Respiratory Syncytial Virus Infection in Infants and Young Children

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Respiratory syncytial virus (RSV) is the most common cause of lower respiratory tract infections in infants and young children. Epidemics occur yearly from December to March or April, leading to 100,000 hospitalizations in the United States at an estimated cost of $300 million. Physical examination findings may include clear coryza, evidence of respiratory distress, wheezing, and dehydration. Complications include apnea. Mortality runs as high as 0.5% to 1.5% in hospitalized patients. Diagnosis is based on clinical presentation, seasonal pattern, and microbiologic testing. Therapy remains largely supportive. The preponderance of evidence argues for the use of bronchodilators, especially epinephrine or albuterol, in the treatment of acute bronchiolitis. Steroids do not seem to confer any advantage. Ribavirin is expensive and should be used very selectively in infants at high risk for serious RSV disease. These infants may benefit from prophylaxis with RSV immune globulin.

KEY WORDS. Respiratory syncytial virus, human; bronchiolitis; infant care; child care. *(J Fam Pract 1997: 45:473-481)*

Respiratory syncytial virus (RSV) is the most common cause of lower respiratory tract infection (LRTI) in infants and young children.[1,2] Infection with RSV is a major health problem during early childhood and primary RSV infection occurs most often between the ages of 6 weeks and 2 years.[3] Approximately one half of all infants become infected with RSV during the first year of life and nearly all by the end of their second year.[4] Reinfection is common, but the clinical severity of subsequent infections is usually less than that of the initial infection because partial immunity is conferred by prior infections.[4,5] It is estimated that 40% to 50% of children hospitalized with bronchiolitis and 25% of children hospitalized with pneumonia have RSV infection as the cause of their disease.[6] In the United States each year, approximately 100,000 children are hospitalized at an estimated cost of $300 million.[4,6] More than half of those admitted for RSV bronchiolitis are between 1 and 3 months of age.[7] Male children are approximately 1.3 to 1.4 times as likely to be admitted to the hospital as are female children. Race and ethnic origin do not appear to influence the frequency or severity of RSV infection.[5,6] Complicated, severe LRTI due to RSV is most often seen in children with chronic underlying conditions of the cardiopulmonary system, including congenital heart disease, bronchopulmonary dysplasia, and cystic fibrosis, and in the immunocompromised patient.[5,6] While infection in most normal infants runs a benign course, mortality among hospitalized infants runs as high as 0.5% to 1.5%.[7]

RSV infections cluster in seasonal epidemics throughout the world, with a yearly upsurge in cases from winter to early spring in temperate climates.[3] Of the other respiratory viruses, only parainfluenza type 1 (with outbreaks clustering biennially in the fall) and influenza (with occurences in the winter to early spring) occur in yearly epidemics.[5]

While RSV is responsible for 45% to 75% of the cases of bronchiolitis, bronchiolitis may be caused by organisms other than RSV, including, in order of prevalence, parainfluenza, rhinovirus, adenovirus, influenza, and *Mycoplasma pneumoniae*.[8]

Given that RSV is a major public health problem that affects young children, we thought it important to review the salient features of this disease and to discuss newer treatments. Articles for the therapy section were chosen based on MEDLINE searches using the terms bronchiolitis, RSV, children, randomized, and treatment, as well as articles referenced in the articles derived from the search. We eliminated all articles in which outcome measures

Submitted, revised, July 8, 1997.
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included various aspects of pulmonary function measured using sedation, since these are surrogate measures that are not necessarily clinically relevant and sedation could confound results.

PATHOPHYSIOLOGY

RSV was initially isolated from a chimpanzee with mild upper respiratory symptoms and named the "Chimpanzee Coryza Agent"[9]; it was renamed RSV when an antigenically identical virus strain was isolated from two human infants.[10] RSV is an RNA paramyxovirus of the genus *Pneumovirus*.[11] The purified RSV virion contains a single, negative-sense strand of RNA,[12] which codes for 10 polypeptides and replicates within the host's cytoplasm.[13] There are two surface glycoproteins, the F protein (70kD) and G protein (84-90kD). The F protein mediates viral penetration and cell fusion (the process by which RSV infects adjacent cells and forms syncytium). The G protein mediates attachment of RSV to cell membranes.[3,14]

Two antigenically distinct strains of RSV virus, A and B, have been identified.[15] Children infected with RSV type A are more likely to have a more virulent clinical picture, including lower respiratory tract symptoms[16,17] and otitis media.[18]

The virus targets the bronchoalveolar epithelium and infects contiguous, uninfected cells by fusing infected cells with uninfected cells (ie, syncytium formation).[10] There is subsequent epithelial cell necrosis, and a peribronchiolar infiltrate of lymphocytes, plasma cells, and macrophages forms in response to infection; this is accompanied by submucosal edema. Mucous plugging and edema lead to partial or complete airway obstruction resulting in ventilation-perfusion mismatch and resulting hypoxemia.[7] Atelectasis and/or hyperinflation may be seen on chest x-ray film. Full recovery of mucociliary function may take 2 to 3 weeks.

The possible role of immunoglobin E (IgE) and cellular mediators of inflammation in RSV lower respiratory tract infection and recurrent wheezing is being actively investigated. RSV-specific IgE has been found in the nasopharyngeal secretions of 45% of those children infected with RSV who have LRTI and wheezing; this IgE is absent in those with an RSV infection who do not have LRTI.[19] In a prospective study, the degree of RSV IgE present during the acute infection predicted those infants at risk for recurrent wheezing.[20]

Besides IgE, leukotriene C_4 may be an important chemical mediator of RSV LRTI. It is a potent smooth-muscle constrictor, stimulates mucus production, and may be a cause of wheezing in RSV bronchiolitis.[21] Concentrations of leukotriene C_4 were higher in nasopharyngeal secretions of children with RSV bronchiolitis than in those with only RSV-related upper respiratory symptoms.[21]

Other studies have looked at the cell-mediated immune response as a cause for severe disease; one model that has been used for study is the use of an RSV vaccine in the 1960s. Subjects who received a formalin-inactivated virus vaccine developed unusually severe infections.[22,23] The reasons for this are not clear, however. It is likely that the vaccine failed to induce a sufficient number of protective local secretory IgA antibodies, and the antibodies that did develop to the F glycoprotein of RSV had low neutralizing capability and stimulated the body's inflammatory reaction.[24] The vaccine also probably induced a high level of RSV-specific $CD4^+$ lymphocytes, which could have led to damage to the sites in which RSV replicated.[24]

CLINICAL FINDINGS

Physical findings are variable and reflect the stage and severity of the illness. RSV infection initially presents with coryza and congestion with or without a low-grade fever.[7] About 40% of infants and children with RSV will progress to have LRTI, either bronchiolitis, pneumonitis, or pneumonia.[1] In those with LRTI, symptoms progress over 2 to 5 days and include cough, wheezing, and dyspnea.[7] If LRTI is present, a lung examination may reveal wheezing and rales. In severe disease, tachycardia, tachypnea, nasal flaring, and retractions may be present, reflecting increased effort in breathing.[7] About 1 of 100 of children with LRTI will require hopitalization.[25]

Findings of RSV infection may be nonspecific in neonates and include low-grade fever, irritability, lethargy, and poor feeding, with no clinical evidence of lower respiratory tract involvement.[8,26] Despite the lack of LRTI, neonates are at significant risk of death and morbidity.[26] More severe disease occurs in infants for two reasons: (1) airways are smaller and therefore more easily obstructed; and (2) infants are immunologically naive with respect to RSV. Passively acquired maternal antibodies to RSV

decline by 1 to 2 months of age, leaving the child especially vulnerable.[24]

Complications of RSV infection include dehydration, apnea, and respiratory failure. Dehydration results from paroxysms of coughing that may trigger vomiting and from inadequate oral intake secondary to respiratory distress and lethargy.[8] Apnea occurred in 20% of 274 infants with culture-proven RSV in one retrospective study.[27] Apnea was more likely to occur in infants born prematurely and in infants less than 4 months old.[27] Mucous plugging and subsequent ventilation-perfusion mismatch can lead to respiratory distress and hypoxemia. Cyanosis is rarely present, despite the increased work of breathing.[8] Patients with RSV may be hypoxemic, with arterial oxygen saturations (Sa_{O_2}) between 74% and 95% (Pa_{O_2} 40 to 75 mm Hg).[14] Measurement of Sa_{O_2} is critical, since clinical examination may not be adequate to assess a patient's degree of respiratory compromise.[28,29] Carbon dioxide retention is rare and heralds respiratory failure.[7]

An example of culture-proven RSV bronchiolitis can be seen in the chest x-ray film of a 2-month-old infant (Figure). Hyperinflation is associated with depressed diaphragms, increased parenchymal lucency, and blunted costophrenic angles.[8] Bronchovascular markings are usually prominent, with linear densities radiating from the hila, and areas of consolidation may be present.[14]

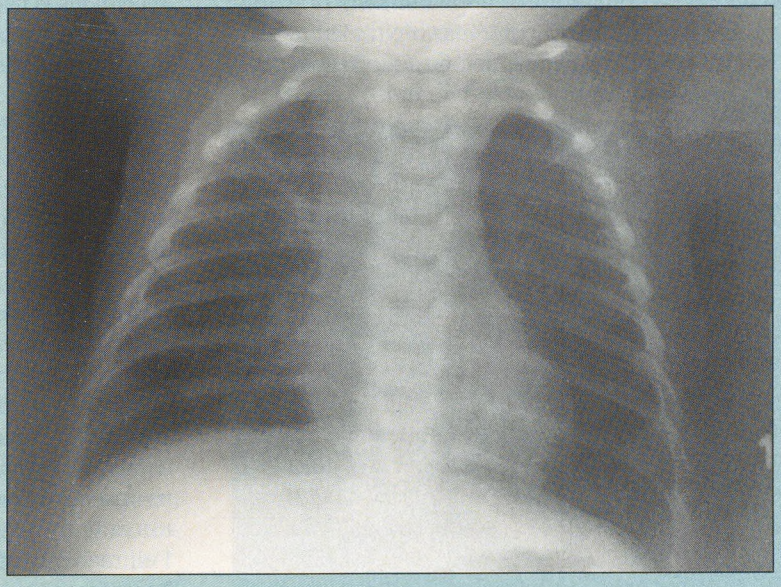
Korppi et al[30] found bacterial coinfection in 39% of children hospitalized with RSV infection compared with 24% of RSV-negative children. *Streptococcus pneumoniae* and non-typable *Haemophilus influenzae* were the most common bacteria involved. Hall et al[31] found, however, that the risk of secondary bacterial infection in patients with RSV was only 1.2%, and that a significantly greater proportion (4.5%) of subsequent bacterial infections developed in infants who received parenteral antibiotics. Brasfield and coworkers[32] studied 205 infants admitted with pneumonitis and found that of 145 patients with an identifiable agent, 55 (38%) were infected with two or more organisms. Of 33 infants with RSV, 14 (42%) were infected with at least one other agent.[32] While the clinical significance of the presence of other organisms is unclear, the clinician should be cognizant of the potential role of bacterial coinfection in the child with severe RSV-related disease[30] and consider treating the child hospitalized with RSV for a bacterial infection in those with the proper indications such as high fever, focal infiltrate on x-ray film, or elevated WBC count with a left shift.

TRANSMISSION

RSV is highly contagious. Spread is mainly by hand-to-nose and hand-to-eye contact, but fomite transmission also plays a role (live virus can be detected on surfaces for several hours after contact).[33] Direct aerosolization plays an insignificant role in virus transmission.[33] The incubation period is 5 to 8 days.[34] The duration and degree of viral shedding correlate

FIGURE

Chest radiograph of this 2-month-old infant with persistent cough and respiratory distress shows hyperinflation and bilateral patchy infiltrates in both lungs. These linear densities extend too far to the periphery to be vascular markings. This child had culture-proven respiratory syncytial virus, required a respirator, but was ultimately discharged in good health with no sequelae.



well with the clinical severity of disease. Virus is shed in the greatest amounts by infants less than 1 month of age, and RSV-infected infants may shed virus for 4 weeks or longer. Older children and adults may shed virus for only 3 to 4 days.[35-37]

Hospitalized patients should be isolated and, ideally, the personnel caring for them should be dedicated to treating patients with RSV.[14] Careful handwashing protocols should be followed[14] and stethoscopes should not go between patients without being disinfected. Support staff should care for RSV-negative patients before seeing RSV-infected patients.[38] Cohorting of RSV-positive patients should be done whenever possible. Data regarding prevention of spread with staff use of protective equipment has been inconsistent.[14]

DIAGNOSIS

The diagnosis of RSV infection is based on the clinical presentation, the seasonal pattern, and microbiologic testing.[7] The leukocyte count is usually normal or slightly elevated, with occasional elevation of immature cells (bands).[8] Commercially available rapid antigen tests are available to detect RSV, including RSV EIA (Abbott), Test Pack RSV (Abbott), and Directigen RSV (Becton Dickenson).[39] The accuracy of these tests, as well as the sensitivity of RSV culture, depends on the source, quality, timing, and handling of the specimen.[40] Specimens should contain moderate to large numbers of exfoliated respiratory tract columnar epithelial cells.[40] Nasopharyngeal wash specimens (see below) are superior to nasal or pharyngeal swabs because more respiratory epithelial cells and antigen are collected.[39-41] Sensitivity of rapid antigen tests is 84% to 91%, when nasopharyngeal wash specimens are collected.[39] Specificity is 94% to 98%,[39] and negative predictive value is approximately 75% to 98%.[40]

Nasopharyngeal washes can be performed by placing the infant in a supine position, instilling 3 mL of normal saline into one of the nares using tubing from a 21-gauge butterfly needle attached to a 5-mL syringe, and immediately suctioning the resultant mixture (1 to 2 mL) back into the syringe (method used at The University of Iowa). The sample is placed in a sterile container on ice and transported for appropriate tests.[39,40]

The gold standard for detection of RSV infection has been examining cells in culture for the characteristic cytopathic effect of RSV and immunofluorescence using monoclonal antibodies to RSV. Cell culture permits viral replication to detectable levels.[40] Disadvantages of cell culture compared with rapid antigen testing include greater costs, requirement for technical expertise and facilities, and longer time to detect virus (2 to 21 days).[40] Sensitivity varies from 60% to 92%, and specificity is nearly 100%.[39,40] Polymerase chain reaction amplification of RSV RNA is more sensitive and specific than other techniques, but it is expensive and not yet widely available.[42] Serologic testing using IgG enzyme immunoassay on paired acute and convalescent specimens is useful in epidemiologic studies, as well as evaluation of subclinical infections and newer diagnostic methods.[43]

TABLE 1

Clinical Criteria for Hospital Admission of Children with Respiratory Syncytial Virus

- O_2 saturation <93% on room air
- Any significant underlying illness such as bronchopulmonary dysplasia or immunosuppression
- Any history of previous need for intubation with wheezing
- Age <3 months
- Retractions or tachypnea
- Toxic appearance, dehydration, or tachycardia out of proportion to fever
- Recent history of apnea or cyanosis
- Social situation that makes follow-up or adequate home care unlikely

DECIDING WHOM TO ADMIT

The first decision faced by the clinician is determining which children to admit to the hospital. While no absolute criteria can be set, the authors use the criteria in Table 1 as guides in their practice. The assumption has been made that the child has lower respiratory tract symptoms such as wheezing; those with only mild upper respiratory symptoms do not need to be admitted, but should be followed closely, especially if less than 3 months of age. Parents should be taught to look for signs of respiratory distress, dehydration, fever, and lethargy, and advised to contact the physician should any of these occur. Full recovery of mucociliary function may take 2 to 3 weeks, especially in the very young infant.

THERAPY

Therapy for RSV depends on the severity of the disease. Most children who present with RSV bronchiolitis can be managed at home with supportive therapy, including adequate hydration, and frequent follow-up to ensure an improving clinical picture. For those older children with mild wheezing, albuterol nebulization as discussed below is appropriate. Humidified air, mucolytics, and cough suppressants have all been used, but information regarding their efficacy is lacking.

For those children requiring hospitalization, therapy is largely supportive and bronchodilators may be helpful. Supportive measures include close monitoring of child's respiratory status, humidified oxygen (if needed) to keep the Sa_{O_2} above 94% to 95%, and adequate hydration.

BRONCHODILATORS

Bronchodilators are widely used for bronchiolitis although efficacy is not completely defined, and the optimal dosage, frequency, and duration of treatment remain unknown.[44] Several double-blind, placebo-controlled trials comparing nebulized albuterol with nebulized normal saline have been conducted in children less than 2 years of age with acute wheezing. There is evidence that albuterol leads to immediate improvement in respiratory distress, but total time of hospitalization and morbidity were not studied as outcome measures.[45-47]

Schuh et al[45] conducted a double-blind, placebo-controlled trial in 40 infants and children between 6 weeks and 24 months of age who had a first wheezing episode and signs and symptoms of bronchiolitis. Nasal swabs were obtained on 34 children, and 21 were positive for RSV. The group that received two doses of nebulized albuterol (0.15 mg/kg/dose) 60 minutes apart had a significant improvement in respiratory distress and oxygen saturation, compared with the group that received two doses of nebulized 0.9% saline.

A similarly designed study of 83 children less than 24 months of age with acute bronchiolitis found that patients who received nebulized salbutamol (albuterol) (0.10 mg/kg) had significantly greater improvement in clinical scores, but not in oxygen saturation compared with the group that received nebulized 0.9% saline.[46] (Salbutamol is the generic name for albuterol used in Canada and Great Britain.)[48]

In another study of 25 infants who presented to the emergency department with wheezing, there was a statistically and clinically significant improvement in the respiratory distress score, but not oxygen saturation in the group that received two doses of nebulized albuterol (0.15 mg/kg) 30 minutes apart.[47] The beneficial response to β_2-agonists has a physiologic basis since bronchial smooth muscle is present in infancy and β_2 -receptors are present and functioning.[49,50]

Other studies have failed to confirm any therapeutic effect of typical β_2-agonists in young wheezy infants. Ho et al[51] studied the use of nebulized salbutamol (2.5 mg/mL) compared with normal saline in a double-blind, randomized crossover design of 21 wheezy infants positive for RSV and with no prior history of respiratory symptoms. They used arterial O_2 saturation (Sa_{O_2}) as the most relevant measure of ventilation-perfusion balance and found desaturation occurred with both salbutamol and saline, but was greater and more prolonged with salbutamol. These infants, however, were not necessarily in the acute phase of their illness.

Other studies that claim no effect or worsening of respiratory measures with albuterol therapy had methodological problems, eg, lack of randomization, and used outcome variables such as total pulmonary resistance[52] or maximal flow at functional residual capacity,[52] which may not reflect clinical status and which require sedation to measure, thereby further compromising the validity of results.[45]

In a randomized, double-blind, placebo-controlled study that compared nebulized albuterol, nebulized saline, oral albuterol, and oral saline in 88 infants being seen for their first episode of wheezing in the ambulatory setting, those too sick to continue the trial were given open-label nebulized albuterol at 60 minutes.[53] There were no differences in respiratory rate, clinical score, or oxygen saturation among the four treatment groups, except for oral albuterol, which produced an increase in heart rate of 15 beats per minute.[53] Unfortunately, outcomes were not reported for the children given open-label albuterol, the very group that required treatment. This study, however, underscores the importance of controlling for change in state of the infant and using a truly inactive placebo group, something previous studies have failed to do.

Recently, three double-blind controlled trials have

compared nebulized epinephrine with either nebulized albuterol or nebulized saline.[49,54,55] These studies find epinephrine to be at least as efficacious as nebulized albuterol, and perhaps more so. Menon et al[54] conducted a double-blind study comparing nebulized epinephrine (3 mL of a standard 1:1000 preparation [3 mg]) to nebulized salbutamol (0.3 mL of 5 mg/mL solution [1.5 mg] + 2.7 mL 0.9% saline) in the treatment of infants with acute bronchiolitis. The children given epinephrine had higher O_2 saturations and lower pulse rates at 60 minutes and were not as likely to be admitted (33% vs 81%).[54] A study by Kristjansson et al[55] found that nebulized racemic epinephrine (a mixture of D- and L- isomers) is superior to placebo at increasing oxygenation, with the best response in those children with baseline Sao_2 ≤93% (precisely the group that we would like to address clinically). In a randomized, double-blind, placebo-controlled trial, Reijonen et al[49] found that mean respiratory distress assessment scores improved significantly among infants with acute bronchiolitis receiving nebulized racemic epinephrine (0.9 mg/kg), albuterol (0.15 mg/kg), or saline (0.9%), with no significant differences among the groups. Unfortunately, the results were confounded because all infants received intramuscular epinephrine (0.01 mg/kg) 60 minutes into the study.[49]

Preliminary studies of nebulized ipratropium bromide have shown no benefit when added to nebulized albuterol.[56]

In summary, the preponderance of evidence argues for the use of bronchodilators, especially epinephrine or albuterol, in the treatment of bronchiolitis. Nebulized epinephrine (5 mL of 1:1000) can be used as needed in children with respiratory distress due to bronchiolitis. This dose has been found to be safe and effective in other illnesses, especially croup.[50,57] Epinephrine is generally more available than racemic epinephrine and less expensive. Future studies of bronchodilators should focus not only on short-term outcomes such as respiratory distress scores, O_2 saturation, and need for supplemental O_2, but also longer-term outcomes such as length of hospital stay, frequency of nebulizer treatments, and duration of oxygen therapy.

TABLE 2

Situations in Which the Use of Ribavirin May Be Considered for Children with Respiratory Syncytial Virus Infection

- Infants with congenital heart disease, pulmonary hypertension, bronchopulmonary dysplasia, or cystic fibrosis
- Previously healthy infants born prematurely (< 37 weeks' gestation) and infants <6 weeks of age
- Severely ill infants (Pao_2 <65 mm Hg or Sao_2 < 90% or increasing $Paco_2$) with or without mechanical ventilation
- Immunosuppressed infants (by disease or therapy)
- Infants with underlying disease such as multiple congenital anomalies, neurologic or metabolic disease (eg, cerebral palsy or myasthenia gravis)

Based on American Academy of Pediatrics Committee on Infectious Diseases. Reassessment of the indications for ribavirin therapy in respiratory syncytial virus infections. Pediatrics 1996; 97:137-40.

ANTI-INFLAMMATORIES

Steroids have no effect in acute bronchiolitis,[58] although they seem to reduce post-bronchiolitis wheezing.[59,60] Reijonen et al[61] evaluated whether early anti-inflammatory therapy with nebulized cromolyn sodium or budesonide reduced wheezing and hospitalizations after an episode of acute bronchiolitis in 100 children younger than 24 months. They compared cromolyn 20 mg four times daily for 8 weeks, followed by 20 mg three times daily for 8 weeks, or budesonide 500 µg twice daily for 8 weeks followed by 250 µg twice daily for 8 weeks, to no treatment. Children in the cromolyn (19%) and budesonide (16%) groups had significantly fewer physician-diagnosed wheezing episodes than those in the control group (47%) during the second 8-week period ($P<.05$).[61] Hospital admissions were also reduced in the treatment groups.[61] Since differences in the groups were apparent only in the second 8-week period, it may be that treatment begun at 6 to 8 weeks after illness would be just as effective, thus targeting treatment to those with post-bronchiolitis wheezing.

ANTIVIRALS

Aerosolized ribavirin is the only specific antiviral drug currently licensed for the treatment of RSV infection in the United States. Ribavirin is a synthetic nucleoside analog resembling guanosine and inosine. It interferes with messenger RNA expression and inhibits viral protein synthesis.[62]

The use of ribavirin has been recently questioned by the American Academy of Pediatrics

(AAP) Committee on Infectious Diseases.[63] The early studies demonstrating the efficacy of ribavirin used nebulized water as a placebo.[64-66] More recent blinded studies using saline as a placebo failed to show any benefit of using ribavirin.[67,68] Current recommendations state that the use of ribavirin in patients with RSV bronchiolitis should be an option based on the preference of each physician.[63] Criteria for consideration of ribavirin therapy are listed in Table 2.[63] The cost of the drug and delivery system is high, running $1740 per day at our hospital. Use of ribavirin does not change the length of hospital stay, days on oxygen therapy, progression to ventilator status, or mortality.[69]

Other Modalities

In a prospective, randomized, double-blind controlled trial, the group receiving intramuscular interferon alpha-2a had a more rapid improvement in their clinical score compared with the placebo group.[70] However, among the infants requiring oxygen, there was no difference in the mean duration of oxygen therapy or duration of viral shedding between groups.[70] In two randomized, placebo-controlled trials, high-dose vitamin A did not have a beneficial effect on the course of RSV disease.[71,72]

In a double-blind, placebo-controlled trial, prophylactic respiratory syncytial virus immune globulin (RSV-IVIG) has been shown to prevent hospitalizations in children with a history of prematurity or bronchopulmonary dysplasia.[73] Five hundred ten children with bronchopulmonary dysplasia and/or a history of prematurity were randomized to receive monthly injections of RSV-IVIG (750 mg/kg) or placebo.[73] Children randomized to the treatment group had a 41% decrease in hospitalizations (absolute risk 13.5% vs 8.0%) and a 53% reduction in the total number of hospital days for RSV treatment per 100 children.[73] RSV-IVIG should be considered for prophylaxis in high-risk subgroups.[73] RSV immune globulin was safe, but not efficacious in the treatment of RSV LRTI in children with bronchopulmonary dysplasia, congenital heart disease, or prematurity.[74]

LONG-TERM SEQUELAE

After the acute episode, patients with bronchiolitis tend to have continued problems with reactive airway disease. Murray et al[75] studied patients who had been seen for bronchiolitis and compared them with a control group (68% were RSV-positive, all were admitted to the hospital for bronchiolitis during an RSV epidemic). At 5.5 years, the group with a history of bronchiolitis had significantly more wheezing, more response to inhaled histamine, and more atopy.[75] Others have documented similar findings.[76-78] These children respond to the usual treatment for reactive airway disease.

CONCLUSIONS

RSV is a common disease that poses a significant health problem in childhood. Nearly all children with RSV can be safely managed at home with close follow-up. The approach to each child requiring hospitalization should be individualized to include oxygen, humidity, and bronchodilators.

ACKNOWLEDGMENT

We would like to thank, Wilbur Smith, MD, for providing information on radiographic findings in RSV infection and the radiograph demonstrating RSV infection.

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