REVIEW ARTICLE

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Viral Bronchiolitis in Children

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Few diseases have a greater effect on the health of young children than viral lower respiratory tract illness. Approximately 800,000 children in the United States, or approximately 20% of the annual birth cohort, require outpatient medical attention during the first year of life because of illness caused by respiratory syncytial virus (RSV).[1] Between 2% and 3% of all children younger than 12 months of age are hospitalized with a diagnosis of bronchiolitis, which accounts for between 57,000 and 172,000 hospitalizations annually.[1-4] Estimated nationwide hospital charges for care related to bronchiolitis in children younger than 2 years of age exceeded $1.7 billion in 2009.[5] Globally, in 2005, RSV alone was estimated to cause 66,000 to 199,000 deaths among children younger than 5 years of age, with a disproportionate number of these deaths occurring in resource-limited countries.[6,7] In the United States, by contrast, bronchiolitis due to RSV accounts for fewer than 100 deaths in young children annually.[8]

This review describes the current understanding of bronchiolitis, including the increasing number of viruses that are known to cause it, the current understanding of its pathogenesis, the importance of environmental and host genetic factors, and the roles of season, race, and sex in bronchiolitis attack rates and subsequent episodes of wheezing. In addition, guidelines from the American Academy of Pediatrics regarding the diagnosis, management, and prevention of bronchiolitis are summarized.[9,10]

Clinical Features

A young child with bronchiolitis typically presents to a health professional during the winter months after 2 to 4 days of low-grade fever, nasal congestion, and rhinorrhea with symptoms of lower respiratory tract illness that include cough, tachypnea, and increased respiratory effort as manifested by grunting, nasal flaring, and intercostal, subcostal, or supraclavicular retractions.[11] Inspiratory crackles and expiratory wheezing may be heard on auscultation. Various definitions of bronchiolitis have been proposed, but the term is generally applied to a first episode of wheezing in infants younger than 12 months of age. Apnea, especially in preterm infants in the first 2 months of life, may be an early manifestation of viral bronchiolitis.[12] Reported rates of apnea among infants with bronchiolitis range from 1 to 24%, reflecting differences in the definitions of bronchiolitis and apnea and the presence of coexisting conditions.

The variable course of bronchiolitis and the inability of medical personnel to predict whether supportive care will be needed often results in hospital admission even when symptoms are not severe. A variety of potential clinical markers have been proposed for use in identifying infants who are at risk for severe disease. Unfortunately, current scoring systems have low power to predict whether illness will progress to severe complications that would necessitate intensive care or mechanical ventilation.

Table 1. Viruses Detected in Nasopharyngeal Secretions from Hospitalized Children with Bronchiolitis.*

Virus	Type	Approximate Frequency	Seasonality in North America
		%	
Respiratory syncytial virus	A and B	50–80	November through April
Human rhinovirus	Groups A, B, and C; >100 serotypes	5–25	Peak activity in spring and autumn
Parainfluenza virus	Type 3 most common, followed by types 1, 2, and 4	5–25	Type 3 is most prominent during spring, summer, and fall in odd-numbered years
Human metapneumovirus	Subgroups A and B	5–10	Late winter and early spring; season typically peaks 1–2 mo later than RSV peak
Coronavirus	OC43, 229E NL63, and HKU1	5–10	Winter and spring
Adenovirus	>50 serotypes	5–10	Year-round, although season for certain serotypes may be more restricted
Influenza virus	A and B	1–5	November through April
Enterovirus	Echovirus and coxsackievirus	1–5	Generally June through October

* Viruses are listed in descending order of frequency as a cause of bronchiolitis. Human bocavirus has been detected as a copathogen in bronchiolitis, but it is isolated infrequently as a single agent in hospitalized children, leading to speculation that this virus is more likely to be an innocent bystander than a true pathogen. No evidence has been found for a primary role of bacteria as a cause of bronchiolitis, although *Bordetella pertussis*, *Chlamydia trachomatis*, or *Mycoplasma pneumoniae* may be included in the differential diagnosis of a lower respiratory tract infection in a young child. Coinfection with viral and bacterial pathogens such as *Haemophilus influenzae* type b or *Streptococcus pneumoniae* is uncommon, mainly because of the widespread use of conjugate polysaccharide vaccines. RSV denotes respiratory syncytial virus.

VIRAL CAUSES

The availability of molecular-detection techniques has made it possible to identify a diverse group of viruses that are capable of causing bronchiolitis (Table 1). Although the reported proportion of hospitalizations that are attributable to each virus differs according to the geographic area and the year, the most common pathogen is RSV, followed by human rhinovirus. RSV accounts for 50 to 80% of all hospitalizations for bronchiolitis during seasonal epidemics in North America.[1-4] Although the clinical features of bronchiolitis due to different viruses are generally indistinguishable, some differences in the severity of disease have been reported. For example, it has been observed that rhinovirus-associated bronchiolitis may result in a shorter length of hospitalization than bronchiolitis that is attributable to RSV.[13] Differences in the response to medical intervention have not been identified consistently among children with bronchiolitis caused by different viruses.

The epidemiologic and clinical importance of coinfection in hospitalized children with bronchiolitis is a focus of active research. Rates of coinfection vary widely among studies and range from 6% to more than 30%.[4,13-15] Greater disease severity, defined as a longer length of hospital stay or more severe hypoxemia, as well as a greater risk of medically attended relapse, have been reported among children with coinfection.[13,16,17] However, other studies have shown no difference in disease severity or have shown even less severe disease in children in whom more than one respiratory virus was isolated.[15,18,19] Studies that have used nucleic acid amplification tests suggest that one or more viral respiratory pathogens can be isolated from the upper respiratory tract of as many as 30% of asymptomatic young children.[20,21] It is not fully understood whether the detection of a viral genome in asymptomatic children represents prolonged shedding after an infection has resolved, an incubation period before a pending infection, a persistent, low-grade infection producing small amounts of virus, or infection by a serotype with limited ability to cause disease.

PATHOGENESIS

The immune response elicited by RSV may be both protective and pathogenic, and there appear to be functional differences between an initial infection in a seronegative infant and reinfection in an older child or adult (Fig. 1). RSV reinfections occur throughout life, despite the induction of both antibody and T-cell responses after a primary infection and the absence of a detectable antigenic change in RSV surface glycoproteins. How RSV evades or inhibits host defenses is not fully understood.[22]

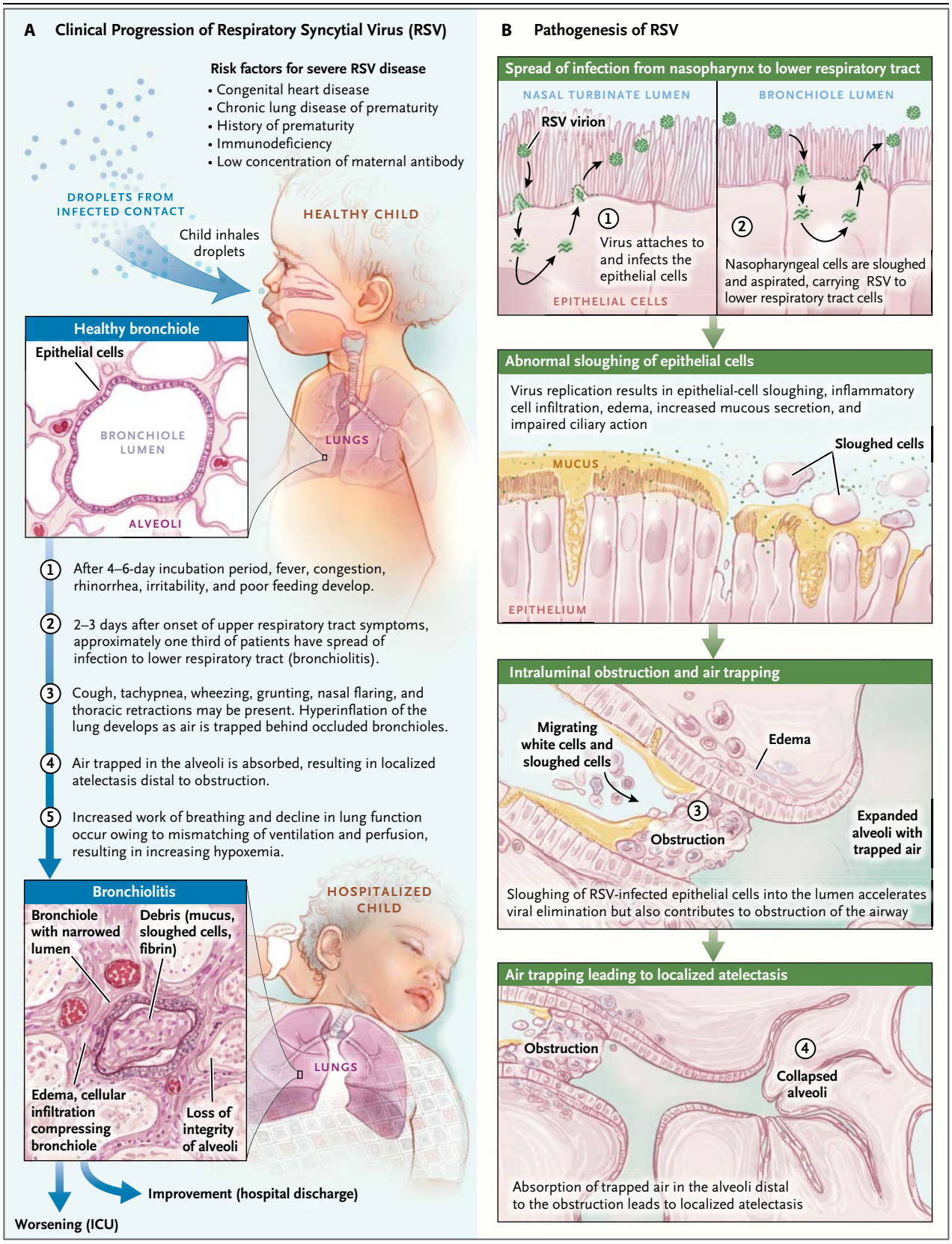
Results from a controlled clinical trial, conducted in the 1960s, of a formalin-inactivated RSV vaccine showed that a protective immune response did not develop in recipients of the vaccine.[11] Vaccine recipients who subsequently acquired natural RSV infection had more severe illness than did control participants. In addition, evidence suggests that both the relative balance between type 1 and type 2 helper T cells that respond to antigenic stimulation by the virus and the profile of evoked chemokines and cytokines determines the extent of RSV disease expression.[11] On the basis of these observations, most theories regarding the pathogenesis of bronchiolitis due to RSV implicate an exaggerated immune response as well as direct cellular damage from viral replication.[22]

Although neutralizing antibodies to viral surface glycoproteins are important for the prevention of RSV infection, T-cell–mediated responses appear to be crucial for viral clearance during infection.[23,24] Postmortem studies of lung tissue obtained from infants who died from RSV infection reveal macrophages and neutrophils and a relative absence of cytotoxic T cells, along with low concentrations of classic T-lymphocyte–derived cytokines (released by CD4+ and CD8+ T cells). These findings are not consistent with a pathologic inflammatory response.[25] Rather, the presence of abundant viral antigen suggests active RSV replication and direct virally induced cytotoxicity.[25]

At least in infants who have not had a previous infection, overwhelming RSV disease appears to be related to the lack of an adaptive cytotoxic T-cell response in the host; the result is dependence on the less effective innate immune response for the termination of viral replication. The fact that a more effective, adaptive cytotoxic T-cell response does not develop in such infants is supported by reports of a direct correlation between RSV load, as measured in nasopharyngeal aspirates obtained from children who have been hospitalized with bronchiolitis, and more severe disease, defined as a higher risk of apnea, a longer hospital stay, and a greater need for intensive care.[26,27] However, not all reports are consistent with an association between a high viral load in respiratory secretions and greater severity of disease.[28-30] A reasonable deduction is that direct cytotoxic injury induced by the virus and a robust host inflammatory response both contribute to the pathogenesis of RSV bronchiolitis, although the relative contribution of each remains uncertain. Resolution of this issue will determine whether a potent antiviral agent administered early in the course of bronchiolitis can reduce the duration and severity of illness without the need for immune modulation.

Figure 1 (facing page). Pathogenesis of Bronchiolitis Due to Respiratory Syncytial Virus (RSV).

Infection is acquired by inoculation of the nasal or conjunctival mucosa with contaminated secretions or by inhalation of large (>5 μm in diameter), virus-containing respiratory droplets within 2 m of an infectious patient. After an incubation period of 4 to 6 days, viral replication in the nasal epithelium results in congestion, rhinorrhea, irritability, and poor feeding. Fever occurs in approximately 50% of infected infants. Once in the lower respiratory tract, the virus infects the ciliated epithelial cells of the mucosa of the bronchioles and pneumocytes in the alveoli. Two RSV surface glycoproteins, F and G, mediate viral attachment to the glycocalyx of the target cell. Viral attachment initiates a conformational change in F protein to a postfusion structure that facilitates fusion of the viral envelope and the plasma membrane of the host cell, resulting in viral entry into the cell. Viral replication initiates an influx of natural killer cells, helper CD4+ and cytotoxic CD8+ T lymphocytes, and activated granulocytes. Cellular infiltration of the peribronchiolar tissue, edema, increased mucous secretion, sloughing of infected epithelial cells, and impaired ciliary beating cause varying degrees of intraluminal obstruction. During inspiration, negative intrapleural pressure is generated and air flows past the obstruction. The positive pressure of expiration further narrows the airways, producing greater obstruction, which causes wheezing. Innate and adaptive immune responses are involved in viral clearance, and most hospitalized children are discharged after 2 to 3 days. Regeneration of the bronchiolar epithelium begins within 3 to 4 days after the resolution of symptoms. ICU denotes intensive care unit.



RISK FACTORS

Most infants who are hospitalized with RSV bronchiolitis were born at full term with no known risk factors.[1,2] Chronologic age is the single most important predictor of the likelihood of severe bronchiolitis, given the observation that approximately two thirds of hospitalizations of infants with RSV infection occur in the first 5 months of life.[1-3] Hospitalization rates that are attributable to RSV bronchiolitis are highest between 30 and 90 days after birth, a period that corresponds to the declining concentration of transplacentally acquired maternal immunoglobulin.[3] Efficient transplacental passage of RSV neutralizing antibody occurs in infants who are born at full term.[31,32] Because most maternal immunoglobulin transfer occurs in the third trimester, preterm infants may miss the period of greatest IgG transfer; this fact partly explains the higher risk of disease among preterm infants.

Children with certain coexisting conditions, including prematurity (delivery at <29 weeks of gestation), chronic lung disease of prematurity, and congenital heart disease, may have more severe RSV disease than children without such conditions.[10,33] Some studies suggest that the risk of severe RSV disease is higher among premature infants born before 29 weeks of gestation than among those born at 29 weeks of gestation or later.[1,3,34,35] In contrast, the available data do not show significantly higher rates of hospitalization for RSV infection among preterm infants born from 29 to 36 weeks of gestation who do not have chronic lung disease of prematurity than among full-term infants (delivery at ≥37 weeks of gestation).[3,34,35]

Chronic lung disease of prematurity is characterized by alveolar loss, airway injury, inflammation and fibrosis due to mechanical ventilation, and high oxygen requirements.[36] Such lung injury increases the risk of severe bronchiolitis to a greater extent than does prematurity alone. Because of the use of antenatal glucocorticoids and surfactant replacement, improvements in methods of ventilatory support, and a better understanding of neonatal nutrition, many preterm infants are healthier at discharge today than in the past.

Infants born with certain types of hemodynamically important congenital heart disease, particularly those with pulmonary hypertension or congestive heart failure, are at greater risk for severe bronchiolitis than other infants, because they have limited ability to increase cardiac output in response to a respiratory infection.[37] Pulmonary hypertension shunts relatively unoxygenated blood away from the lung into the systemic circulation, leading to progressive hypoxemia. However, most data defining the relative risk of bronchiolitis among children born with congenital heart disease are more than 10 years old and may not reflect recent advances in corrective cardiac surgery that is undergone early in life.

The extent of the possible increase in the risk of severe bronchiolitis that can be attributed to other conditions (e.g., cystic fibrosis or Down's syndrome) has been difficult to quantify because of the low rates of occurrence of bronchiolitis and inconsistent study results. Most reported host and environmental factors are associated with only a small increase in the risk of hospitalization for RSV infection and thus have a limited contribution to the overall burden of RSV disease.[10] A prospective, population-based surveillance study sponsored by the Centers for Disease Control and Prevention (CDC) involved 132,000 infants, of whom 2539 were hospitalized because of an acute viral respiratory infection before 24 months of age.[1,3] Multiple logistic-regression analyses of frequently cited risk factors showed that only younger chronologic age and prematurity (born at <29 weeks of gestation) were independently associated with RSV illness that required hospitalization.[1] Inconsistent study results regarding host and environmental factors may be attributed to variations in practice patterns, living conditions, and climate, to differences in the virulence of circulating viral strains, to poorly understood genetic factors, and to differences in study design.

In temperate climates in the Northern Hemisphere, such as that in the United States, outbreaks of bronchiolitis typically begin in November, peak in January or February, and end by early spring.[38] Global surveillance data indicate that distinct annual epidemics of bronchiolitis occur in all countries, but the peak season and duration vary.[6,7] Maternal RSV antibody concentrations vary seasonally, with significantly higher serum concentrations being observed later in the RSV season than earlier in the season.[39,40]

Lower serum concentrations of maternal RSV antibody (resulting from waning maternal immunity from infection during the previous season) may account for the more severe disease that is observed among infants born early in the RSV season, as compared with those who are born later.[39,40] These observations raise the possibility that active maternal vaccination against RSV during gestation could have a beneficial clinical effect on the infant.[41]

Both environmental and meteorologic factors influence the timing of the respiratory-virus season by affecting viral stability, patterns of human behavior, and host defenses. Rainy seasons and cold weather prompt indoor crowding, which may facilitate viral transmission, especially in areas with high population density. A complex interaction has been identified among latitude, temperature, wind, humidity, rainfall, ultraviolet B radiation, cloud cover, and RSV activity.[42] Human susceptibility to viral infections may be altered by certain weather-related factors, such as the inhalation of cold, dry air that desiccates airway passages and alters ciliary function, or by the inhibition of temperature-dependent antiviral responses in the host.[43,44]

Racial and ethnic-group disparities in rates of hospitalization for bronchiolitis have been assessed in several reports. Rates of hospitalization for RSV infection among Alaska Native children living in the Yukon–Kuskokwim Delta in southwestern Alaska and in certain indigenous Canadian populations are reported to be five times as high as the rate among age-matched children in the continental United States.[45,46] Navajo and White Mountain Apache children younger than 2 years of age who are living on a reservation have rates of hospitalization for RSV infection that are up to three times as high as the overall rate among children younger than 2 years of age in the United States.[45,47] Possible explanations for these disparities include household crowding, indoor air pollution, lack of running water, and a lower threshold for hospital admission because of residence in a remote village that is distant from health care facilities. Data from several population-based CDC-sponsored reports indicate no disparity in the rates of hospitalization for RSV infection between black children and white children.[1-3,48] Because of the limited numbers of studies, reliable estimates for other ethnic and racial groups are not available.

Some studies have indicated that boys may be at greater risk for severe RSV bronchiolitis than girls; this finding is similar to the sex difference observed with other respiratory viral infections.[2,3] Sex differences in lung and airway development and genetic factors have been suggested as explanations of these findings.[49]

BRONCHIOLITIS AND ASTHMA

Severe bronchiolitis early in life is associated with an increased risk of asthma, especially after rhinovirus or RSV bronchiolitis, and an increased risk of asthma may persist into early adulthood.[50-52] An unresolved question is whether bronchiolitis early in life results in injury that alters normal lung development and predisposes the child to subsequent wheezing or whether certain infants have a preexisting aberration of the immune response or of airway function that predisposes them to both severe bronchiolitis and recurrent wheezing.[53]

Some data support the interesting possibility that premorbid lung function may be abnormal among infants who have severe bronchiolitis in the first year of life.[54-57] Pulmonary-function studies conducted before discharge from the neonatal unit and then repeated after each child's first RSV season show persistent pulmonary abnormalities in some infants, regardless of whether they had bronchiolitis. This finding suggests that preexisting pulmonary abnormalities are separate from bronchiolitis and not a complication of it.[57] For example, some infants may have narrow airways when they are well; as a result, bronchioles are less likely to remain patent once they become further narrowed by infection. Confirmation of this possibility would make it possible to identify infants who would be most likely to benefit from active or passive prophylaxis.

A genetic predisposition to severe bronchiolitis early in life and to the subsequent development of asthma is supported by reported associations between polymorphisms in genes involved in the innate immune response and genes mediating allergic responses, surfactant proteins, and inflammatory cytokines.[58-60] An association between rhinovirus infection early in life and an increased risk of childhood-onset asthma is associated with genetic variation at the chromosome 17q21 locus.[52] The fact that this associa-

tion was not found to extend to young children with severe RSV infection indicates that there is a complex interaction between genetic and environmental factors in the development of asthma. Results from a Danish study involving twins suggested that severe RSV bronchiolitis is an indicator of a genetic predisposition to asthma and that, in the absence of this predisposition, asthma is less likely to develop even if they had previously had bronchiolitis.[61]

Whether the prevention of severe RSV bronchiolitis will reduce the number of episodes of recurrent wheezing has been studied, but the answer remains elusive. A randomized, double-blind, placebo-controlled trial conducted in the Netherlands involving preterm infants born at 33 to 35 weeks of gestation addressed the possible benefit of prophylaxis with palivizumab (a humanized anti-RSV antibody) in preventing wheezing during the first year of life.[62] Recipients of RSV immunoprophylaxis had a significant relative reduction of 61% in the number of days of wheezing; this difference resulted in their having 2.7 fewer days of wheezing per 100 patient-days than did participants who received placebo. Because the viral cause of wheezing episodes was determined inconsistently and the primary end point of the study was audible wheezing as reported by a parent, rather than a medically verified event, the small reduction in the number of days with wheezing is of uncertain clinical significance.

A prospective randomized, placebo-controlled trial with motavizumab (a second-generation monoclonal antibody with greater potency against RSV than palivizumab) that involved 2696 healthy, full-term Native American infants showed a significant between-group difference (in favor of motavizumab) in both inpatient and outpatient medically attended RSV lower tract disease.[63] However, no reduction in wheezing occurred among prophylaxis recipients during 3 years of careful follow-up. This result is consistent with the concept that prevention of RSV infection with immunoprophylaxis does not have a measurable effect on subsequent episodes of wheezing.

SUPPORTIVE MANAGEMENT

Despite the high burden of disease due to bronchiolitis, it has been difficult to define the best possible care for a young child with this illness because of the lack of curative therapy. No available treatment shortens the course of bronchiolitis or hastens the resolution of symptoms. Therapy is supportive, and the vast majority of children with bronchiolitis do well regardless of how it is managed. The intensity of therapy among hospitalized children has been shown to have little relationship to the severity of illness.[64,65]

To improve the standardization of the diagnosis and management of bronchiolitis in children, the American Academy of Pediatrics published a clinical practice guideline, which was based on a Grading of Recommendations, Assessment, Development and Evaluation (GRADE) analysis, to clarify the level of evidence required for diagnosis and to assess the relationship of benefit to harm and the strength of recommendations regarding various aspects of the diagnosis, treatment, and prevention of bronchiolitis.[9,10,66] The evidence-based guidelines emphasize that a diagnosis of bronchiolitis should be based on the history and physical examination and that radiographic and laboratory studies should not be obtained routinely (Table 2). Short-acting β_2-agonists, epinephrine, and systemic glucocorticoids are not recommended for the treatment of children with bronchiolitis. Clinicians may elect not to administer supplemental oxygen when oxyhemoglobin saturation exceeds 90%. Intravenous or nasogastric fluids may be used for children with bronchiolitis who cannot maintain hydration orally. A complete discussion regarding the management of bronchiolitis is available in the clinical practice guidelines.[9]

IMMUNOPROPHYLAXIS

Palivizumab, a humanized mouse IgG1 monoclonal antibody directed against a conserved epitope on the surface fusion protein of RSV, was licensed by the Food and Drug Administration in June 1998 for monthly prophylaxis for infants at high risk for RSV infection.[10] Licensure was based largely on the results of a randomized, double-blind, placebo-controlled trial conducted during the 1996–1997 RSV season, which showed a reduction of 5.8% in the rate of hospitalization attributable to RSV among preterm infants (10.6% in the placebo group vs.

Table 2. American Academy of Pediatrics Guidance for Diagnosis and Management of Bronchiolitis.*

Intervention	Recommendation	Comment
Diagnostic Test		
Chest radiography	Not recommended for routine use	Poor correlation with severity of disease or risk of progression; studies show increase in inappropriate use of antimicrobial therapy owing to similar radiographic appearance of atelectasis and infiltrate
Testing for viral cause	Not recommended for routine use	May influence isolation of symptomatic patients, but infection-control procedures are similar for most respiratory viruses
Treatment		
Bronchodilator therapy	Not recommended	Randomized trials have not shown a consistent beneficial effect on disease resolution, need for hospitalization, or length of stay
Epinephrine	Not recommended	Large, multicenter, randomized trials have not shown improvement in outcome among outpatients with bronchiolitis or hospitalized children
Glucocorticoid therapy	Not recommended	Large, multicenter, randomized trials provide clear evidence of lack of benefit
Nebulized hypertonic saline	May be considered	Nebulized 3% saline may improve symptoms of mild-to-moderate bronchiolitis if length of stay is >3 days (most hospitalizations are <72 hr)
Supplemental oxygen	Routine use not recommended if oxyhemoglobin saturation is >90% in the absence of acidosis	Transient episodes of hypoxemia are not associated with complications; such episodes occur commonly in healthy children
Pulse oximetry	Not recommended for patients who do not require supplemental oxygen or if oxygen saturation is >90%	Oxygen saturation is a poor predictor of respiratory distress; routine use correlates with prolonged stays in the emergency department and hospital
Chest physiotherapy	Not recommended	Deep suctioning is associated with a prolonged hospital stay; removal of obstructive secretions by suctioning the nasopharynx may provide temporary relief
Antimicrobial therapy	Not recommended for routine use	Risk of serious bacterial infection is low; routine screening is not warranted, especially among infants 30 to 90 days of age
Nutrition and hydration	Hospitalization for observation of hydration and nutritional status may be needed for infants with respiratory distress	Intravenous or nasogastric hydration may be used

* Adapted from the clinical practice guidelines for the diagnosis and management of bronchiolitis in children 1 through 23 months of age.[9]

4.8% in the prophylaxis group, P<0.001).[23] Recommendations for more restrictive use of passive immunoprophylaxis have evolved since palivizumab was licensed as additional information has become available regarding the epidemiology of RSV and the limited benefit of prophylaxis. Guidance from the American Academy of Pediatrics regarding the use of palivizumab is stratified according to risk, targeting the infants who are most likely to benefit from prophylaxis.[9,10] Table 3 presents an overview of the current guidelines regarding immunoprophylaxis.

FUTURE DIRECTIONS

RSV is one of the last viruses to cause annual worldwide outbreaks of disease against which no safe and effective vaccine is available. Several approaches to vaccine development are being investigated.[68] A live attenuated vaccine for intranasal administration would stimulate both topical and systemic immunity; such a vaccine is being developed with the use of reverse genetics to modify specific genes. Efforts to date have been hampered by the difficulty of achieving

Table 3. American Academy of Pediatrics Guidance for Palivizumab Immunoprophylaxis.*

Category	Prophylaxis Recommendation	Comment
Preterm infants without chronic lung disease of prematurity or congenital heart disease and <12 mo of age at start of RSV season		
Born at <29 wk of gestation	Maximum five monthly doses or until end of RSV season, whichever comes first	Rate of hospitalization for RSV infection is higher than among infants born at ≥29 wk of gestation[3,34,35]
Born at ≥29 wk of gestation	Not recommended	No significant difference, as compared with full-term infants, in rate of hospitalization for bronchiolitis[3,34,35]
Infants born at <32 wk of gestation with chronic lung disease of prematurity and requirement for supplemental oxygen for first 28 days of life	Maximum five monthly doses or until end of RSV season, whichever comes first	Palivizumab prophylaxis reduced rates of hospitalization for RSV by 4.9% among 762 preterm infants with chronic lung disease (12.8% in the control group vs. 7.9% in the prophylaxis group, P=0.04)[23]
Infants born with congenital heart disease		
Cyanotic disease	Not recommended routinely	No significant reduction in rates of hospitalization for RSV (7.9% in the placebo group vs. 5.6% in the palivizumab group, P=0.28)
Acyanotic disease	Five monthly doses or until end of RSV season, whichever comes first	Prophylaxis associated with a 6.8% reduction in rate of hospitalization for RSV (11.8% in the placebo group vs. 5.0% in the palivizumab group, P=0.003)[37]
Children >12 mo of age	Not recommended except for children with chronic lung disease who continue to require supplemental oxygen or diuretic or glucocorticoid therapy	Except for children with chronic lung disease, RSV hospitalization rates in second year of life are less than rates for first 6 mo of life among healthy, full-term infants for whom prophylaxis is not recommended[34]

* Guidance for the use of palivizumab for immunoprophylaxis was first provided in 1998.[67] It has been revised periodically to reflect ongoing assessments of peer-reviewed studies regarding the minimal benefit of palivizumab prophylaxis on the hospitalization rate among preterm infants, the absence of a significant reduction in mortality or the need for mechanical ventilation among RSV-infected children who received palivizumab as compared with those who received placebo, the enhanced understanding of the pharmacokinetics of palivizumab, the seasonality of RSV circulation in the United States (as shown in data from the Centers for Disease Control and Prevention[38]), the declining incidence of hospitalization for all-cause bronchiolitis, decreasing mortality among children hospitalized with laboratory-confirmed RSV infection, and data showing clinically minimal or no reduction in wheezing episodes among children who received prophylaxis.[62,64]

adequate attenuation of the vaccine strain, so that symptoms do not develop in the vaccine recipient, while at the same time maintaining adequate immunogenicity so that immunity is conferred. Subunit vaccines are being explored and may be appropriate for seropositive patients; concern about possible enhancement of disease in seronegative vaccine recipients (particularly seronegative infants) must be resolved, however, before trials can proceed. A third approach involves maternal immunization during pregnancy with use of a nonreplicating vaccine. Results from a trial with an RSV recombinant fusion protein nanoparticle vaccine indicate safety and immunogenicity in women of childbearing age.[69] If neutralizing antibodies undergo transplacental passage, protection may be provided for the infant during the first months of life. This approach would circumvent the need for vaccination in the first weeks of life, when an infant's immune response is limited.

Until safe and effective vaccines are available, reduction of the burden of disease due to bronchiolitis will focus on education about the importance of decreasing exposure to and transmission of respiratory viruses. The application of new forms of technology to the development of vaccines and antiviral therapies such as fusion inhibitors and nucleoside analogues may improve the prevention of RSV infection and the treatment of children with bronchiolitis throughout the world.[68,69]

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Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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