the off season and at the onset and end of the respiratory virus season.

MANAGEMENT

General Measures

Most infants with bronchiolitis can be managed at home with supportive care, but hypoxia or inability to feed adequately necessitate hospitalization. Once hospitalized, most infants respond to administration of supplemental oxygen and replacement of fluid deficits.[1] The value of mist inhalation by vaporizer or tent is not proven; its use can provoke reflex bronchoconstriction. The specific treatment strategies used differ widely across children's medical centers.[71] Fewer than 10% of previously healthy infants hospitalized for bronchiolitis require intubation and mechanical ventilation because of respiratory failure or apnea; the percentage is higher for prematurely born infants and infants with chronic lung disease or congenital heart malformations.

Bronchodilator Therapy

The therapeutic role of bronchodilator agents in bronchiolitis is controversial.[1,85] Bronchodilator therapy is not recommended for routine management of first time wheezing associated with RSV bronchiolitis. Occasionally, a single administration of an aerosolized bronchodilator elicits a response, but this improvement is not seen in most infants with bronchiolitis and is not generally reproducible with subsequent doses.[86–92] Modest improvement in clinical scores and in tests of pulmonary function have been reported with use of inhaled racemic epinephrine [91–93] and β-adrenergic agents, principally salbutamol and albuterol.[92–94] However, clinical improvement following repeated doses of epinephrine is not sustained and favorable response to β-adrenergic agents, as measured by clinical score and oxygenation, is inconsistent.[95–100] Flores and Horwitz[101] performed a meta-analysis of eight studies with similar designs. Overall, their analysis supported a beneficial effect in certain infants, but identifying those infants could not be consistently accomplished at the time of initial presentation. On balance, an initial trial of bronchodilator therapy for the hospitalized infant with bronchiolitis is reasonable, although brief episodes of hypoxia can be precipitated by adrenergic agents. Bronchodilator therapy should only be continued if consistent improvement in respiratory distress or oxygen saturation is observed. Racemic epinephrine should not be continued beyond one or two doses.

Corticosteroid Therapy

Although corticosteroids reduce the inflammatory changes observed with bronchiolitis, they may increase viral replication and prolong shedding. Most studies examining the role of corticosteroids alone in the treatment of bronchiolitis have not demonstrated a consistent clinical benefit.[102–110] Although one meta-analysis of previously published reports of corticosteroid use in bronchiolitis concluded that there may be slight improvements in duration of symptoms, length of hospital stay, and clinical scores, these benefits appear to be limited.[111] The routine use of corticosteroids in bronchiolitis is not recommended. However, a national collaborative, blinded, placebo-controlled trial conducted in Canada demonstrated that the combination of nebulized epinephrine and oral dexamethasone treatment for children with bronchiolits evaluated in emergency departments reduced the subsequent rate of hospitalization by 9% compared with placebo or either treatment alone (P=0.07) and was less costly.[112,113]

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 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 may produce bronchospasm in individuals with hyperreactive airways. Clinical trials with ribavirin have not demonstrated a consistent decrease in 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 potential toxic effects among exposed healthcare professionals, aerosol route of administration, and high cost have all resulted in limited use of ribavirin.[114–116] Guidelines for the use of ribavirin in RSV disease are presented in Chapter 225, Respiratory Syncytial Virus.

Potential options for the treatment of bronchiolitis, if caused by influenza A or B viruses, are discussed in Chapter 229, Influenza Viruses.[117–121]

Immune Globulins and Other Therapies

Antibody preparations containing high titers of neutralizing antibody against RSV as well as a preparation of monoclonal antibodies directed against one of the two major RSV surface glycoproteins (fusion glycoprotein) reduce the risk of hospitalization due to RSV infection.[50,51] Used therapeutically, they result in more rapid clearing of virus from the respiratory tract but do not alter the course of illness and should not be used for the treatment of RSV infection.[122–126] Although vitamin A levels have been demonstrated to be low in infants with RSV bronchiolitis, a therapeutic benefit of vitamin A therapy has not been demonstrated.[127–129]

PROGNOSIS, COMPLICATIONS, AND SEQUELAE

Most otherwise healthy infants recover completely from acute bronchiolitis, although subtle pulmonary abnormalities can persist for weeks.[38] An important question is whether bronchiolitis in infancy increases the likelihood of childhood asthma. Numerous studies have defined a higher risk of recurrent wheezing throughout childhood after bronchiolitis in infancy, and abnormalities of small-airway function have been identified in school-aged children with a history of bronchiolitis in infancy. However, each of these findings may simply be a reflection of hereditary tendencies that are expressed both at the time of bronchiolitis and upon allergen exposure in later childhood.[130–134] Moreover, by adolescence, the rate of recurrent wheezing in subjects who had bronchiolitis in infancy appears to fall to the rate observed in subjects without a history of bronchiolitis.[134] Thus, it is uncertain whether bronchiolitis is causally associated with long-term respiratory morbidity.

PREVENTION

Strategies that reduce contact of vulnerable infants with individuals with respiratory tract infections, minimizing passive exposure to cigarette smoke, and limiting nosocomial transmission of causative agents offer immediate opportunities to reduce bronchiolitis morbidity. Monthly administration of monoclonal anti-F antibody (palivizumab) throughout the RSV season reduces the incidence of hospitalization due to RSV infection in infants with bronchopulmonary dysplasia, congenital heart disease, and prematurity by about 50% (see Chapter 225, Respiratory Syncytial Virus). The high cost and modest effect of palivizumab limit its use for passive immunoprophylaxis to the most medically fragile infants.

No vaccine to prevent infection with RSV or parainfluenza viruses, the most common causes of bronchiolitis, is licensed or near licensure. Trivalent influenza vaccine is recommended for all infants older than 6 months of age during the influenza season. Because this is not approved for use in infants younger than 6 months, routine influenza vaccination is important for family members and caregivers of these young patients. Potential RSV vaccine candidates currently being evaluated include inactivated preparations of the purified fusion protein of RSV, DNA vaccines coding for the major immunogenic proteins of the virus, and replicating mutants of the virus that replicate in the upper respiratory tract but are inactivated at the higher temperatures of the lung.[135]

REFERENCES

1. American Academy of Pediatrics. Diagnosis and management of bronchiolitis. Pediatrics 2006;118:1774–1793.
2. Hall CB, Weinberg GA, Iwane MK, et al. The burden of RSV infection in young children. N Engl J Med 2009;360:588–598.
3. Shay DK, Holman RC, Newman RD, et al. Bronchiolitis-associated hospitalizations among US children, 1980–1966. JAMA 1999;282:1440.
4. Selwyn BJ. The epidemiology of acute respiratory tract infection in young children: comparison of findings from developing countries. Rev Infect Dis 1990;12:S870.
5. Glezen WP, Loda FA, Clyde WAJ, et al. Epidemiologic patterns of acute lower respiratory disease of children in a pediatric group practice. J Pediatr 1971;78:397.
6. van den Hoogen BG, de Jong JC, Groen J, et al. A newly discovered human pneumovirus isolated from young children with respiratory tract disease. Nat Med 2001;7:719.
7. Foy HM, Cooney MK, Maletzky AJ, et al. Incidence and etiology of pneumonia, croup and bronchiolitis in preschool children belonging to a prepaid medical care group over a four-year period. Am J Epidemiol 1973;97:80.
8. Kim HW, Arrobio JO, Brandt CD, et al. Epidemiology of respiratory syncytial virus infection in Washington, DC. I: Importance of the virus in different respiratory tract disease syndromes and temporal distribution of infection. Am J Epidemiol 1973;98:216.
9. Andreolettie L, Lesay M, Deschildre A, et al. Differential detection of rhinovirus and enterovirus RNA sequences associated with classical immunofluorescence assay detection of respiratory virus antigens in nasopharyngeal swabs from infants with bronchiolitis. J Med Virol 2000;61:341–346.
10. Weissenbacher M, Carballal G, Avila M, et al. Etiologic and clinical evaluation of acute lower respiratory tract infections in young Argentinean children: an overview. Rev Infect Dis 1990;12(Suppl 8):S889.
11. Meissner HC. Reducing the impact of viral respiratory infections in children. Pediatr Clin North Am 2005;52:695.
12. Henrickson KJ. Parainfluenza viruses. Clin Microbiol Rev 2003;16:242.
13. Fry AM, Curns AT, Harbour K, et al. Seasonal trends in human parainfluenza viral infections: United States, 1990–2004. Clinical Infect Dis 2006;43:1016–1022.
14. Loda FA, Arrobio JO, Brandt CD, et al. Studies on the role of viruses, bacteria and *M. pneumoniae* as causes of lower respiratory tract infections in children. J Pediatr 1968;72:1612.
15. Myers JL, Colby TV. Pathologic manifestations of bronchiolitis, constrictive bronchiolitis, cryptogenic organizing pneumonia, and diffuse panbronchiolitis review. Clin Chest Med 1993;14:611.
16. Becroft DM. Bronchiolitis obliterans, bronchiectasis, and other sequelae of adenovirus type 21 infection in young children. J Clin Pathol 1971;24:72.
17. Brown RS, Nagrady MB, Spence L, et al. An outbreak of adenovirus type 7 infection in children in Montreal. Can Med Assoc J 1973;108:434.
18. Macek V, Sorli J, Kopriva S. Persistent adenoviral infection and chronic airway obstruction in children. Am J Respir Crit Care Med 1994;150:7.
19. Henderson FW, Clyde WAJ, Collier AM, et al. The etiologic and epidemiologic spectrum of bronchiolitis in pediatric practice. J Pediatr 1979;95:183.
20. Glezen WP, Taber LH, Frank AL, et al. Risk of primary infection and reinfection with respiratory syncytial virus. Am J Dis Child 1986;140:543.
21. Gilchrist S, Torok TJ, Gary HEJ, et al. National surveillance for respiratory syncytial virus, United States, 1985–1990. J Infect Dis 1994;170:986.
22. Joffe S, Escobar GJ, Black SB, et al. Rehospitalization for respiratory syncytial virus among premature infants. Pediatrics 1999;104:894.
23. Milner ME, de La Monte SM, Hutchins GM. Fatal respiratory syncytial virus infection in severe combined immunodeficiency syndrome. Am J Dis Child 1985;139:1111.
24. Meissner HC. Selected populations at increased risk from RSV infections. Pediatr Infect Dis J 2003;22:S40–S45.
25. Groothuis JR, Gutierrez KM, Lauer BA. Respiratory syncytial virus infection in children with bronchopulmonary dysplasia. Pediatrics 1988;82:199.
26. Simoes EA, King SJ, Lehr MV, et al. Preterm twins and triplets: a high-risk group for severe respiratory syncytial virus infection. Am J Dis Child 1993;147:303.
27. Meissner HC, Anderson LJ, Pickering LK. Annual variation in RSV season and decisions regarding immunoprophylaxis with palivizumab. Pediatrics 2004;114:1082.
28. Shay DK, Homan RC, Roosevelt GE, et al, Bronchiolitis associated mortality and estimates of RSV associated deaths among United States children 1979–1997. J Infect Dis 2001;183:16.
29. Mullins JA, Lamonte AC, Bresee JS, et al. Substantial variability in community RSV season timing. Pediatr Infect Dis J 2003;22:857.
30. Gilca R, DeSerres G, Tremblay M, et al. Distribution and clinical impact of human respiratory syncytial virus genotypes in hospitalized children over two winter seasons. J infect Dis 2006;193;54.
31. Anderson LJ, Hendry RM, Pierik LT, et al. Multicenter study of strains of respiratory syncytial virus. J Infect Dis 1991;163:687.
32. Hall CB, Walsh EE, Schnabel KC, et al. Occurrence of groups A and B of respiratory syncytial virus over 15 years: associated epidemiologic and clinical characteristics in hospitalized and ambulatory children. J Infect Dis 1990;162:1283.
33. Martinello RA, Chen MD, Weibel C, et al. Correlation between RSV genotype and severity of illness. J Infect Dis 2002;186:839.
34. Meissner HC. The unresolved issue of risk factors for hospitalization of infants with RSV infection born after 33–35 weeks gestation. Pediatr Infect Dis J 2004;23:821.
35. Simoes EAF. Environmental and demographic risk factors for RSV lower respiratory tract disease. J Pediatr 2003;143:S118.
36. Anderson LJ, Parker RA, Strikas RA, et al. Day-care center attendance and hospitalization for lower respiratory tract illness. Pediatrics 1988;82:300.
37. Hall CB, Hall WJ, Gala CL, et al. Long-term prospective study in children after respiratory syncytial virus infection. J Pediatr 1984;105:358.
38. Reese AC, James IR, Landau LI, et al. Relationship between urinary cotinine level and diagnosis in children admitted to hospital. Am Rev Respir Dis 1992;146:66.
39. Holberg CJ, Wright AL, Martinez FD, et al. Risk factors for respiratory syncytial virus-associated lower respiratory illnesses in the first year of life. Am J Epidemiol 1991;133:1135.
40. Camilli AE, Holberg CJ, Wright AL, et al. Parental childhood respiratory illness and respiratory illness in their infants. Group Health Medical Associates. Pediatr Pulmonol 1993;16:275.
41. Pifferi M, Bertelloni C, Viegi G, et al. Airway response to a bronchodilator in healthy parents of infants with bronchiolitis. Chest 1994;105:706.

42. Le Saux N, Gaboury I, MacDonald N. Maternal RSV antibody titers: season and children matter. Pediatr Infect Dis J 2003;22:563.
43. Glezen WP, Paredes A, Allison JE, et al. Risk of respiratory syncytial virus infection for infants from low-income families in relationship to age, sex, ethnic group, and maternal antibody level. J Pediatr 1981;98:708.
44. Colby TV. Bronchiolitis: pathogenic considerations. Am J Clin Pathol 1997;109:233.
45. Aherne W, Bird T, Court SDM, et al. Pathological changes in virus infections of the lower respiratory tract in children. J Clin Pathol 1970;23:7–18.
46. Wohl ME, Chernick V. State of the art: bronchiolitis. Am Rev Respir Dis 1978;118:759.
47. Adams JM, Imagawa DT, Zike K. Epidemic bronchiolitis and pneumonitis related to respiratory syncytial virus. JAMA 1961;176:1037.
48. Price JF. Acute and long-term effects of viral bronchiolitis in infancy (review). Lung 1990;168:414.
49. Hogg JC, Williams J, Richardson JB, et al. Age as a factor in the distribution of lower-airway conductance and in the pathologic anatomy of obstructive lung disease. N Engl J Med 1970;282:1283.
50. Groothuis JR, Simoes AF, Levin MJ, et al. Prophylactic administration of respiratory syncytial virus immune globulin to high-risk infants and young children. N Engl J Med 1993;329:1524.
51. Groothuis JR. Role of antibody and use of respiratory syncytial virus (RSV) immune globulin to prevent severe RSV disease in high-risk children (review). J Pediatr 1994;124:S28.
52. PREVENT Study Group. Reduction of respiratory syncytial virus hospitalization among premature infants and infants with bronchopulmonary dysplasia using respiratory syncytial virus immune globulin prophylaxis. Pediatrics 1997;99:93.
53. Feltes TF, Cabalka AK, Meissner HC et al. Palivizumab prophylaxis reduces hospitalization due to RSV in young children with hemodynamically significant congenital heart disease. J Pediatr 2003;143:532–540.
54. IMpact-RSV Study Group. Palivizumab, a humanized respiratory syncytial virus monoclonal antibody, reduces hospitalization from respiratory syncytial virus infection in high-risk infants. Pediatrics 1998;102:531.
55. Welliver RC, Kaul A, Ogra PL. Cell-mediated immune response to respiratory syncytial virus infection: relationship to the development of reactive airway disease. J Pediatr 1979;94:370.
56. Welliver RC, Kaul TN, Ogra PL. The appearance of cell-bound IgE in respiratory-tract epithelium after respiratory syncytial virus infection. N Engl J Med 1980;303:1198.
57. Welliver RC, Wong DT, Middleton EJ, et al. Role of parainfluenza virus-specific IgE in pathogenesis of croup and wheezing subsequent to infection. J Pediatr 1982;101:889.
58. Welliver RC, Sun M, Rinaldo D, et al. Predictive value of respiratory syncytial virus-specific IgE responses for recurrent wheezing following bronchiolitis. J Pediatr 1986;109:776.
59. Murphy BR, Walsh EE. Formalin-inactivated respiratory syncytial virus vaccine induces antibodies to the fusion glycoprotein that are deficient in fusion-inhibiting activity. J Clin Microbiol 1988;26:1595.
60. Kim HW, Leikin SL, Arrobio J, et al. Cell-mediated immunity to respiratory syncytial virus induced by inactivated vaccine or by infection. Pediatr Res 1976;10:75.
61. Shaw KN, Bell LM, Sherman NH. Outpatient assessment of infants and children with bronchiolitis. Am J Dis Child 1991;145:151.
62. Mullholland EK, Olinsky A, Shann FA. Clinical findings and severity of acute bronchiolitis. Lancet 1990;335:1259.
63. Church NR, Anas NG, Hall CB, et al. Respiratory syncytial virus related apnea in infants. Am J Dis Child 1984;138:247.
64. Schiller O, Levy I, Pollak U, et al. Central apneas in infants with bronchiolitis admitted to the paediatric intensive care unit. Acta Paediatr 2010 September 3. doi:10.1111/j.1651-2227.2010.02004.x. [Epub ahead of print].
65. Meissner HC, Long SS. Revised indications for the use of palivizumab and RSV immune globulin intravenous for the prevention of RSV infections. Pediatrics 2003;112:1447.
66. American Academy of Pediatrics. Revised indications for the use of palivizumab and RSV immune globulin intravenous for the prevention of RSV infections. Pediatrics 2003;112:1442.
67. Simoes EAF, Sondheimer HM, Top FH, et al. RSV immune globulin for prophylaxis against RSV disease in infants and children with congenital heart disease. J Pediatr 1998;133:492.
68. Feltes TF, Cabalka AK, Meissner HC, et al. Palivizumab prophylaxis reduces hospitalization due to RSV in young children with hemodynamically significant congenital heart disease. Pediatrics 2003;143:532.
69. McMillan JA, Tristram DA, Weiner LB, et al. Prediction of the duration of hospitalization in patients with respiratory syncytial virus infection: use of clinical parameters. Pediatrics 1988;81:22.
70. Green M, Brayer AF, Schenkman KA, et al. Duration of hospitalization in previously well infants with respiratory syncytial virus infection. Pediatr Infect Dis 1989;8:601.
71. Wilson DF, Horn SD, Hendley JO, et al. The effect of practice variation on resource utilization in infants hospitalized for viral lower respiratory illness. Pediatrics 2001;108:851.
72. Brooks AM, McBride JT, McConnonchie KM, et al. Predicting deterioration in previously healthy infants hospitalized with RSV infection. Pediatrics 1999;104:463.
73. Hall CB, Hall WJ, Speers DM. Clinical and physiological manifestations of bronchiolitis and pneumonia: outcome of respiratory syncytial virus. Am J Dis Child 1979;133:798.
74. Osborne D. Radiologic appearance of viral disease of the lower respiratory tract in infants and children. Am J Roentgenol 1978;130:29.
75. Petuzella FD, Gorelick MH. Duration of illness in infants with bronchiolitis evaluated in the emergency department. Pediatrics 2010;126:285–290.
76. Wildin SR, Chonmaitree T, Swischuk LE. Roentgenographic features of common pediatric viral respiratory tract infections. Am J Dis Child 1988;142:43.
77. Michaels MG, Serdy C, Barbadora K, et al. Respiratory syncytial virus: a comparison of diagnostic modalities. Pediatr Infect Dis 1992;11:613.
78. Ray CG, Minnich LL. Efficiency of immunofluorescence for rapid detection of common respiratory viruses. J Clin Microbiol 1987;25:355.
79. Ryan-Poirer KA, Katz JM, Webster RG, et al. Application of Directigen FLU-A for the detection of influenza A virus in human and nonhuman specimens. J Clin Microbiol 1992;30:1072.
80. Landry ML, Ferguson D. SimulFluor respiratory screen for rapid detection of multiple respiratory viruses in clinical specimens by immunofluorescence staining. J Clin Microbiol 2000;38:708.
81. Rabalais GP, Stout GG, Ladd KL, et al. Rapid diagnosis of respiratory viral infections by using a shell vial assay and monoclonal antibody pool. J Clin Microbiol 1992;30:1505.
82. Cherian T, Bobo L, Steinhoff MC, et al. Use of PCR-enzyme immunoassay for identification of influenza A virus matrix RNA in clinical samples negative for cultivable virus. J Clin Microbiol 1994;32:623.

83. Eugene-Ruellan G, Freymuth F, Bahloul C, et al. Detection of respiratory syncytial virus A and B parainfluenzavirus 3 sequences in respiratory tracts of infants by a single PCR with primers targeted to the L-polymerase gene and differential hybridization. J Clin Microbiol 1998;36:796.
84. Fan J, Hendrickson KJ. Rapid simultaneous diagnosis of infections with respiratory syncytial viruses A and B, influenza viruses A and B, and human parainfluenza viruses types 1, 2, and 3 by multiplex quantitative reverse transcription-polymerase chain reaction-enzyme hybridation assay (Hexaplex). Clin Infect Dis 1998;26:1397.
85. Kellner JD, Ohlsson A, Gadomski AM, et al. Bronchodilators for bronchiolitis. Cochrane Database Syst Rev 2000; CD001266.
86. Roan Y, Galant SP. Decreased neutrophil beta-adrenergic receptors in the neonate. Pediatr Res 1982;16:591.
87. Reid L. Influence of the pattern of structural growth of lung on susceptibility to specific infectious diseases in infants and children. Pediatr Res 1977;11:210.
88. Henderson AJ, Young S, Stick SM, et al. Effect of salbutamol on histamine-induced bronchoconstriction in healthy infants. Thorax 1993;48:317.
89. Stick SM, Turner DJ, LeSouef PN. Lung function and bronchial challenges in infants. Pediatr Pulmonol 1993;16:177.
90. Turner DJ, Landau LI, LeSouef PN. The effect of age on bronchodilator responsiveness. Pediatr Pulmonol 1993;15:98.
91. Sanchez I, De Koster J, Powell RE, et al. Effect of racemic epinephrine and salbutamol on clinical score and pulmonary mechanics in infants with bronchiolitis. J Pediatr 1993;122:145.
92. Menon K, Sutcliffe T, Klassen TP, et al. A randomized trial comparing the efficacy of epinephrine to salbutamol in acute bronchiolitis. J Pediatr 1995;126:1004.
93. Lodrup Carlsen KC, Carlsen KH. Inhaled nebulized adrenaline improves lung function in infants with acute bronchiolitis. Respir Med 2000;94:709.
94. Modl M, Eber E, Weinhandle E, et al. Assessment of bronchodilator responsiveness in infants with bronchiolitis: a comparison of the tidal and the raised volume rapid thoracoabdominal compression technique. Am J Respir Crit Care Med 2000;161:763.
95. Klassen TP. Recent advances in the treatment of bronchiolitis and laryngitis. Pediatr Clin North Am 1997;44:249.
96. Tepper RS, Rosenberg D, Eigen H, et al. Bronchodilator responsiveness in infants with bronchiolitis. Pediatr Pulmonol 1994;17:81.
97. Wang EE, Milner R, Allen U, et al. Bronchodilators for treatment of mild bronchiolitis: a factorial randomised trial. Arch Dis Child 1992;67:289.
98. Gadomski AM, Aref GH, el Din OB, et al. Oral versus nebulized albuterol in the management of bronchiolitis in Egypt. J Pediatr 1994;124:131.
99. Dobson JV, Stephens-Groff SM, McMahon SR, et al. The use of albuterol in hospitalized infants with bronchiolitis. Pediatrics 1998;101:361–368.
100. Wainwright C, Altamirano L, Cheney M, et al. A multicenter, randomized, double blind, controlled trial of nebulized epinephrine in infants with acute bronchiolitis. N Engl J Med 2003;349:27.
101. Flores G, Horwitz RI. Efficacy of beta 2-agonists in bronchiolitis: a reappraisal and meta analysis. Pediatrics 1997;100:233.
102. Klassen TP, Sutcliffe T, Watters LK, et al. Dexamethasone in salbutamol-treated inpatients with acute bronchiolitis: a randomized, controlled trial. J Pediatr 1997;130:191.
103. Ermers MJJ, Rovers MM, van Woensel JB, et al. The effect of high dose inhaled corticosteroid on wheeze in infant after RSV infection: randomized double blind placebo controlled trial. British Medical Journal 2009;338:b897–04.
104. Corneli HM, Zorc JJ, Mahajan P, et al. A multicenter randomized controlled trial of dexamethasone for bronchiolitis. N Engl J Med 2007;357:331–339.
105. Springer C, Bar-Yishay E, Uwayyed K, et al. Corticosteroids do not affect the clinical or physiological status of infants with bronchiolitis. Pediatr Pulmonol 1990;9:181.
106. Van Woensel JB, Kimpen JL, Sprikkelman AB, et al. Long-term effects of prednisolone in the acute phase of bronchiolitis caused by respiratory syncytial virus. Pediatr Pulmonol 2000;30:92.
107. Richter H, Seddon P. Early nebulized budesonide in the treatment of bronchiolitis and the prevention of postbronchiolitic wheezing. J Pediatr 1998;132:849–853.
108. Berger I, Argaman Z, Schwartz SB, et al. Efficacy of corticosteroids in acute bronchiolitis: short-term and long-term follow-up. Pediatr Pulmonol 1998;26:162–166.
109. Schuh S, Coates AL, Binnie R, et al. Efficacy of oral dexamethasone in outpatients with acute bronchiolitis. J Pediatr 2002;140:27.
110. Csonka P, Kaila M, Laippala P, et al. Oral prednisolone in the acute management of children age 6 to 35 months with viral respiratory infection-induced lower airway disease: a randomized, placebo-controlled trial. J Pediatr 2003;143:725.
111. Garrison MM, Christakis DA, Harvey E, et al. Systemic corticosteroids in infant bronchiolitis: a meta-analysis. Pediatrics 2000;105:E44.
112. Plint AC, Johnson DW, Patel H, et al. Pediatric Emergency Research Canada (PERC). Epinephrine and dexamethasone in children with bronchiolitis. N Engl J Med 2009;360:2079.
113. Sumner A, Coyle D, Mitton C, et al. Cost-effectiveness of epinephrine and dexamethasone in children with bronchiolitis. Pediatrics 2010;126:623–631.
114. American Academy of Pediatrics, Committee on Infectious Diseases. Reassessment of the indications for ribavirin therapy in respiratory syncytial virus infections. Pediatrics 1996;97:137–140.
115. Hall CB, McBride JT, Walsh EE, et al. Aerosolized ribavirin treatment of infants with respiratory syncytial viral infection: a randomized double-blind study. N Engl J Med 1983;308:1443.
116. Taber LH, Knight V, Gilbert BE, et al. Ribavirin aerosol treatment of bronchiolitis associated with respiratory syncytial virus infection in infants. Pediatrics 1983;72:613.
117. Centers for Disease Control and Prevention. Prevention and control of influenza with vaccines. MMWR 2010;59(RR-8): 1–62.
118. Centers for Disease Control and Prevention. Neuraminidase inhibitors for treatment of influenza A and B infections. MMWR 1999;48:1139.
119. Hayden FG, Treanor JJ, Fritz RS, et al. Use of the oral neuraminidase inhibitor oseltamivir in experimental human influenza infection: randomized controlled trials for prevention and treatment. JAMA 1999;282:1240.
120. Clinical efficacy and safety of the orally inhaled neuraminidase inhibitor zanamivir in the treatment of influenza: a randomized, double-blind, placebo-controlled European study. J Infect 2000;40:42.
121. Hendrick JA, Barzilai A, Behre U, et al. Zanamivir for treatment of symptomatic influenza A and B infection in children five to twelve years of age: a randomized controlled trial. Pediatr Infect Dis J 2000;19:410.
122. Hemming VG, Rodriguez W, Kim HW, et al. Intravenous immunoglobulin treatment of respiratory syncytial virus infections in infants and young children. Antimicrob Agents Chemother 1987;31:1882.

123. Meissner HC, Fulton DR, Groothuis JR, et al. Controlled trial to evaluate protection of high risk infants against RSV by using standard intravenous immune globulin. Antimicrob Agents Chemother 1993;329:1524.
124. Rodriguez WJ, Gruber W, Welliver RC, et al. Respiratory syncytial virus (RSV) immunoglobulin therapy for RSV lower respiratory tract infection in infants and young children at high risk for severe RSV infection. Pediatrics 1997;99:454.
125. Rodriguez WJ, Gruber WC, Groothuis JR, et al. Respiratory syncytial virus immune globulin treatment of RSV lower respiratory tract infection in previously healthy children. Pediatrics 1997;100:937.
126. Malley R, DeVincenzo J, Ramilo O, et al. Reduction of respiratory syncytial virus (RSV) in tracheal aspirates in intubated infants by the use of humanized monoclonal antibody to RSV F protein. J Infect Dis 1998;178:1555.
127. Hussey GD, Klein M. A randomized controlled trial of vitamin A in children with severe measles. N Engl J Med 1990;323:160.
128. Neuzil KM, Gruber WC, Chytil F, et al. Serum vitamin A levels in respiratory syncytial virus infection. J Pediatr 1994;124:433.
129. Quinlan KP, Hayani KC. Vitamin A and respiratory syncytial virus infection. Arch Pediatr Adolesc Med 1996;150:25–30.
130. Burrows B, Knudson RJ, Leibowitz MD. The relationship of childhood respiratory illness to adult obstructive airway disease. Am Rev Respir Dis 1977;115:751.
131. McBride JT. Pulmonary function changes in children after respiratory syncytial virus infection in infancy. J Pediatr 1999;135:S28.
132. Welliver RC, Duffy L. The relationship of RSV-specific immunoglobulin E antibody responses in infancy, recurrent wheezing, and pulmonary function at age 7–8 years. Pediatr Pulmonol 1993;15:19.
133. Martinez FD, Wright AL, Taussig LM, et al. Asthma and wheezing in the first six years of life. N Engl J Med 1995;332:133.
134. Stein RT, Sherrill D, Morgan WJ, et al. Respiratory syncytial virus in early life and risk of wheeze and allergy by age 13 years. Lancet 1999;354:541.
135. Belshe BB, Newman FK, Anderson EL, et al. Evaluation of combined live, attenuated RSV and parainfluenza 3 virus vaccines in infants and young children. J Infect Dis 2004;190:2096.