Respiratory Syncytial Virus Bronchiolitis

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Respiratory syncytial virus, the most common cause of bronchiolitis, is the leading cause of infant hospitalization in developed countries and accounts for substantial mortality and morbidity in developing countries. Children at increased risk of developing severe bronchiolitis are those <6 weeks of age, those born prematurely and those with an underlying cardiopulmonary disorder or immunodeficiency. Approximately 80% of cases occur in the first year of life. By two years of age, virtually all children have been infected by at least one strain of the virus. Classically, respiratory syncytial virus bronchiolitis manifests as cough, wheezing and respiratory distress. The mainstay of treatment is supportive care, consisting of adequate fluid intake, antipyretics to control fever and use of supplemental oxygen if necessary. Frequent and meticulous hand-washing is the best measure to prevent secondary spread. Treatment of respiratory syncytial virus bronchiolitis beyond supportive care should be individualized. Palivizumab has been shown to be effective in preventing severe respiratory syncytial virus bronchiolitis in high-risk children when given prophylactically. In the majority of cases, the disease is usually self-limited. The mortality rate is <1% and occurs predominantly in children at high risk for severe disease.

Key words: respiratory syncytial virus ■ bronchiolitis ■ prematurity ■ cardiopulmonary disease ■ immunodeficiency ■ palivizumab

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INTRODUCTION

Bronchiolitis is a clinical syndrome of acute viral lower respiratory tract illness characterized by fever, coryza, cough, expiratory wheezing and respiratory distress.[1,2] It is the most common lower respiratory tract infection in infants and young children.[3] Respiratory syncytial virus (RSV) is the most common cause of bronchiolitis.[4,5] RSV bronchiolitis is the leading cause of infant hospitalization in developed countries.[6] Approximately 2–3% of children infected with RSV require hospitalization.[7,8] RSV bronchiolitis accounts for substantial mortality and morbidity in developing countries. Worldwide, RSV claims 3–5 million human lives annually.[9] Children at increased risk of developing severe and occasionally, fatal, RSV bronchiolitis include those <6 weeks of age, those born prematurely and those with chronic lung disease, congenital heart disease or immunodeficiency.[10-13]

THE ORGANISM

RSV is an enveloped RNA virus that belongs to the *Paramyxoviridae* family, within the Pneumovirus genus.[9,14] The virus has a nonsegmented, single-stranded, negative-sense genome.[15] The genome encodes ≥11 proteins.[14] Surface glycoproteins F and G exert fusogenic and attachment properties, respectively.[16] Two major RSV subtypes (A and B) have been identified based on structural variations in the G protein. The virus lacks neuraminidase and hemagglutinin surface glycoproteins.[17] RSV is so named because of the characteristic syncytial pattern observed in tissue culture.[15] The virus withstands changes in temperature and pH relatively poorly and is rapidly inactivated by chloroform, ether and detergents, such as sodium deoxycholate.[18]

EPIDEMIOLOGY

Approximately 80% of cases of RSV bronchiolitis occur in the first year of life, with a peak age of incidence between 2–6 months.[3,19] By two years of age, virtually all children have been infected by RSV

at least once and about half of them, twice.[9,20] Boys are more frequently affected by RSV bronchiolitis; the male-to-female ratio is approximately 1.5:1.[21] Other predisposing factors to the development of bronchiolitis include prematurity, cardiopulmonary disease, immunodeficiency, tobacco exposure, day-care attendance, lower socioeconomic status, overcrowding and lack of breastfeeding.[14,19]

In temperate climates, RSV bronchiolitis is most frequently seen during winter and early spring. In tropical climates, the disease occurs more frequently during the rainy season.

RSV bronchiolitis is extremely contagious. RSV is transmitted mainly by contact with infected respiratory secretions.[17] Hand carriage of contaminated secretions is the most frequent mode of transmission.[21] Droplets and fomites do not play as important a role.[19,21]

PATHOGENESIS AND PATHOPHYSIOLOGY

RSV infection causes inflammation and necrosis of the bronchiolar epithelial cells. The initial pathologic findings in RSV bronchiolitis consist of a lymphocytic peribronchiolar infiltration and submucosal edema.[18,19] Cytokines and chemokines, released by infected respiratory epithelial cells, amplify the immune response by increasing cellular recruitment into the infected airways.[14,22,23] Interferon-γ, interleukin-4, interleukin-8 and interleukin-9 are found in high concentrations in respiratory secretions of infants with RSV bronchiolitis.[20,22] Clinical manifestations and severity of RSV bronchiolitis are likely determined by, at least in part, local immunological responses to infection.[20,22]

The lumina of the bronchioles become obstructed from edema of the airway wall, increased mucus secretion, sloughed epithelium and cellular debris.[18,24] The small-diameter airways in infants are particularly vulnerable to obstruction.[21] Bronchioles normally dilate on inspiration and narrow on expiration.[18] The resultant ball-valve bronchiolar obstruction leads to air trapping and hyperinflation. In lung segments in which bronchiolar obstruction is complete, trapped air becomes absorbed, and atelectasis results.[18]

CLINICAL MANIFESTATIONS

The incubation period varies from 2–8 days.[17] Coryza, mild cough, fever, lethargy and decreased appetite are common at the onset of illness. This then progresses to noisy, raspy breathing and wheezy cough. Physical examination is characterized by prolonged expiratory phase, wheezing, tachypnea, dyspnea, intercostal retractions, hyper-resonance on chest percussion and tachycardia. Rales and rhonchi may be heard. In one study, crackles were found in 47% of patients with RSV bronchiolitis.[25] With progression of the disease, there may be flaring of the alae nasae, expiratory grunting, severe subcostal, supraclavicular and intercostal retractions, marked tachypnea and marked tachycardia. Cyanosis may occur.

COMPLICATIONS

Complications are common in infants with severe RSV bronchiolitis. In one retrospective study of 684 infants hospitalized for bronchiolitis or RSV pneumonia, 540 (79%) infants had one or more complications. Serious complications occurred in 24%.[6] Respiratory complications were most frequent (60%), but infections (41%), cardiovascular abnormalities (9%), electrolyte imbalance (19%) and other complications (9%) were common.[6] Former premature infants and infants with congenital abnormalities were at signifi-

Table 1. Recommendations by the American Academy of Pediatrics, Committee on Infectious Diseases and Committee on Fetus and Newborn for the use of palivizumab prophylaxis in high-risk children[42]

A. Chronic lung disease
Those under two years at start of RSV season who have required medical therapy for chronic lung disease within the past six months

B. Prematurity
a) Gestational age ≤28 weeks, age <12 months at start of RSV season
b) Gestational age 29 weeks to 32 weeks, age <6 months at start of RSV season
c) Gestational age 32 weeks 1 day to 35 weeks, age <6 months at start of RSV season, if ≥2 of the following risk factors are present
- child-care attendance
- school-aged siblings
- exposure to environmental air pollutants
- congenital abnormalities of the airways
- severe neuromuscular disease

C. Hemodynamically significant congenital heart disease
≤2 years at start of RSV season

cantly greater risk for complications.[6]

Respiratory complications include apnea and hypoxemia. RSV-related apnea is central in origin and observed in approximately 10–25% of infants hospitalized for bronchiolitis.[3,26] Most at risk for developing apnea are preterm infants born at <32 weeks' gestation age, infants with a history of apnea of prematurity and infants with pulmonary hypertension.[18,19]

Hypoxemia results from ventilation-perfusion mismatch. In RSV bronchiolitis, hypoxemia is often out of proportion to the severity of respiratory distress.[3] Hypercapnia is seen only in severe cases. Respiratory failure is rare with proper management.

Secondary bacterial infection is an uncommon complication.[27,28] In a nine-year prospective study of 565 children hospitalized with RSV lower respiratory tract infections, the rate of secondary bacterial pneumonia was 1.2%.[28] On the other hand, otitis media due to RSV is not uncommon.[15]

Cardiovascular abnormalities have been occasionally reported during bronchiolitis.[29] Sreeram studied 21 children with acute bronchiolitis and no history of known underlying cardiac disease.[29] Doppler echocardiography showed tricuspid regurgitation in 11 of 21 patients and the majority of them had evidence of pulmonary hypertension. Serial studies showed that tricuspid regurgitation disappeared with clinical improvement. Since the studied number was small, Sreeman's findings need to be confirmed by larger studies. Other cardiovascular complications include arrhythmias and, rarely, ventricular tachycardia.[6]

Dehydration may occur because oral intake is often reduced secondary to lethargy, nausea/vomiting, and dyspnea and fluid requirements are increased secondary to tachypnea and fever.[30] Paroxysms of cough may trigger vomiting. Children with RSV bronchiolitis are particularly at risk for hyponatremia because of increased antidiuretic hormone secretion, compounded by administration of hypotonic fluid.[31]

There may be a transient increased risk of swallowing dysfunction and aspiration in infants with RSV bronchiolitis.[32] Affected infants may not be able to coordinate their rapid breathing with sucking and swallowing.[33]

Children with RSV bronchiolitis in early life are at increased risk of developing asthma later in childhood, although the association is lost by 13 years of age.[34-36] Kneyber et al. performed a quantitative review of four controlled studies to determine whether or not RSV bronchiolitis induces asthma in later life.[36] A total of 517 children with RSV bronchiolitis were included in the analysis. After up to five years of follow-up, 40% of children reported wheezing as compared to only 11% in the control group. Between 5–10 years of follow-up, 22% of the bronchiolitis group reported wheezing compared to 10% of the control group. It has been suggested that RSV infection induces T-helper (Th)-2 responses to allergens.[35,37] Interleukin-9 is a type-2, cell-derived cytokine. Genetic linkage studies have suggested that interleukin-9 might play an important role in the pathogenesis of asthma.[38]

DIFFERENTIAL DIAGNOSIS

Bronchiolitis may also be caused by other viruses such as parainfluenza virus, influenza virus, adenovirus, rhinovirus, enterovirus, *Mycoplasma pneumoniae* and metapneumovirus. It is difficult, if not impossible, to differentiate RSV bronchiolitis from the first episode of asthma, especially if the asthma exacerbation is triggered by an upper respiratory infection. Age of >18 months, repeated episodes of wheezing, absence of a preceding upper respiratory tract infection, and family or personal history of atopic disease support a diagnosis of asthma. The differential diagnosis of bronchiolitis also includes foreign-body aspiration, anaphylaxis, whooping cough, exacerbation of bronchopulmonary dysplasia, congestive heart failure, cystic fibrosis, gastroesophageal reflux, tracheomalacia/bronchomalacia, tracheoesophageal fistula and vascular rings.[1,39]

LABORATORY INVESTIGATIONS

The diagnosis of bronchiolitis is mainly a clinical one. Laboratory investigations are usually not necessary for healthy children treated as outpatients.[40] Typical chest radiographic findings are hyperinflation with associated depressed diaphragms, hyperlucency of the lung parenchyma and decreased costophrenic angles. Areas of atelectasis are often noted in the right, upper or middle lobe and may be difficult to differentiate from the infiltrates of pneumonia.[18] In RSV infection, bronchiolitis and pneumonia may coexist.[18] Clinicians basing the diagnosis on radiographic findings should be aware that there is variation among radiologists in intra- and interobserver agreement on the radiographic features used for diagnosis.[41]

Definitive diagnosis of RSV as the causative agent for bronchiolitis can be established by rapid diagnostic assays, including enzyme-linked immunosorbent assay (ELISA) and fluorescent antibody techniques for detection of the viral antigen. For children admitted to the hospital, diagnostic tests are advisable to confirm RSV or another pathogen so that children can be cohorted appropriately in multibed rooms. Nasal wash is the preferred method of specimen collection.[15] The sensitivity of these tests is usually 80–90%, and their specificity is 90–95%.[18,42] Amplification of the virus using the shell vial method and

amplification of viral genome by polymerase chain reaction (PCR) has been used to improve the sensitivity of rapid diagnostic assays. However, these new techniques are expensive, not available commercially and not as rapid as the rapid diagnostic assays. RSV can be cultured in appropriate cell lines, such as Hep-2 and HeLa cells.[15] Viral culture is expensive and requires 3–7 days.[15,17] Viral culture is the current reference laboratory gold standard.

MANAGEMENT

Supportive Care

Most healthy children who have RSV bronchiolitis do not require specific treatment and can be managed at home. Hospitalization may be necessary for children with inadequate fluid intake, lethargy or respiratory distress.[24] The mainstay of therapy is supportive care, consisting of adequate fluid intake, antipyretics and use of supplemental oxygen if necessary.[2,30] Care should be taken to avoid fluid overload with subsequent pulmonary congestion.[30] Careful clinical assessment of respiratory status, including the use of pulse oximetry, is essential for hospitalized children.[43] Supplemental oxygen should be given if the patient's oxygen saturation is consistently <92% on room air (level-C evidence).[30,44] The use of mist is discouraged by some, as such use may lead to reflex bronchospasm.[45] There is no evidence to support the use of chest physiotherapy.[19,46] Treatment of RSV bronchiolitis beyond supportive care should be individualized.

Bronchodilators

Kellner et al. performed a meta-analysis of bronchodilator therapy in infants with bronchiolitis and reported that bronchodilators produced a modest short-term improvement in clinical scores.[47,48] The rate and duration of hospitalization, however, were not affected by bronchodilator therapy. The authors conclude that routine use of bronchodilators in those who wheeze for the first time is not justified, given the modest short-term clinical improvement along with the high cost of the medication. Theoretically, epinephrine has an added advantage over β_2 adrenergic selective bronchodilators because its α adrenergic component may diminish catarrhal secretions and mucosal edema of the airway.[30,49] A meta-analysis of 14 randomized, controlled trials that included inhaled or systemic epinephrine as one of the bronchodilators showed that epinephrine may be favorable to salbutamol and placebo among outpatients with bronchiolitis.[50] However, there is insufficient evidence to support its use for the treatment of bronchiolitis among inpatients.[50] Because some children will respond to bronchodilators, if bronchodilators are to be tried, careful clinical evaluation of the response to the first few doses must be made in order for a decision to be made about continuance or discontinuance of the medication.

Corticosteroids

Corticosteroids are not indicated for routine management of RSV bronchiolitis. A recent meta-analysis of 13 randomized, controlled trials (n=1,198) showed no benefits in either length of hospital stay or clinical score in children treated with corticosteroids.[51] Goebel et al. showed that the use of a corticosteroid plus a bronchodilator offered more benefit than either agent alone.[52] Schuh et al. have demonstrated that children with moderate-to-severe acute bronchiolitis may benefit from early (first four hours of therapy), high-dose (1 mg/kg) oral dexamethasone.[53] New studies should be carried out to confirm or refute Schuh et al.'s findings.

Antiviral Therapy

Ribavirin is a synthetic guanosine analog that suppresses viral RNA polymerase activity and inhibits protein synthesis.[2,15] A meta-analysis of eight randomized, controlled trials failed to demonstrate statistically significant effects on morbidity and mortality rates.[54] King et al., after excluding some studies that Randolph et al. had included, because those studies did not have an adequate control group or because of inability to assign outcomes to a relevant subset of randomized patients, found no evidence that ribavirin therapy led to consistent or more-than-transient improvements in clinical outcomes.[55] The American Academy of Pediatrics has recommended that decisions about ribavirin administration should be made on the basis of the particular clinical circumstances and physicians' experience.[17]

Montelukast

Cysteinyl-leukotrienes (Cys-LT) are potent, proinflammatory mediators and bronchoconstrictors and are released in the respiratory tract during RSV bronchiolitis.[56] One study suggests that the use of montelukast, a Cys-LT receptor antagonist, may reduce postbronchiolitis reactive airway disease. More studies are needed before the routine use of montelukast in the treatment of RSV bronchiolitis can be recommended.

Antibiotics

The routine use of antibiotics is not indicated because bacterial pneumonia or bacteremia is rare in bronchiolitis.[28,45] Antibiotics should only be used if there is secondary bacterial infection. Indiscriminate use of antibiotics for viral infection should be strongly discouraged.

PREVENTION

Control Measures

As RSV is transmitted mainly by contact with infected respiratory secretions, frequent and meticulous handwashing is the best preventive measure.[15] Contaminated environmental surfaces should be cleaned.[57] In the hospital, infected children should be identified early and placed in contact isolation.[15,21] The use of gowns, gloves, masks and goggles by caretakers can help to reduce transmission in the hospital.[17,21] Staff with respiratory tract illness should not care for high-risk infants.[17,18] Other preventive strategies include limiting exposure to crowded places (e.g., day-care centers) and eliminating passive exposure to cigarette smoke.[3,24,57]

Immunoprophylaxis

Respiratory syncytial virus immune globulin intravenous (RSV-IGIV, RespiGam) and palivizumab (Synagis), a recombinant humanized murine monoclonal immunoglobulin G that binds to the RSV F protein, have been shown to be effective in preventing severe RSV bronchiolitis in high-risk children when given prophylactically.[42,58,59] Palivizumab is preferred because of its ease of administration, safety, potency, effectiveness and noninterference with the vaccines in the immunization schedule.[15,19,42] Moreover, RSV-IGIV is contraindicated for use in children with hemodynamically significant heart disease, while palivizumab is effective for this.[42,58] RSV-IGIV has been practically supplanted by palivizumab and is no longer marketed in the United States.[14] Palivizumab is administered intramuscularly at a dosage of 15 mg/kg monthly, beginning just before onset of the RSV season, for a total of five months.[17] The American Academy of Pediatrics recommends the use of palivizumab for prophylaxis in high-risk children (Table 1).[42] The primary benefit of immunoprophylaxis is a decrease in the hospitalization rate due to RSV bronchiolitis.[60-63] So far, none of the randomized, controlled trials have shown a significant decrease in the mortality rate.[60-63] Cost-effective analyses suggest that there is no savings in healthcare dollars if all at-risk children were to receive immunoprophylaxis.[63]

There is currently a phase-III efficacy trial comparing an enhanced potency humanized monoclonal antibody (NumaxTM, Medimmune) with palivizumab in infants at high risk of RSV disease. Results from phase-I and II studies suggest that Numax appears to be safe and well-tolerated, with an acceptable pharmacokinetic profile in such infants.

Vaccines

Immunization offers the best hope for RSV prophylaxis. During the past decade, considerable progress has been made in RSV vaccine development.[64,65] Currently, a number of candidate RSV vaccines are being evaluated, including subunit vaccines and live attenuated virus vaccines, and both have shown promising results.[64,65]

PROGNOSIS

The disease is usually self-limited. Except in those at increased risk of severe disease, improvement is expected in 5–7 days. The mortality rate is <1% and occurs predominately in children with preexisting cardiopulmonary disease or immunodeficiency and in children born very prematurely.[10,66,67]

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