Respiratory Syncytial Virus: Update on Infection, Treatment, and Prevention

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Respiratory syncytial virus (RSV) infection, which primarily manifests as bronchiolitis or pneumonia, is the leading cause of lower respiratory tract infection in infants and young children. It is associated with more than 100,000 pediatric hospitalizations each year in the United States. Infants who were premature; have chronic lung disease, congenital heart disease, or immunodeficiency disorders; or have underlying metabolic or neuromuscular disorders are at increased risk for especially severe RSV disease. Treatment of children hospitalized with RSV disease is primarily supportive, with administration of supplemental oxygen and fluid replacement therapy. Bronchodilators may benefit at least a subset of such patients. Antiviral therapy with aerosolized ribavirin is available for high-risk, severely ill patients. Handwashing, cleaning of environmental surfaces, and cohorting in hospital settings may decrease RSV transmission. In children born premature and younger than 1 year of age, and in patients with bronchopulmonary dysplasia younger than 2 years of age, passive protection against severe RSV disease may be achieved through monthly injections of anti-RSV antibody (palivizumab) during winter months. No vaccine is available to provide active immunity against RSV, but live attenuated and subunit cloned surface protein vaccines are in development.

Introduction

Respiratory syncytial virus (RSV) infection, which manifests primarily as bronchiolitis or viral pneumonia, is the leading cause of lower respiratory tract infection in infants and young children. The peak incidence occurs at 2 to 8 months of age. Infection with RSV occurs annually during midwinter epidemics in temperate climates. In warmer climates, more extended periods of infection may occur or the incidence may increase during rainy seasons.

Overall, 3.5 to 4 million children younger than 4 years of age acquire RSV infection annually, and more than 100,000 children are hospitalized every year in the United States because of RSV-related illnesses [1•]. Stated another way, up to 32 out of every 1000 children younger than 1 year of age are hospitalized annually for this condition. Almost all children have had at least one RSV infection by their second birthday. Given the magnitude and potential severity of this condition, it is not surprising that RSV has been targeted by the World Health Organization for vaccine development. In this paper we review the virology, epidemiology, spectrum of clinical illness, diagnosis, treatment, and prevention of RSV-related illness.

Virology and Epidemiology

Respiratory syncytial virus is a negative-sense, single-stranded RNA paramyxovirus. Other members of the class include the parainfluenza viruses, measles, and mumps. In the 1950s and 1960s, researchers at the National Institutes of Health first isolated RSV and associated RSV infection with the clinical syndrome of bronchiolitis. Subsequent studies have shown that RSV is the leading cause of epidemic bronchiolitis, accounting for more than 40% of cases in this setting. Other respiratory viruses (*eg*, influenza, parainfluenza type 3, and adenovirus) account for most of the other cases [2].

Two subtypes of RSV (A and B) have been described; significant plasticity (antigenic variation) among strains has been noted, primarily in the surface glycoprotein. It has been suggested that disease caused by type A strains may be more severe [3]. The fusion surface protein is more stable across strains, and antibodies to this protein can neutralize the virus.

Even with these strain differences, almost all older children and adults have antibodies that will neutralize RSV in vitro. Despite these antibodies, reinfection with RSV occurs at all ages. With recurrent infection and increasing age, however, RSV infections remain more limited to the upper respiratory tract. Symptoms are more severe than those of the common cold, as evidenced by the 7- to 10-day duration of symptoms and prolonged work absence (mean, 6 days) associated with RSV disease in adults. Thus, immunity to RSV appears incomplete but protects against lower respiratory tract infections. This is consistent with the 2- to 8-month age peak for severe RSV infection, because transplacentally acquired antibodies wane over this period. Consistent with this information, higher cord blood levels of RSV antibodies are relatively protective

against severe RSV infection, and premature infants, who are at risk for more severe RSV disease, miss the major transplacental transfer of maternal antibodies [4].

Upper respiratory tract infection with RSV is also frequent: Studies have observed that up to 50% of pediatric housestaff and nurses on pediatric units develop an RSV infection each year. These upper respiratory tract RSV illnesses in older children and adults are the source of infection for most infants who develop RSV bronchiolitis or pneumonia.

The virus appears to be transmitted through infected secretions by contact (hand-to-hand or fomites) and through spread of respiratory droplets that have an incubation period of 3 to 5 days. Aerosolized secretions (small particles that travel more than 6 feet across a room) appear to be less important in RSV transmission. Thus, handwashing and cleaning of environmental surfaces are likely to be important in preventing RSV transmission. In the hospital setting, cohorting of RSV-infected patients and wearing of masks and gowns during close contact with the infected child are important in controlling nosocomial RSV spread [5]. Transmission of RSV on pediatric units has been shown to be a significant problem [6].

In the community setting, many factors have been associated with an increased risk of acquiring RSV disease. These include lower socioeconomic status, crowding (two or more children per bedroom), day care attendance, older siblings in preschool or school, being in a multiple birth set (*ie*, twin, triplet), passive exposure to cigarette smoke, and birth within 6 months before onset of RSV season [7].

Risk factors for more severe RSV infection in infants, defined as requiring hospitalization, include prematurity (less than 35 weeks gestation); male sex; body mass less than 5 kg at time of RSV infection; underlying lung disease (*eg*, bronchopulmonary dysplasia, cystic fibrosis); congenital heart disease with increased pulmonary blood flow; T-cell immunodeficiency states; multiple births; neuromuscular disorders; metabolic diseases; passive exposure to cigarette smoke; and lower socioeconomic status [7].

Clinical Illness

The clinical syndrome of bronchiolitis has been recognized for at least 100 years. The illness may begin with upper respiratory tract symptoms that over 1 to 2 days progress rapidly to the development of lung disease characterized by cough, coryza, wheezing and rales, low-grade fever (body temperature less than 101°F), and decreased oral intake. A family history of asthma or atopy is frequent. In more advanced disease, retractions and cyanosis may develop, and up to 10% to 20% of patients may develop higher temperatures. The incidence of concomitant or secondary serious bacterial infection in association with RSV infection appears low (< 1%), except for otitis media—this condition may occur in up to 40% of cases [8].

Young infants may have apnea out of proportion to respiratory signs and symptoms. In infants younger than 6 weeks of age, a more nonspecific sepsis-like picture has been described [9].

In assessment of disease severity, many factors have been correlated with the need for hospitalization: a history of prematurity, age younger than 3 months at time of infection, chronic lung disease or congenital heart disease, "toxic" appearance, respiratory rate greater than 70 breaths/min in room air, atelectasis or pneumonitis on chest radiography, and oxygen saturation less than 95% on room air [10]. Assessment of the infant's hydration state is also an important part of the examination of the infant with acute bronchiolitis. Indications for hospitalization in this condition are primarily related to the degree of hypoxia, tiring with CO_2 retention, or dehydration secondary to inadequate oral intake and increased fluid losses (*eg*, vomiting, tachypnea, and fever).

Laboratory Diagnosis

Laboratory studies are frequently not indicated in the infant with bronchiolitis who is comfortable in room air, is well hydrated, and is feeding adequately. Nonspecific laboratory studies obtained may include a complete blood count, serum electrolytes, urinalysis, and oxygen saturation measurement. Arterial blood gas measurement may be indicated if there is concern about CO_2 retention. The complete blood count may reveal an elevated percentage of band forms. Blood cultures are frequently performed but are rarely, if ever, positive for pathogenic bacteria. Chest radiography, when performed, typically reveals hyperinflated lung fields with a diffuse increase in interstitial markings. In 20% to 25% of cases, focal areas of atelectasis or pulmonary infiltrates are also noted.

Specific diagnostics tests to confirm RSV infection are readily available. These tests can be performed on samples of secretions obtained by washing, suctioning, or swabbing of the nasopharynx. The first two methods have a higher yield. These secretions can be analyzed for virus in the laboratory by culture or antigen detection techniques. The antigen detection methods offer the potential for rapid diagnosis (within hours) and may be performed reliably in the absence of a sophisticated diagnostic virology laboratory [11]. Monitoring of test performance, however, is critical for maintaining appropriate sensitivity and specificity [12]. Specific tests for RSV may be indicated in a particular patient for making decisions about therapy, cohorting of patients, and educating parents or physicians about the nature of RSV disease. It can also be argued that in typical acute viral disease, monitoring, supportive care, and cohorting are indicated and RSV testing is not routinely necessary.

Long-term Outcome

Most children hospitalized with RSV infection do well in the short term. Full-term infants older than 3 months of age who are hospitalized typically can be discharged home in 3 to 4 days. Younger infants and those with the risk factors described above have a more severe and prolonged hospital course. In select high-risk patients hospitalized for RSV disease, the mortality is increased (3% to 5%) [13].

In addition, it has long been recognized that children who have been hospitalized for bronchiolitis are at risk for subsequent wheezing and abnormal pulmonary function for 10 years or more later [14–16,17••,18•]. Whether RSV is causal in this regard or merely a marker for children destined to develop reactive airway disease remains uncertain at present. However, data support both concepts in part. Follow-up studies of children who received ribavirin therapy for RSV infection have been inconclusive; some studies showed long-term pulmonary benefits [19,20], whereas others have not confirmed this observation [21,22]. Future studies in this area, including follow-up of patients who have received RSV prophylaxis, should yield important information on this issue.

Therapy

The mainstay of therapy for RSV infection is supportive care. If the child can take in fluids by mouth and is tolerating room air, outpatient management with close physician contact as needed is reasonable, especially in the absence of significant underlying risk factors. Although bronchodilators have been used, no data support their benefit in alleviating the illness in this setting.

For children who require hospitalization for RSV infection, supportive therapy is still the mainstay. This may include administration of supplemental oxygen (guided by respiratory rates, oxygen saturation, and arterial blood gases as indicated), mechanical ventilation, and fluid replacement therapy as necessary. Additionally, bronchodilator therapy with β-agonists is frequently used, although data on their efficacy in this condition are conflicting [23–25]. At least a subset of patients with lower respiratory tract RSV infection appears to benefit from such therapy, and a trial may be reasonable with monitoring for effect on respiratory rate, pulse, and oxygenation. Recently, studies have suggested that α-agonists (*eg*, vaporized epinephrine) have greater benefit than β-agonists [26].

Ribavirin, a broad-spectrum antiviral agent in vitro, was licensed by the Food and Drug Administration in 1986 for the aerosolized treatment of children with severe RSV disease. The approved regimen is 6 g of drug in 300 mL of distilled water delivered via a small-particle aerosolized generator over 12 to 20 hours per day for 3 to 5 days, based on clinical response. Subsequent studies have suggested equivalent efficacy with a higher concentration of drug (6 g/100 mL distilled water) given over three, 2-hour periods per day [27]. Because of the high acquisition cost of the drug, the lack of demonstrated benefit in decreasing hospitalization or mortality, and past unproven theoretical concerns about secondary toxicity to health care workers from exposure to aerosolized drug, ribavirin is primarily reserved for patients with significant underlying risk factors and acute RSV disease [28••]. Several recent studies indicate that ribavirin therapy may benefit older children and adults with symptomatic RSV infection after bone marrow transplantation [29]. If preliminary studies suggesting a long-term benefit on pulmonary function outcome (as noted above) are confirmed, broader indications for ribavirin therapy may become a consideration.

Prevention

As discussed earlier, serum antibody appears to protect against RSV lower respiratory tract infection. On the basis of this observation, trials of immunoglobulin products with high anti-RSV antibody titers were undertaken. Two such products are available for clinical use. RSV immunoglobulin (RespiGAM; MedImmune, Gaithersburg, MD) is a pooled polyclonal human immunoglobulin product prepared from donors with high titers of RSV antibodies. When administered to high-risk infants with prematurity or chronic lung disease, RSV-related hospitalization decreased significantly. In addition, compared with placebo recipients, treated infants had less severe hospital courses if they were admitted with RSV disease, had fewer hospitalizations for other respiratory infections, and had less otitis media [30].

This product requires intravenous administration at a dose of 100 mg/kg of body weight monthly during RSV season (typically November through March or April in temperate climates). Given the need for monthly intravenous infusion and fluid volume load, the number of children who can receive prophylaxis in this manner is limited. This product is contraindicated in children with congenital heart disease because the one trial conducted in these patients suggested a possible increase in mortality in RSV intravenous immunoglobulin recipients [31].

More recently, passive prevention of RSV has been successfully achieved through monthly intramuscular injection of the humanized monoclonal anti-RSV antibody palivizumab (Synagis, MedImmune). This product demonstrated a 55% reduction in RSV hospitalization in premature infants less than 35 weeks gestational age and younger than 1 year chronological age or younger than 2 years chronological age with underlying lung disease [32•]; as a result, the Food and Drug Administration approved the drug in 1998. Subsequent postlicensure studies have continued to demonstrate efficacy (MedImmune, Data on file).

These products, given the nature of their preparation and limited candidate populations, are expensive to administer (approximately $3000 to $5000 per child per year), leading to debate about which children should

receive prophylaxis [33,34•]. The Committee on Infectious Diseases of the American Academy of Pediatrics established guidelines (Table 1) for RSV prophylaxis; the committee attempted to address these issues by grading the indications for preventive therapy according to degree of prematurity or risk factor [28••]. Pending further follow-up and economic impact studies, those recommendations provide a rational approach to selecting candidates for RSV prophylaxis. Our recommendations for palivizumab administration basically follow these guidelines; we emphasize additional risk factors in the 32- to 35-week gestational age range.

Vaccine

Attempts to develop a vaccine against RSV have been unsuccessful to date. A formalin-inactivated RSV vaccine was developed in the 1960s. Although initial serologic response to this vaccine appeared promising, children who received it developed more severe disease, and several died, when exposed to natural RSV infection. This increased disease severity has been attributed to altered host immune responses to the vaccine, although the exact mechanism is not completely understood.

To affect severe RSV disease, a successful RSV vaccine must address this issue and achieve protection in very young infants [35].

Recent progress in this area has included development of stable, live attenuated, cold-adapted, temperature-sensitive RSV strains that can be administered by nasal spray [36]. Preliminary studies are encouraging, and future clinical trials are planned.

Another approach to RSV vaccine development involves the use of cloned RSV surface proteins as potential subunit vaccines [36]. RSV fusion and glycoproteins can induce neutralizing and protective antibodies and are the principal components in development. These are being evaluated for potential immunization of young children and also for administration to pregnant women during the last trimester to boost anti-RSV antibody levels that would be transferred to the infant.

Conclusions

Infection with RSV, which primarily manifests as bronchiolitis or pneumonia, remains a major cause of morbidity and death in infants and young children. Much progress has been made in the treatment and prevention of RSV disease, and as a result morbidity and mortality have markedly decreased in recent decades. The future holds promise for even greater advances in treatment and development of a vaccine against this important pediatric pathogen.

Table 1. Candidates for palivizumab prophylaxis

Infants with chronic lung disease (primarily bronchopulmonary dysplasia) < 2 years of age at onset of RSV season who have required medical management of their lung disease within the previous 6 months
Infants who were born at or before 28 weeks gestation and are < 1 year of age at onset of RSV season
Infants who were born at 29 to 32 weeks gestation and are < 6 months of age at onset of RSV season
Infants who were born at 33 to 35 weeks gestation, are < 6 months of age at onset of RSV season, and have additional risk factors (see text) for severe RSV disease

Adapted from the American Academy of Pediatrics [28••].
RSV—respiratory syncytial virus.

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