Systematic Review of the Biology and Medical Management of Respiratory Syncytial Virus Infection

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Respiratory syncytial virus, the leading cause of serious upper and lower respiratory tract infection in infants and children, accounts for 125,000 hospitalizations and 450 deaths annually in the United States. It also may predispose to development of asthma later in life. Annual epidemics occur from November to April, and virtually all infants are infected by age 2. Immunity is not durable; hence,

reinfection occurs throughout life, although subsequent infections are nearly always mild. Certain populations (eg, premature infants, infants with chronic lung disease, and immunocompromised individuals) are at risk for severe morbidity and have higher risk of mortality. Infection is spread to the nose and eyes by large droplets and direct contact with secretions, and fomites may remain infectious for up to 12 hours. Nosocomial infection is common. The virus infects airway ciliated epithelial cells, spreading by the formation of syncytia. Cellular debris and inflammation cause airway obstruction, hyperinflation, localized atelectasis, wheezing, and impaired gas exchange. Both humoral and cellular immune response are critical to ending the acute infection, but wheezing and reactive airways may persist for as long as 5–10 years after acute infection. No cure exists for respiratory syncytial virus infection, but commonly employed palliative treatments include oxygen, inhaled β_2 agonists, racemic epinephrine, dornase alfa, systemic and inhaled corticosteroids, inhaled ribavirin, and nasopharyngeal suctioning. Infants suffering severe lower airways disease may require mechanical ventilation. Prophylactic measures include rigorous infection control and administration of polyclonal (RSV-IGIV [respiratory syncytial virus - immunoglobulin intravenous]) and monoclonal (palivizumab) antibodies. The cost of the prophylactic antibody treatment is high; it is cost-effective for only the highest risk patients. Development of a vaccine remains far in the future. Application of evidence-based clinical practice guidelines is making both out-patient and in-patient therapy as effective and economical as possible. *Key words: pediatric, RSV, respiratory syncytial virus.* [Respir Care 2003;48(3):209–231. © 2003 Daedalus Enterprises]

Introduction

Respiratory syncytial virus (RSV) is the leading cause of serious respiratory tract infections in infants and young children throughout the world. It is a major public health problem, resulting annually in several million deaths worldwide of children under age 5 as well as the expenditure of hundreds of millions of health care dollars for the care of infected patients.[1] In the United States it is estimated that 100,000 to 125,000 hospitalizations and up to 450 deaths can be attributed to RSV lower respiratory tract infections each year.[2] It can be particularly devastating for infants born prematurely and for those with chronic lung disease (CLD).[3] In addition, evidence suggests that infection in infancy predisposes children to hyperreactive airways and the development of asthma later in life, further adding to the burden on the health care system.[4] Finally, it has been recognized as a major cause of morbidity and mortality in the frail elderly and in immunocompromised children and adults.[5]

RSV's pathophysiology and epidemiology have been well described, but the development of either a successful treatment or an effective vaccine has thus far eluded investigators. As a result a variety of palliative treatments have been applied to patients with RSV infections; however, these treatments consume substantial health care resources, and for the most part their effectiveness remains poorly documented.

Some progress in reducing the impact of RSV has occurred within the last few years. Outcomes research is beginning to demonstrate which palliative measures are effective in both the out-patient and hospital setting, and an effective (although very costly) human recombinant monoclonal antibody preparation, palivizumab (Synagis), has been developed, which significantly lowers infection rates in recipients. Because of RSV's highly infectious character, the ultimate solution to the annual RSV epidemics remains development of an effective vaccine, but that goal remains far in the future.

History

Severe respiratory infection in infants and young children was first recognized over 150 years ago and termed "congestive catarrhal fever." Clinical descriptions published at the time leave little doubt that the disease described can be attributed to RSV.[6] In 1941 the viral etiology of the disease and its seasonal epidemiological pattern were described in the medical literature.[7]

In the late 1950s and early 1960s Robert M Chanock isolated and characterized the virus. In a series of landmark papers he established that the virus was serologically

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identical to a virus that infects the respiratory system of captive chimpanzees (chimpanzee coryza agent). He proposed the name "respiratory syncytial virus," based on a description of the cellular changes that occur within airways and lung parenchyma following infection.[8]

During the 1960s RSV was established positively as the cause of the numerous, highly communicable epidemics of infancy and early childhood respiratory infections that occur throughout the world, particularly during winter in the temperate regions and in the rainy season in tropical areas.[6] Also during that period, work proceeded on development of a vaccine. In the mid-1960s Drs Chanock and Parrott developed a polyvalent vaccine containing formalin-killed RSV, killed *Mycoplasma pneumoniae*, and killed parainfluenza virus. The vaccine was administered to a group of infants and children of military dependents in Washington DC and Colorado in mid-1966. The results were disastrous; not only did the vaccinated infants develop RSV infections at the same rate as the placebo-injected group, but 80% of the vaccinated infants developed bronchiolitis or pneumonia serious enough to require hospitalization, whereas hospitalization was required for only 5% of the placebo-injected group. Further, 2 of the vaccinated infants died.[6,9] The reason for the increased virulence of infection in the vaccinated children has never been understood, and this event has cast a pall over RSV vaccine research for the last 30 years.[6]

Research into RSV molecular biology and epidemiology accelerated through the 1970s and continues today. In the 1980s ribavirin (Virazole) was found to significantly decrease RSV replication in vitro, and initial clinical trials were promising, showing that the drug's maximum activity occurred when it was administered in the early phases of infection.[10,11] However, during the 1990s ribavirin's effectiveness was questioned, and use of the drug has decreased dramatically. Today its use is recommended only for infants with infections so severe as to require mechanical ventilation[12] and for infected immunocompromised patients.[13,14]

Although the development of a vaccine remains elusive, 2 immunoglobulin (Ig) products, RSV-IGIV (respiratory syncytial virus - immunoglobulin intravenous, also known as RespiGam) and palivizumab (Synagis), developed and tested during the 1990s, proved to be effective (albeit very costly) prophylactic agents. Today their use is confined to infants considered to be at highest risk.[15,16]

Epidemiology

Timing and Rate of Infection

RSV is a ubiquitous pathogen in all human populations. Epidemics occur in virtually all areas of the United States, waxing and waning with seasonal changes, generally oc-

curring between the months of November and April and peaking in December, January, and February,[17] with outbreaks lasting an average of 22 weeks.[1] During RSV season it is usually the predominant respiratory virus in the pediatric community,[18] although outbreaks of influenza A may overlap with RSV.[1]

Because of the universal presence of RSV in the community, at least 50% of children in the United States are infected during their first RSV season, and virtually all children have been infected by 2 years of age. Few infants are infected prior to the second month of life, but infection rates then increase rapidly, with the highest rates during the third and fourth months of life.[19]

An RSV infection does not produce substantial immunity to subsequent infection; thus, reinfections are common. However, the severity of the disease generally decreases with subsequent reinfections. In a study carried out in a series of families in Houston, Texas, 33% of RSV-infected infants had substantial lower airway disease, but the incidence of lower airway disease decreased to 13% in the second year of life, 10.8% in the third year of life, and 7.7% in the fourth year of life.[1] However, other studies suggest a higher rate of 20–50% lower airway disease in preschool children with reinfections.[19] Although reinfections are common, their frequency decreases with age. In a series of epidemiological studies of respiratory infections (the Tecumseh Studies), 20% of children ages 5–9 had documented RSV infections during 1 year, but the rate fell to 10% in children ages 15–19, and was about 5% in adults 20–50 years of age.[20]

Risk Factors

The most serious RSV infections occur in infants. First infections are the most common that result in bronchiolitis and/or pneumonia. Approximately 80% of childhood bronchiolitis cases[21,22] and 50% of infant pneumonias[23] are attributable to RSV.

In the United States approximately 0.1 to 1% of infants with RSV infections require hospitalization, depending on location and socioeconomic factors.[1] In a recent analysis of hospitalization data for RSV infections between 1980 and 1996, Shay et al[24] found that 57% of hospitalizations due to RSV infection were for infants younger than 6 months of age, and 81% were for infants younger than 1 year. The study also revealed that hospitalization rates for infants have increased dramatically during the study's time frame. The rate of hospitalization for infants with bronchiolitis increased from 12.9 per 1,000 cases in 1980 to 31.2 per 1,000 in 1996. It is interesting to note that pulse oximetry came into common use during that period. Most clinicians will hospitalize any infant who has a respiratory infection and a pulse oximetry reading of $\leq 92\%$, even if

other factors suggest that hospitalization may not be necessary.

Certain factors increase the likelihood of RSV infection in infants.[25] These include birth between April and the end of September, attendance at daycare centers,[17] crowded living conditions,[26] presence of school-age siblings in the home,[27] prematurity,[28] exposure to passive smoke in the home,[27] being in a multiple-birth cohort,[29] and lack of caregiver education.[26]

Risk Factors for Severe Infection

Not only are certain infants at higher risk for contracting RSV, but a number of factors are statistically associated with a higher rate of severe as opposed to mild infections. The most important of these is prematurity (birth at gestational age < 36 wk) and the presence of bronchopulmonary dysplasia (chronic lung disease [CLD]). In a review of 14 studies of infants born in North America and Europe, Simoes and Groothuis[30] found that the hospitalization rate for RSV-infected children with CLD who were < 2 years of age was 18.4%. For premature infants without CLD, the hospitalization rate was 10.3% for infants born at 29–32 weeks gestational age and 9.8% for infants born at 32–35 weeks gestation. Compared to these, the overall hospitalization rate for RSV in term infants in the United States is only about 1–2.5%.[31] Other chronic lung conditions that increase the risk for severe RSV infection in both infants and children are cystic fibrosis,[32,33,34] recurrent aspiration pneumonitis, tracheoesophageal fistula, and neurologic and genetic disorders that prevent good secretion clearance.[35]

Infants with congenital heart disease are at much higher risk for very severe RSV infections. The mortality rate for infants with congenital heart disease was reported to be 37% in a study conducted in the 1970s,[36] though mortality had fallen to 2.5–3.5% in pediatric patients in 2 studies from the early 1990s.[37,38]

Immunocompromised children also have a much higher risk for severe RSV infection. This includes children undergoing chemotherapy for leukemia, children who have undergone transplantation, children infected with human immunodeficiency virus, and children with combined immunodeficiency syndrome.[1,39] These children show greater severity of infection, more viral shedding, and longer viral shedding periods.[39]

Several factors increase the risk of particularly severe infection in otherwise healthy infants and children. Although girls and boys are stricken with RSV infections at an equal rate,[40] the rate of hospitalization for boys is approximately twice that for girls,[41] indicating that the disease may be more severe in boys. Infants from families of lower income and socioeconomic status tend to have more severe infections, at least in part because they are more likely to be in daycare centers and tend to become infected at an earlier age.[42,43] Infants exposed to high levels of particulate air pollution[44] and infants chronically exposed to cigarette smoke[27,45] are also more likely to suffer more severe RSV infections.

Nosocomial Infections

One of the greatest risk factors for contracting RSV is hospitalization. This is primarily because of the highly infectious nature of the disease. RSV is the most common cause of nosocomial infection in pediatric wards, among patients hospitalized for other causes.[46,47] Factors associated with higher risk of nosocomial infection include young age, chronic disease, long hospitalization, and crowded hospital conditions. For example, MacDonald et al[3] found that 21% of RSV-infected infants with congenital heart disease acquired the infection nosocomially.

Hospital workers appear to be a major source of nosocomial RSV infections.[48] In some cases more than 50% of the staff on a pediatric ward have become infected.[49] Among staff these infections usually manifest as a cold or flu-like illness. In addition, 15–20% of infections in staff are asymptomatic but still produce substantial shedding of the virus. Medical students and staff new to the unit are at highest risk of RSV infection.[48]

Several characteristics of RSV and its transmission increase the likelihood of nosocomial infection. First, individuals of all ages are susceptible to RSV infection. Second, although an RSV infection will confer some immunity to reinfection, this immunity is limited. Reinfection certainly can occur annually, but it also can occur much more frequently, even within a few weeks of the previous infection.[50] Third, shedding of RSV in children may be at high levels and for periods ranging from a few days to as long as several months in immunocompromised patients.[39] By contrast, adults generally shed the virus for only about 3–7 days.[48] Fourth, RSV remains viable in the environment for extended periods and is spread by several different mechanisms.

Pathophysiology of Respiratory Syncytial Virus

Biology of Respiratory Syncytial Virus Infection

RSV is classified as a paramyxovirus.[51,52] Closely related viruses include parainfluenza virus (types 1, 2, and 3), measles, and mumps.[52,53] The genome of the virus is composed of a single strand of ribonucleic acid (RNA) containing only 10 genes. A total of 11 proteins are encoded within this RNA genome. Nine of these are structural proteins and surface glycoproteins that form the viral coat and bring about attachment of the virus to the host cell. The remaining 2 direct the replication process of the virus once it infects its host cell.[51,52]

The virus infects the ciliated epithelial cells that line the airways. The first step in viral replication is attachment of the viral particle to a host cell, generally in the nasal epithelium. The viral RNA then enters the cell along with the viral enzymes that direct production of new viral RNA and proteins. Multiple new viruses are assembled within the cell, and the cell is ultimately destroyed.[53] The rapid destruction of ciliated epithelial cells lining the airways ultimately causes the symptoms characteristic of the infection.

Two different strains of the virus, A and B, have been identified. Both are infectious: one strain tends to dominate during an individual epidemic in an individual location, although at times both strains can be isolated from patients in the same area.[51] In the United States and United Kingdom Strain A is found more commonly, although it has been observed to alternate with Strain B in a somewhat irregular pattern from year to year.[54] Strain B appears more commonly in epidemics in Europe.[55] In addition, a number of studies suggest that Strain A may result in more virulent infections than Strain B.[56]

Along with the 2 strains, several subtypes of each strain have been identified.[51,52] Most of the variability among the RSV strains and subtypes can be traced to variability within the G protein, a glycoprotein located on the surface of the viral coat, which is involved in attachment of the virus to the host cell. Antibodies to RSV, which develop within the body during an infection, are specific to the G protein from the particular strain producing the individual's infection. Several authors have speculated that the variability within this particular protein among various RSV strains and subtypes reduces the effectiveness of the body's immune response and allows frequent reinfections to occur.[51,52,57] It also makes production of an effective vaccine quite difficult.[50,51]

In addition to fusion of the virus with the membrane of individual cells and injection of the viral RNA into the cells, another glycoprotein on the surface of the viral coat, glycoprotein F, causes fusion of infected cells with adjacent uninfected cells. This results in the merging of membranes from infected cells, allowing for cell-to-cell transmission of the replicated viral RNA. This results in the appearance of epithelial cell syncytia (formations that appear to be large, multinucleate cells), which give the virus its name.[58] This mode of transmission from cell to cell also allows the virus to spread without coming into contact with antibodies in the nasal secretions.

Once an RSV infection has begun, extensive destruction of epithelial cells lining the respiratory tract occurs. If this destruction is limited to cells in the upper airway, then the symptoms are similar to those of a severe upper respiratory infection. In previously uninfected individuals (usually infants) and immunocompromised individuals, the infection frequently makes its way down into the lower airways, producing typical signs of lower respiratory tract infection.

As epithelial cells are destroyed, they release a number of pro-inflammatory mediator substances, including cytokines (eg, histamine and interleukin 1 and 6), which cause increased capillary permeability and elevated secretion production, and chemokines that attract additional pro-inflammatory cells such as macrophages, neutrophils, eosinophils, and natural killer cells to the site of infection.[59] Increased capillary permeability results in leakage of plasma proteins into interstitial areas, small airways, and alveoli. This causes generalized interstitial swelling and also appears to inhibit pulmonary surfactant function.[60] In addition, some of the pro-inflammatory mediator substances (specifically, leukotrienes C_4 and D_4), which are known to be potent bronchoconstrictors, have been isolated from secretions of individuals with severe lower respiratory tract infections.[61] The combination of increased secretion production, decreased secretion clearance due to compromised mucociliary elevator function, and ineffective surfactant function results in small airways filling with secretions and debris from destroyed cells. The release of bronchoconstrictor substances may cause small airways to narrow even further, resulting in increased airway resistance, air trapping, and wheezing, which are characteristic of severe lower respiratory tract RSV infections.[59]

Immune Response to Infection

The body responds to an RSV infection by mounting an immune response. This results in the production of RSV-specific antibodies of the IgG, IgM, and IgA types, which can then be found in both serum and airway secretions.[59,62] However, the formation and effectiveness of these antibodies is a highly complex topic. Three lines of evidence support the importance of their presence. First, they clearly participate in the elimination of the specific infection that caused their formation, but they do not necessarily protect against subsequent infections, although the presence of serum antibodies probably accounts for the observed decrease in both the severity and frequency of reinfections.[62] Second, infants born at or near term generally carry maternal RSV antibodies, which appear to significantly decrease the likelihood of infection in the first month of life.[40,26] Third, administration of sera containing high-titer RSV-IGIV, obtained from adult donors with high antibody titers, are effective in reducing both the incidence and severity of severe RSV infections in high-risk infants.[15]

In addition to the role of circulating antibodies, there is also evidence of a T cell-mediated immune response. First, secretory products with known antiviral activity (eg, interferon γ and interleukin 4 and 5), which are produced by CD4+ (cluster of differentiation 4) helper T cells, appear in bronchoalveolar lavage fluid following infection. Also,

studies have shown movement of T cells into the lungs of mice infected with murine RSV.[63] Finally, individuals with immune system defects that lack the cellular part of the immune response but have the humoral (antibody producing) portion of the immune system intact show severe morbidity and prolonged shedding of the virus following RSV infection, indicating that the cellular portion of the immune system plays an important role in ending the infection.[39]

Infection Transmission

RSV is transmitted through close contact with a person who has an active infection or direct contact with infectious secretions on environmental surfaces. Nasal secretions on tissue or cloth are infectious for up to 30 min, whereas those on hard surfaces such as countertops, stethoscopes, silverware, or crib rails are infectious for at least 6–12 hours. The main routes of infection transmission into the body are large-particle aerosols (eg, from sneezes) over short distances, and hand-to-eye or hand-to-nasal-epithelium following hand contact with infectious secretions. Infectious secretions can even be passed from the hands of one individual to the hands of another.[64,65] Small-particle aerosol does not appear to be a common mode of transmission.[66] The incubation period is 2–8 days after initial contact, with the most likely period being 4–6 days.[67]

As long as virus is being shed, infected persons remain contagious. Shedding of the virus begins within a day or so of infection, often before the onset of major symptoms.[65] Shedding of the virus is highly variable and appears to correlate roughly with the age of the person infected, the severity of the infection, and whether the infected person is immunocompromised. Typically, adults shed virus for 3–7 days following infection.[48] Infants normally shed for up to 14 days in lighter infections, but infants < 6 months of age with severe infections may shed for 3 weeks. Immunocompromised individuals may shed for several months following an infection.[68]

Related Effects of Respiratory Syncytial Virus Infection

A number of sequelae from RSV infection have been observed. About a third of children with RSV infections develop acute otitis media.[69] Ng et al[70] observed that encephalopathy developed in about 1.8% of hospitalized, RSV-infected patients monitored over a period of 4 years. MacDonald et al,[71] in a study of 32 children with nephrotic syndrome, found that exacerbations of renal disease occurred more than twice as often in patients who had a respiratory infection and that RSV was the most common cause of the observed respiratory infections. RSV is the causative agent in about 50% of infant pneumonias and

10–30% of pediatric bronchitis.[1] It also may trigger acute respiratory distress syndrome, with substantial accompanying morbidity and mortality.[72] RSV is particularly devastating to cystic fibrosis patients, causing a greater rate of hospitalization, reduced lung function,[33,34] and lower Brasfield chest radiograph score than uninfected infants with cystic fibrosis.[32] Finally, RSV infections appear to have similar long-term negative consequences for patients with heart defects, immunocompromised patients, and patients with other pulmonary disease (eg, Duchenne muscular dystrophy).[51]

The most frequently noted sequela of RSV infection is persistent wheezing/increased airway hyperreactivity/atopic asthma. Although this link has been observed in one form or another for about 30 years,[73] it remains a highly controversial subject.[51,59] A number of studies appear to have established at least a statistical connection between severe lower respiratory tract RSV infection and asthma in young children.[74–77] Much of the confusion with regards to this link arises because of the complex relationships between wheezing, atopy, and asthma, particularly in infants and young children, since the precise pathogenesis of asthma is not well understood.[78]

There is general agreement that wheezing persists well beyond the period of acute RSV infection in infants who have severe lower respiratory tract disease. Most studies show that wheezing and even decreased peak expiratory flow and increased susceptibility to bronchial challenge persist until at least 5–8 years of age,[79] although at least one study suggests these effects may last for up to 11 years.[76]

Although the persistence of wheezing is well established, the relationship between RSV and subsequent asthma and atopy is not nearly as clear. For example, in a meta-analysis of 6 studies, Kneyber et al[80] found that wheezing clearly persists in children for up to 5 years following a severe lower respiratory tract RSV infection, but there is no difference in the frequency of wheezing between infected children and those in control groups after 5 years. They also found no difference in the frequency of atopy between the severe lower respiratory tract infection groups and control groups in the studies they reviewed. On the basis of that finding they conclude that "it seems unlikely that RSV bronchiolitis is a cause of atopic asthma in later life." Wennergren and Kristjansson[81] carried out a similar review and concluded that, though increased wheezing lasting a number of years is a frequently observed sequela of RSV infection in infancy, most follow-up studies do not show increased atopy after RSV bronchiolitis. Further, they observed that the RSV-induced wheezing probably does not indicate asthma, based on the lack of response of most post-RSV wheezing infants to steroid therapy (a therapy that is normally effective for true asthma). In their opinion, many of the infants who develop wheezing may have atopy

prior to the RSV infection. They conclude that "to decide whether respiratory syncytial virus bronchiolitis causes, or is associated with the respiratory sequelae (or with subsequent allergy), it will be necessary to conduct prospective, randomized studies, where the cytokine profile prior to bronchiolitis onset is known."

In spite of the uncertain link between RSV and atopic asthma, a number of investigators have sought to describe the events occurring within the developing immune system that lead from a lower respiratory tract RSV infection to the development of atopic asthma, through studies with humans and with a mouse model of RSV.[82,83] Indeed, if this link exists, it is almost certainly connected to events occurring as the cellular component of the immune system develops in the first 6 months of antenatal life.

The development of the cellular portion of the immune response in the infant is highly complex and only partially understood. Recently published evidence indicates that the infant's cellular immune response to RSV infection depends on the maturity of the immune system at the time of infection.[84]

Much of the cellular immune response to disease is potentiated through the action of CD4+ helper T cells. Two distinct populations of CD4+ helper T cells exist (Th1 and Th2) in the mature immune system, but only one (Th2) predominates during fetal development and the immediate antenatal period. The Th1 response does not become mature until about 6 months of age. It is postulated that if an RSV infection occurs prior to maturation of the Th1 cell population, the main cellular immune response will be that produced by the action of the Th2 cell population, namely proliferation of eosinophils and release of interleukin 4, leukotrienes, and IgE antibodies,[51,85] all of which are associated with an enhanced inflammatory response that will produce symptoms more typical of atopic asthma. Further, this first infection sets the pattern of the immune response "memory" to future viral (especially RSV) infections.[85] On the other hand, if infection occurs after maturation of the Th1 cellular population, a more balanced combined Th1/Th2 response will occur. The Th1 cellular response results in the production of interferon γ and other cytokines that do not cause as much of an inflammatory response.[85,86] This research not only may explain the pathophysiologic basis for the link between RSV infection and subsequent asthma, but it also has important consequences for the future development of an RSV vaccine.

Diagnosis

Signs and Symptoms

Within a few days of exposure and transmission of the virus to the nasal or ocular epithelium, the patient will generally exhibit mild to moderate nasal congestion and low-grade fever (which frequently disappears within a day or 2) and a productive cough. These symptoms may persist as an upper respiratory infection for several weeks and then resolve without further incident, particularly in patients who have had a previous RSV infection.[66]

In infants, however, it is more common (30–50%)[1] to see development of a lower respiratory tract infection within 2–3 days of the appearance of URI signs and symptoms. Typically coughing becomes more severe, secretions are more copious and thicker, and pharyngitis occurs in one quarter to one half of affected infants. Also the infant may exhibit signs of respiratory distress, including tachypnea, nasal flaring, retractions, and prolonged expiratory phase. Chest auscultation reveals coarse rales throughout, with wheezes in one half to three quarters of infants.[66,87] Finally, vomiting occurs in about half of affected infants.[66]

A chest radiograph typically shows hyperinflation, with flattened diaphragm. In severe lower respiratory tract infections, areas of interstitial infiltration also frequently appear, most commonly in the right upper or middle lobes.[66]

Very young infants may present only with lethargy and poor feeding, as opposed to the more typical signs of respiratory infection. Also, apnea accompanied by bradycardia is a frequent finding in very young infants, particularly those with a history of apnea of prematurity or congenital heart defect.[51,88] This represents one of the most life-threatening aspects of RSV. These infants usually also exhibit severe hypoxemia, dehydration, and may have aspirated prior to their appearance at a doctor's office or hospital emergency room.

A patient with a pulse oximetry reading of < 93% on room air, with indications of uncontrolled vomiting and/or dehydration, and any patient with apnea or other signs of impending respiratory failure should be hospitalized. Assisted ventilation should be considered for patients with apnea or respiratory failure.

Laboratory Diagnostic Testing

At least 3 different laboratory techniques exist for detection of RSV. A sterile collection of nasal washing is required to provide material for all 3 techniques. Two of the techniques, immunofluorescence and enzyme immunoassay, detect the presence of RSV antigens in nasal washings. The third technique, viral culture, requires viable virus that will grow in cell culture. The enzyme immunoassay is used most commonly and has the advantage of relative economy, rapid turn-around time (15–30 min), and ease of use. Commercially available immunoassay kits can be used by personnel who have no training in virology techniques, and they have a high level of specificity and sensitivity.[89]

Table 1. Characteristics of Studies Examining the Effect of Bronchodilator Administration on Infants and Children with Respiratory Syncytial Virus Infection

Characteristic	No. of Studies	References
Total number of studies	24	93–116
Study design		
Double-blind, placebo-controlled	15	94, 99–101, 103–106, 108, 109, 112–116
Patient was own control	9	93, 95–98, 102, 107, 110, 111
Nonintubated patients	20	93–98, 100–107, 111–116
Intubated patients	4	99, 108–110
Drug administered		
Albuterol	20	93–105, 108–113, 116
Metaproterenol	2	106, 107
Ipratropium bromide	5	94, 105–107, 114
Albuterol + ipratropium bromide	2	105, 115
Outcome measures		
Change in S_{aO_2}	9	100–103, 105, 106, 113, 114, 116
Respiratory score	7	100, 101, 105, 106, 113, 114, 116
Pulmonary function measures	14	93–99, 104, 107, 108–112
Results (changes in outcome measures)		
Improvement	12	94*, 95, 99, 100, 101, 104, 106, 107, 108, 109, 110, 111
No benefit	8	93, 94*, 98, 112–116
Worsening	5	94*, 96, 97, 102, 103, 105

S_{aO_2} = arterial oxygen saturation
*Stokes et al[94] showed significant improvement in 40% of infants given ipratropium and significant deterioration in most of the infants receiving albuterol.

Diagnostic testing is useful to identify the presence of RSV in patients who are hospitalized with signs and symptoms described above. It is frequently difficult to distinguish a bacterial pneumonia from RSV, but a positive identification of RSV will reduce the need for antibiotics, and it will allow for proper infection control measures to be instituted as quickly as possible. This is critical because nosocomial infection is one of the most common avenues of RSV transmission.

Therapeutics

Attempts to develop effective therapy for RSV infections have been ongoing for as long as the virus has been recognized; however, no effective treatment beyond palliative measures has appeared. Many treatment strategies have been advanced and practiced, but most of these have proven to be ineffective when examined in rigorous clinical trials.

Oxygen

Individuals exhibiting the typical signs of lower respiratory tract infection should have pulse oximetry readings taken. Supplemental oxygen should be administered to maintain a saturation of > 92%.[90,91]

β_2 Agonists

Because of the frequent presence of wheezing in RSV infections, β_2 agonists have been used to treat them for over 35 years. However, despite numerous clinical trials, the effectiveness of β_2 agonists remains doubtful.[92] A total of 24 published studies examining the effect of bronchodilators (albuterol, metaproterenol, or ipratropium) were reviewed.[93–116] Table 1 shows the characteristics of these studies. When these studies are examined as a group, few consistent generalizations can be made.

The studies were rigorously designed: all had controls and 63% were double-blind and placebo-controlled. Rigorous comparisons are extremely difficult, however, since there is no consistency from study to study in variables such as patient inclusion criteria, drug dose and schedule, or evaluation of disease severity. For example, there was no attempt to identify patients with pre-existing atopy for exclusion from the studies, in order to clarify whether a positive bronchodilator response during an RSV infection is truly efficacious for the RSV infection rather than for underlying asthma.

Also, outcomes criteria varied considerably among the studies. Nearly two thirds of the studies used changes in pulmonary function variables, such as maximum expiratory flow at functional residual capacity, airways resistance, system compliance, or work of breathing, to deter-

mine bronchodilator effect. Though all of these measures are sensitive to relatively small changes in lung function, they are also impractical for application in most bedside settings. The remainder of the studies used respiratory distress scorings systems, length of stay, or changes in arterial oxygen saturation to evaluate outcomes, but these may not be as sensitive as pulmonary function variables. Unfortunately, none of the studies attempted to validate practical bedside outcome variables by correlating them with observed pulmonary function changes.

Fifty percent of the studies reported some type of positive response to the administration of a bronchodilator. This is somewhat misleading, however, since within each of these studies only about 30–50% of the subjects had a positive response. The remainder had no response or in some cases actually became worse. It is particularly troubling to note that in nearly a quarter of the studies patient condition substantially deteriorated in response to bronchodilators.

Four studies looked at response in the most severely ill patients who were intubated and on mechanical ventilation.[99,108–110] On the basis of pulmonary function measures made through the ventilator, all 4 of these studies concluded that bronchodilator therapy is effective for this subset of patients.

Despite the differences among the studies, 4 different meta-analyses of RSV/bronchodilator studies have been published since 1996.[117–120] Since each evaluated a somewhat different group of studies, conclusions from these meta-analyses are not completely consistent. Two of the studies[117,119] concluded that bronchodilators are safe and efficacious in a subset of RSV patients; however, no known criteria exist to prospectively identify that subset. Therefore, a trial of 1–2 doses of albuterol followed by assessment of the effect is recommended. The use of ipratropium was not recommended by any of the meta-analyses, although 2 of the studies did see a positive response with ipratropium.[94,107] The other 2 meta-analyses[118,120] concluded that there is no compelling evidence to use bronchodilators at all in the treatment of RSV infections.

The rationale for both the use of β_2 agonist bronchodilators and understanding their idiosyncratic outcomes lies in the pathogenesis of RSV. Bronchodilators are intended to relieve wheezing, air trapping, and increased airways resistance caused only by constriction of bronchiolar smooth muscle. In RSV, reduction in airway diameter and the accompanying wheezing it produces has at least 4 separate causes: (1) increased secretion production, (2) sloughing of damaged airway epithelium into the airway lumen, (3) interstitial and mucosal edema, and (4) possibly humorally or neurogenically mediated bronchoconstriction. Further, the relative contribution of each of these, particularly bronchoconstriction, probably varies considerably among individuals. β_2 agonists address only bronchocon-

striction. Thus, the greater the contribution of bronchoconstriction to the narrowing of small airways, the more effective β_2 agonists will be in relieving symptoms of respiratory distress, and vice-versa.

Finally, poor aerosol penetration into the peripheral airways of an infant also may limit bronchodilator effectiveness. Amirav et al,[121] using radiolabeled albuterol, showed that only about 0.6% of the albuterol leaving the nebulizer actually reached the small airways of infected infants. They suggest that this is very inadequate and that delivery of medication to peripheral airways in the infant lung could be improved by the use of super-fine aerosols. This correlates with the observation by some investigators that bronchodilator therapy seems to be most effective in the early stages of the infection, presumably at a time when small airways are not as obstructed with secretions and cellular debris.

Racemic Epinephrine

Epinephrine, given either via injection or nebulized (racemic epinephrine), has also been used in an attempt to ameliorate the symptoms of RSV infection. Ten studies examining the efficacy of epinephrine were reviewed.[122–131] Table 2 summarizes the characteristics of those studies. Racemic epinephrine administration improved oxygenation, transcutaneously measured P_{O_2}, respiratory distress score, and

Table 2. Characteristics of Studies Examining the Effect of Racemic Epinephrine Administration on Infants and Children With Respiratory Syncytial Virus Infection

Characteristic	No. of Studies	References
Total number of studies	10	122–131
Study design		
Double-blind, placebo-controlled	7	122–126, 129, 131
Patient was own control	3	127, 128, 130
Nonintubated patients	9	122–129, 131
Intubated patients	1	130
Drug administered		
Epinephrine	8	122–124, 127–131
Epinephrine + albuterol	2	125, 126
Outcome measures		
Change in S_{aO_2}	2	126, 131
Change in transcutaneous P_{O_2}	1	124
Respiratory score	6	122–125, 129, 131
Pulmonary function measures	3	127, 128, 130
Hospital admission	1	126
Results (changes in outcome measures)		
Improvement	8	122–126, 128–130
No benefit	2	127, 131
Worsening	0	

S_{aO_2} = arterial oxygen saturation

pulmonary function measures in all but 2 of the studies cited. In one study in a hospital emergency department,[126] it also lowered the hospital admission rate by more than 50%, compared to infants treated only with albuterol. One of the 2 studies that did not show improvement[127] tested infants who had recovered from RSV infection but still had recurrent wheezing. As with albuterol, not all patients responded positively to administration of racemic epinephrine. With the exception of one study,[122] infants were not classified as responders or nonresponders in any of the studies. When a positive response occurred, it seemed to occur in nearly all patients. Lowell et al[122] reported that 70% of the patients with RSV responded positively. A meta-analysis of 5 studies of the effects of epinephrine on patients with bronchiolitis[120] reported that all 5 showed significant clinical improvement, decreased respiratory rate, and decreased wheezing. Two of the studies examined showed lower hospital admission rates and earlier discharge also.

The difference in patient response to epinephrine versus albuterol again can best be understood in terms of the pathogenesis of RSV infection. Epinephrine, because of its α adrenergic agonist activity, is more effective at decreasing interstitial and mucosal edema and may therefore be more effective at opening small airways than a β adrenergic bronchodilator.[132]

Aerosolized Recombinant Human DNase

One randomized, placebo-controlled study[133] and one case series of 5 infants[134] have examined the effect of aerosolized recombinant human DNase (Pulmozyme) in infants with RSV infections. In the study, chest radiograph scores improved significantly after DNase administration, whereas scores for infants receiving placebo worsened during the same period.[135] However, other measures such as improvement in respiratory rate, wheezing, and retractions during hospitalization were not significantly different between the DNase group and placebo group. In the case series, DNase was administered to 5 RSV-infected infants, 2 with "massive unilateral atelectasis" and imminent respiratory failure and 3 already on mechanical ventilation. Intubation was avoided in the 2 infants, and the 3 on mechanical ventilation quickly showed clinical and radiologic improvement.[136]

Inhaled and Systemic Corticosteroids

Corticosteroids are commonly prescribed for the treatment of bronchiolitis, both during the acute phase and during the period of recurrent wheezing that follows RSV infection in many infants. Results from 17 studies examining the effectiveness of this treatment were reviewed.[135–151]

Table 3 summarizes the characteristics of these studies. When studies are examined individually, the authors in only 3 of the 17 concluded that patients benefited from steroids. This would strongly suggest that little or no benefit is to be gained from the use of steroids in the treatment of RSV. However, Garrison et al carried out a meta-analysis of steroid therapy[152] and found 6 studies[135,136,138,139–141] that had sufficient similarities for data to be combined. Although the authors in 4 of those 6 studies[136,138,139,141] individually stated that their studies showed no benefit from steroid treatment, the pooled data subjected to the meta-analysis demonstrate that length of hospitalization was significantly shorter in the steroid-treated group, although the reduction was relatively small (0.43 d). The small sample size of the individual studies and the relatively small benefit observed probably account for the difference between the conclusions of the individual studies and that of the meta-analysis.[152]

The studies summarized in Table 3 used both systemic and inhaled corticosteroids. Two of the 3 that showed beneficial results[137,151] used inhaled budesonide, whereas the other study, by van Woensel et al,[140] used prednisolone. The latter study also was the only one to include mechanically ventilated patients. The results from the van Woensel et al study suggest that the sickest patients may draw the greatest benefit from corticosteroid administration. Length of hospitalization among mechanically ventilated, RSV-infected patients ($n = 14$) given systemic steroids was 6 days shorter than that of the placebo group (11 ± 0.7 d vs 17 ± 2.0 d).[140]

A number of the studies had prolonged follow-up periods, which again showed mixed results. Of the 5 studies that had follow-up in the 1–5 year post-infection period, only one[151] had results that showed a significant benefit from steroid use.

Pulmonary function testing does not appear to be necessary to show benefit from steroid use. All 3 of the studies that showed benefit from steroids used respiratory scoring, pulse oximetry, or incidence of wheezing as the outcome variable, and the one primary outcome variable used by Garrison et al[152] in the meta-analysis was length of hospitalization.

Garrison el al[152] also noted 2 confounding variables that make it difficult to study the effectiveness of steroids for RSV: the presence of prior atopy or asthma and the prior use of steroids. Most of the studies reviewed here either do not exclude patients with prior history of wheezing or steroid use, or else they make no mention when describing their patient selection procedures. However, 4 of the 6 studies used by Garrison et al[152] did specifically exclude patients with history of wheezing,[136,138,139,141] but only 2 of the studies specifically excluded patients with prior steroid use.[139,140]

Table 3. Characteristics of Studies Examining the Effect of Corticosteroid Administration on Infants and Children With Respiratory Syncytial Virus Infection

Characteristic	No. of Studies	References
Total number of studies*	17	135–151
In-patient†	14	135–142, 144–146, 148, 149, 151
Out-patient	3	143, 147, 150
Drug administered		
Systemic corticosteroid‡	10	135, 136, 138–141, 143, 144, 147, 149, 150
Inhaled corticosteroid§	6	137, 142, 145, 146, 148, 151
During hospitalization (1–7 d)	11	135, 136, 138–141, 143, 144, 147–150
Post-hospitalization	5	137, 142, 145, 146, 151
Outcome measures		
Respiratory score	9	136, 138, 139, 140–143, 147, 150
Wheezing	8	137–139, 142, 143, 148, 149, 151
S_{aO_2}	6	138, 139, 141–143, 145
Duration of symptoms	9	136, 137, 138, 140, 142–146
Pulmonary function measures	3	136, 141, 145
Decreased hospital admissions	4	137, 143, 147, 150
Decreased length of hospital stay	6	135, 136, 139, 140, 142, 144, 146
Development of asthma	2	148, 149
Follow-up schedule after discharge		
1–4 wk	5	136–138, 144, 147, 151
8–16 wk	2	137, 148, 151
6 mo	2	142, 148, 151
1–5 yr	4	143, 144, 148, 149, 151
Results (changes in outcome measures)		
Favored treatment	3	137, 140, 151
No benefit	13	136, 138, 139, 141–149, 151

*All studies were double-blind, placebo-controlled
†One study[140] had patients on mechanical ventilation
‡Systemic corticosteroid was prednisone, prednisolone, methylprednisone, hydrocortisone, or dexamethasone
§Inhaled corticosteroid was budesonide
S_{aO_2} = arterial oxygen saturation

The pathophysiology of RSV suggests that the anti-inflammatory action of corticosteroids should provide effective therapy for infections. However, despite all the clinical research to date, the efficacy of steroid use for RSV remains unclear. Well-designed, multicenter trials with strict patient selection criteria, tightly defined drug administration regimens, and long-term follow-up are badly needed. Two recommendations seem reasonable at this time, however. First, inhaled corticosteroids, with their lower adverse effect profile, appear to be as effective as systemic corticosteroids for hospitalized patients with moderately severe infections. Second, corticosteroids appear to be highly effective in severely infected patients requiring mechanical ventilation. Garrison et al[152] also noted that infants with the most severe infections appear to benefit most from steroids.

Ribavirin

Ribavirin (Virazole) is the only anti-viral preparation approved for RSV infections. It inhibits the synthesis of viral structural proteins, thereby slowing viral replication, and it results in a reduced IgE response.[153] Results from more than 100 studies examining the efficacy of ribavirin were reviewed (PubMed index of the National Library of Medicine). A very large number of double-blind, placebo-controlled studies have been published; however, most of these suffer from relatively small sample size (20–50 infants), and the results have been frustratingly inconsistent and contradictory.[154] In addition, because administration of ribavirin is very labor intensive and presents some hazard to caregivers, its use has been further questioned on economic and safety grounds.

Early double-blind, placebo-controlled studies were extremely encouraging, indicating that ribavirin aerosol resulted in more rapid clinical improvement in previously well infants,[10,11,155–157] in infants with underlying cardiopulmonary disease,[158,159] and in infants requiring mechanical ventilation for severe infections.[12] The use of ribavirin was editorially embraced with great enthusiasm in the pediatric literature.[160,161]

More recent studies have not borne out earlier positive results, however. For example, 2 more recent randomized, placebo-controlled studies examining the effects of ribavirin on mechanically ventilated infants[162,163] found no statistically significant positive effect. Also, 2 other studies examined data from multiple centers on mechanically ventilated RSV-infected patients[164,165] and found no statistically significant positive effect from ribavirin. One, in fact, showed that even after correcting for severity of illness factors, length of hospital stay was greater in the ribavirin-treated groups than in the placebo-treated groups.[165] This same longer length of stay for ribavirin-treated patients was also observed in a different multi-year, retrospective study that evaluated the treatment of 768 RSV-infected children over a 7-year period.[166]

Another question addressed in a number of studies is whether ribavirin can decrease the severity of post-RSV infection wheezing. Five studies addressing this question were identified.[167–171] Table 4 summarizes the characteristics of those studies. All 5 studies identified the presence of wheezing and/or reactive airway disease in children who suffered RSV infections in infancy; however, the benefit of ribavirin treatment is not clear. Although the outcome measures used varied somewhat among the studies, they were similar enough that inter-study comparisons can be made. Two of the 5 studies showed positive benefit[169,171] from ribavirin, whereas 3 showed no benefit.[167,168,170] Study design did not seem to matter; both positive and negative results occurred in both retrospective and prospective studies. Both of the studies showing a positive effect from ribavirin had their follow-up at 1 year, whereas both of the 5-year follow-up studies had negative results. This is consistent with the previously noted observation that measurable pulmonary sequelae seem to disappear within 5–10 years of initial infection.

Clearly, enthusiasm for the use of ribavirin has diminished in recent years. In 1996 the American Academy of Pediatrics issued guidelines on the use of ribavirin,[13] recommending that it be used at the discretion of the individual physician for children with substantial comorbidities (eg, cardiopulmonary disease or immunosuppressive disease or therapy) or those with exceptionally severe RSV infection. In light of the contradictory and confusing clinical research results noted above, these guidelines seem appropriate.[172]

Nasopharyngeal Suctioning

During an RSV infection, copious secretions are present in the nose, pharynx, and lower airways. Given that approximately 60% of the resistance to breathing is located in the upper airway, and given that young infants are primarily nose breathers, clearance of these secretions should

Table 4. Characteristics of Studies Examining the Effect of Ribavirin Administration During Acute Respiratory Syncytial Virus Infection on the Occurrence of Post-Infection Wheezing and/or Reactive Airway Episodes at 1 Year or 5 Years

Characteristic	No. of Studies	References
Total number of studies	5	167–171
Study design		
Randomized, placebo-controlled	3	168, 170, 171
Retrospective selection of patients	2	167, 169
Outcome measures		
Wheezing	3	168, 170, 171
Reactive airway episodes	4	167, 168, 169, 171
Pulmonary function measures	3	167, 168, 170
Hospital admissions	1	171
Frequency of use of bronchodilators and corticosteroids during follow-up period	1	170
Frequency of lower respiratory tract reinfection	1	168
Follow-up after discharge		
1 year	3	169–171
5 years	2	167, 168
Results (changes in outcome measures)		
Ribavirin group better	2	169, 171
No benefit from ribavirin	3	167, 168, 170

have a positive impact on work of breathing and provide symptom relief.

Nasopharyngeal suctioning (defined as extending a suction catheter up through the nose, passing the tip to the hypopharynx, and then applying suction as the catheter is withdrawn) has proven to be a remarkably effective palliative measure for infants with RSV. The efficacy of this procedure has been investigated, both as a single intervention and in combination with albuterol aerosol treatment at the Primary Children's Medical Center in Salt Lake City, Utah. In a series of 474 patients, whose disease severity was evaluated with a 4-point bronchiolitis symptom scoring system[173] developed as an assessment tool, 81% showed improvement of at least 1 point following nasopharyngeal suctioning.[174] In a series of 421 patients requiring oxygen to maintain arterial oxygen saturation $\geq 88\%$, 31% could be weaned following the first suctioning episode, and 24% could be weaned following the second or third suctioning episode.[175] When suctioning was used in conjunction with albuterol treatments as part of a bronchiolitis clinical pathway in a series of 166 patients in each of 2 RSV seasons, the suctioning was found to be more effective at lowering the bronchiolitis score than was the albuterol treatment.[176] In over 3,000 separate suctioning procedures, no adverse events were recorded. Formal investigation of the effectiveness of this procedure should be carried out in other

centers; however, at this time it would seem to be a proven, logical, safe, and inexpensive intervention that should be incorporated into every RSV treatment protocol.

Helium-Oxygen Gas Mixtures

Helium-oxygen mixture (heliox) decreases work of breathing and improves gas exchange in obstructive conditions such as croup[177] and chronic obstructive pulmonary disease.[178] Three studies have examined the effect of heliox in RSV-infected infants.[179–181] In nonintubated infants with severe RSV bronchiolitis, heliox administered via nonrebreather mask significantly improved clinical score,[179] respiratory rate, heart rate, and arterial oxygen saturation.[181] Intensive care unit length of stay was also significantly shorter in one of the studies.[181] In the third study, heliox was administered at 3 different concentrations (50% He/50% O_2, 60% He/40% O_2, and 70% He/30% O_2) through a ventilator to intubated, sedated, paralyzed infants.[180] Results were compared to ventilation with a 50% N_2/50% O_2 mixture. The various gas mixtures showed no difference in their effects on P_{aCO_2}, the ratio of P_{aO_2} to fraction of inspired oxygen (P_{aO_2}/F_{IO_2}), or the ratio of arterial partial pressure of oxygen to alveolar partial pressure of oxygen (P_{aO_2}/P_{AO_2}). They concluded that heliox does not benefit intubated RSV patients. Although it was not specifically stated in any of the studies, administering heliox may be a useful adjuvant to avoid respiratory failure and intubation.

Nitric Oxide

Two case reports describe successful inhaled nitric oxide (INO) treatment of infants suffering severe RSV pneumonia and bronchopulmonary dysplasia. In one case INO was used with conventional mechanical ventilation and improved both oxygenation and respiratory system resistance.[182] In the other case INO used with high-frequency ventilation improved oxygenation more than the high-frequency ventilation alone.[183]

In addition to the 2 case reports, a prospective study[184] with 12 intubated infants with severe RSV infection compared respiratory system resistance measurements after 1 hour of INO at concentrations of 20, 40, and 60 ppm versus administration of albuterol. In both instances about half of the infants benefited from the treatments and about half either got worse or derived no benefit. The authors concluded that INO does not improve lung mechanics. None of the infants in this study had refractory hypoxemia or evidence of pulmonary hypertension, whereas the 2 infants described in the case studies had deteriorated due to acute respiratory distress syndrome. At this time INO has United States Food and Drug Administration approval only for the treatment of persistent pulmonary hypertension of the newborn. It is most effective at relief of severe, refractory hypoxemia, and its use in RSV-infected patients should be reserved for that condition.

Extracorporeal Membrane Oxygenation

Three studies reviewed the use of extracorporeal membrane oxygenation for the treatment of severe RSV infection.[185–187] In the study that reviewed data from 1982 through 1992, survival to hospital discharge was 49% (26/53).[185] In the study that reviewed data from 1983 through 1988, survival to hospital discharge was 58% (7/12).[186] Risk factors for increased mortality included male gender, longer time on mechanical ventilation prior to start of extracorporeal membrane oxygenation, higher peak ventilatory pressure, and lower oxygen index.[185] The third study reviewed 24 cases from 3 centers in England between 1989 and 1995. Survival was 96% (23/24). Two of the studies carried out follow-up,[186,187] and both found that neurologic outcome in survivors was excellent. All 3 studies concluded that extracorporeal membrane oxygenation is a good option for patients with severe RSV disease who cannot be supported on mechanical ventilation.

Prophylaxis

RSV is incurable by medical intervention, and although it is self-limited by the body's own immune response, the individuals most susceptible to severe infection are those who are least capable of dealing with it. RSV is also ubiquitous, and no effective vaccine exists. These facts ultimately make prophylaxis the most effective way to handle the disease. Effective prophylaxis requires multiple approaches. The goals of prophylaxis should include (1) infection prevention in term newborns less than 6 months of age, (2) infection prevention in newborns at high risk for severe infection who are less than 9–12 months of age, (3) prevention of nosocomial infections, and (4) development of an effective vaccine.

Infants Born at Term

Although it is widely acknowledged that virtually all infants will suffer their first RSV infection by age 2, the likelihood of that infection becoming severe lessens as the newborn ages. In most newborns the cellular component of the immune system, which is critical to ending an RSV infection, matures by about 6 months.[51,84–86] Thus the immune response to the infection is more likely to limit it to the upper respiratory tract and less likely to produce a response that will result in prolonged wheezing and possibly asthma.

The key to preventing RSV infection prior to the age of 6 months lies in education of parents and caregivers about the seriousness of RSV infection in the young infant, its routes of transmission, and the measures most effective at preventing transmission. This is particularly true for infants born during the months May through November. The 2 most effective steps in preventing infection are hand-washing and limiting contact between the newborn and other individuals, especially other children with "colds." Finally, breast feeding should be encouraged for many reasons, but parents should be told that minimal or no breast feeding increases risk of severe RSV lower respiratory tract infection in the first 5 months of life.[74,188]

Infants at Risk for Severe Infection

Infants at risk for severe infection include those born prematurely and those with underlying cardiopulmonary disease or compromised immune function. Prevention of infection in these infants for as long as possible is particularly important.

In addition to the measures described above, the American Academy of Pediatrics recommends that palivizumab (Synagis) be administered to certain at-risk infants. These include (1) children ≤ 2 years old who have required therapy to treat CLD within 6 months prior to the next RSV season; (2) infants without CLD born at ≤ 28 weeks gestation, up to the age of 12 months; (3) infants born at 29–32 weeks gestation, up to the age of 6 months; and (4) infants born at 32–35 weeks gestation who have risk factors such as daycare attendance or school-age siblings, up to the age of 6 months.[189] Also, palivizumab is not currently FDA-approved for children with congenital heart disease, but a large, multicenter trial is nearing completion and this recommendation may be revised in the near future.[190]

Palivizumab is a human recombinant monoclonal antibody directed against the F glycoprotein (a viral surface protein that promotes fusion of infected cells with adjacent cells) of RSV. The structure of the F glycoprotein is highly conserved, which makes the antibody effective against virtually all RSV strains and subtypes.[191] Palivizumab is administered as an intramuscular injection (15 mg/kg) once a month during RSV season.

The effectiveness of palivizumab was tested in a randomized, double-blind, 139-center trial that included 1,502 infants who met the criteria described above.[16] The primary outcome measure was incidence of hospitalization. Secondary outcome measures included days of hospitalization, time of oxygen requirement, time of increased respiratory severity score, time in the intensive care unit, time on mechanical ventilation, and incidence of otitis media. The overall rate of hospitalization was 55% lower in the treated groups, and the difference was even larger in some subgroups (eg, infants who were premature but did not have CLD had 78% fewer hospitalizations). Also, respiratory severity scores, hospital days, days of oxygen requirement, and the rate of intensive care unit admission were all significantly lower in the treated group.

A second antibody preparation, RSV-IGIV (RespiGam), produced from the sera of adult humans, is a polyclonal preparation that was developed in the early 1990s and tested on at-risk newborns. In a 54-center trial carried out in 1994–1995, with 510 infants, those who received RSV-IGIV had an overall decrease in hospitalization rate of 41%.[15] Other outcomes were similar to those shown for palivizumab,[15] although when palivizumab was compared to RSV-IGIV in an animal model, it was found to be 50–100 times more potent.[192]

The American Academy of Pediatrics recommends use of palivizumab over RSV-IGIV, for several reasons.[189] Palivizumab is more convenient, since it can be administered by intramuscular injection rather than by intravenous infusion. RSV-IGIV interferes with the measles-mumps-rubella vaccine (vaccination must be delayed 5 mo after last RSV-IGIV treatment). And palivizumab was found to be more cost-effective than RSV-IGIV.[193]

Because both RSV-IGIV and palivizumab are so expensive, their cost-effectiveness has been analyzed in several studies.[193,194] Taking into account only the cost of administering the preparation to a whole group versus hospital costs for that group, it was determined that palivizumab was cost-effective only for premature infants with CLD. Another study, from New Zealand, determined that palivizumab was not cost-effective for any group, but still recommended that it be given to infants discharged on home oxygen and on those born at ≤ 28 weeks gestation.[195]

Prevention of Nosocomial Infections

During RSV season, when pediatric wards are filled to capacity and caregiver resources are stretched to the maximum, RSV is a major nosocomial hazard. Both patients and caregivers are at risk, and only the application of strict infection control procedures can deter transmission of the virus from infected caregivers and patients to uninfected caregivers and patients. The major routes of transmission are by large-droplet aerosol (eg, from sneezes) and contact through the passing of infected secretions. Fomites are particularly problematic since the virus remains infectious on some surfaces for up to 10–12 hours.[64] Table 5 summarizes recommended infection control procedures.

Hand-washing is the single most important infection control measure. The key to promoting frequent and effective hand-washing is the acceptability of hand-washing products and convenience of hand-washing sites. Also, alcohol-based hand rubs are a satisfactory substitute for soap and water. They are quick to use, can be conveniently placed, and are effective against RSV.[49]

Infection control procedures consume valuable time and resources; it is therefore important that infected patients be

Patient suspected to have RSV infection
   Diagnosis of RSV should be confirmed as soon as possible
   While awaiting diagnosis, contact-isolation procedures should be observed
Patient with confirmed RSV diagnosis
   Should be in contact-isolation
   Family members should be educated regarding modes of infection transmission and infection control procedures by caregivers
   More than one RSV-infected patient may be placed in a room
Hand-washing: all caregivers, family members, and visitors
   Prior to patient contact
   Prior to leaving patient room
   After contact with patient toys, dishes, clothing, bed linens, diapers
Gloves: all caregivers, family members, and visitors
   Donned prior to entry into patient room
   Discarded into infectious waste container in the room prior to leaving
   Changed after contact with secretions and before touching potential fomites
Gowns: all caregivers, family members, and visitors
   Donned when coming into immediate contact with patient or secretions; otherwise, not necessary
   Discarded into laundry or infectious waste container in the room prior to leaving
Masks: all caregivers, family members, and visitors
   Not necessary unless likely to inhale large aerosol particles.
   Mask with eye guard is most useful, since transmission is either to nose or eyes
Patient room
   Should be cleaned and disinfected thoroughly and all infectious waste discarded after patient discharge
   All toys and equipment should be wiped down with disinfectant
Caregivers
   Practice good isolation procedures
   Avoid touching fingers to eyes or nose, especially prior to washing hands
   Do not pass on your own respiratory infection
Uninfected patients
   Kept from contact with other patients, especially those who are infected
   Kept from contact with toys or equipment that has not been wiped down with disinfectant
   Immunocompromised or other uninfected, at-risk patients should be closely supervised to avoid contact with potential vectors (eg, caregivers, other patients, fomites, family members/visitors who have respiratory infections)
   Immunocompromised or other uninfected, at-risk patients should be kept in area of the hospital where no RSV patients are present or should be placed in reverse isolation

RSV = respiratory syncytial virus
(Adapted from Reference 48.)

identified to prevent the nosocomial spread of the virus.[48] Simple, rapid diagnostic tests are readily available and will enable patients to be placed at the appropriate level of isolation as soon as possible. Also, infection control procedures should be limited to those that are most effective, in order to minimize staff "burn out" from having to perform time-consuming, and unnecessary activities. For example, at least one study has shown that gowns and masks have little impact on the nosocomial transmission of the RSV.[196] Thus, they are not necessary every time a caregiver goes into a patient's room, but only when direct contact with secretions or large droplets is expected.

Education of caregivers regarding the importance of infection control procedures is critical. Education programs should be implemented each year prior to the beginning of RSV season and repeated as needed, since compliance tends to decrease as the season progresses.[48] Compliance should be monitored, and it is critical that persons in leadership positions (eg, physicians, supervisory nursing, and respiratory supervisory personnel) follow the same procedures expected of staff.

Vaccines

Given the complete lack of effective treatment for RSV infection, the ultimate best solution is a vaccine; however, many obstacles remain to be overcome before a vaccine becomes available. The body's immune response to RSV infection is complex and incomplete. Response to initial infection normally results in a balanced response by both the humoral and cellular components of the immune system,[51] but even this does not confer durable and complete immunity, as reinfection is common. Furthermore, initial infection frequently occurs in newborn or very young infants, and the immature infant immune system is barely competent to mount a response to the native infection. Thus, if a vaccine is to be effective, it will have to be given at a very early age and will have to stimulate a response in an only partially competent immune system.[197]

Although the presence of maternal antibodies from placental transmission and breast milk apparently confers some immunity in the first 1–2 months of life, it also might inhibit the infant's own immune response to a vaccine.[198] In addition, an RSV vaccine might interfere with the action of other vaccines administered during the same time frame.[197]

Several strategies are being pursued to develop a vaccine. The first RSV infection normally does not prevent subsequent upper respiratory infection, but in the immunocompetent individual it normally does prevent the more severe lower respiratory tract infection from recurring. If the goal of a vaccine is to mimic the immunity conferred by natural infection, then it may not be possible to totally prevent infection; rather, the goal of a vaccine would be to

prevent severe lower respiratory tract disease while allowing a mild upper respiratory tract infection to occur.

RSV has a unique trait in that it causes an infection right at the point where it enters the body. Many other viruses enter at the nose or eyes, but then most must move into the blood stream before causing disease. This gives the immune system time and opportunity to respond. RSV, on the other hand, begins its primary infection right at the point of entry. Further, once it enters nasal epithelial cells, viral particles are transmitted directly from cell to cell without exiting from the cell membrane, via the cell fusion process described earlier. This confers some protection to the virus from humoral antibodies. The more severe lower respiratory tract infection takes several days to develop, which gives the immune system time to respond if it has been primed by a previous infection (or possibly a vaccine).

Attempts to develop a live, attenuated vaccine have been made for many years.[199] These candidate viruses have been tested in animals, but in trials on adult humans have proven to be either too virulent, too attenuated, or too unstable.[51] These trials were discontinued, but work is now underway on a genetically engineered attenuated viral strain, made possible by the newly developed ability to copy and modify the viral genome at the level of the individual nucleotide.[197]

Another approach being considered is to vaccinate pregnant women in the last trimester of pregnancy so that they pass a large antibody load to the infant just prior to birth.[200] With this approach the challenge is to design a vaccine that will stimulate the infant's immune system to replace those maternal antibodies as they are lost. Attempts are also underway to produce a vaccine that would augment antibody production to glycoproteins F and G in immunocompromised individuals who have already had at least one RSV infection.

A successful vaccine is still many years away. Once it is developed, it must first be tested in animals (a difficult task since there is not a good animal model for RSV), and then tested in the most robust human groups such as healthy adults, children, and then newborns before it can be tried on the most at-risk groups. Ultimately a successful approach to an RSV vaccine may require the development of several vaccines targeted at different groups.[51,197]

Disease Management Strategies for Respiratory Syncytial Virus

Out-Patient Management

The vast majority of infants and children infected with RSV (97–99%) are successfully treated as out-patients. Although it may be difficult for physicians and parents to do little or nothing, no palliative treatment has proven to be effective in the out-patient setting. Most importantly, parents should be informed of the signs of worsening disease, particularly in infants < 6 months of age and those at higher risk of severe infection.

Very young infants are more likely to present with lethargy, irritability, and poor feeding, rather than with the typical signs of respiratory infection, and are at increased risk for apnea and bradycardia. These infants may progress from what appears to be a nearly asymptomatic state to full respiratory deterioration without the appearance of signs of respiratory infection.[153] Aminophylline should not be started in response to an RSV infection,[201] but infants already on theophylline, aminophylline, or caffeine for apnea of prematurity should maintain their intake.

Hypoxemia is a potential complication and can be easily checked via pulse oximetry in the out-patient setting. Oxygen saturation is the single best identifier of more severe lower respiratory tract disease.[202] Infants with pulse oximetry readings < 92% usually are admitted to the hospital for closer monitoring and administration of oxygen.[203]

Appropriate fluid management is also important. Generally RSV is not a dehydrating disease, so only normal fluid intake should be maintained. RSV infection can result in increased antidiuretic hormone secretion.[204] This, combined with increased fluid intake, has resulted in hyponatremia and even seizures in some infants.[153]

Normal feeding should be maintained as much as possible; however, parents should be cautioned to monitor respiratory rate, and physicians should be alerted if the respiratory rate of any infant becomes > 50–60/min. Because of increased risk of aspiration,[205] these infants should not be fed. Aspiration will result in rapid deterioration of respiratory status and increased likelihood of severe lower respiratory tract disease.[206] Along with the typical respiratory symptoms, a mild fever is normal in the first few days of infection.

Clearly vigilance is necessary in the out-patient setting during the course of the disease, but parents should be encouraged that in the vast majority of cases the disease is self-limiting and will usually resolve in 7–10 days. Close contact between parent and caregiver during the worst days of the infection will bolster that encouragement.[153]

Use of Practice Guidelines in In-Patient Management

To reduce the utilization of medical resources in the treatment of RSV infection, many institutions have adopted clinical practice guidelines that specify admission and treatment procedures. Ideally, these are based on evidence from studies published in peer-reviewed journals. Investigators have evaluated the effectiveness of a number of these practice guidelines in published studies.[207–213]

Table 6 summarizes the results from 6 published studies evaluating the effectiveness of clinical practice guidelines. Clearly the implementation of clinical practice guidelines decreases resource utilization. Further, in all 6 studies reviewed there was no perceived or measured decrease in

Table 6. Comparison of Changes in the Utilization of Resources Associated With the Treatment of RSV Infection Following Implementation of CPGs

	Increased Utilization	Decreased Utilization	No Change
Hospital admission rate		209	
RSV immunoassay		208, 212	
Chest radiograph		209	210
Isolation order	208		
Supplemental oxygen		212	
Antibiotic use		208, 211	209, 210
Bronchodilator use		208, 209, 210, 212, 213	
Chest physical therapy use		212	
Ribavirin use		212	
Length of stay		209, 211, 213	208, 210
Readmission rate			208–213

Data are from 6 different centers following implementation of clinical practice guidelines.
Not all centers evaluated all practices.
Numbers refer to the references.
RSV = respiratory syncytial virus
CPG = clinical practice guideline.

quality of care. Most studies used readmission rate after discharge as the principle indicator of quality of care, and this stayed constant in all studies following implementation of practice guidelines.

The most striking result was the decrease in the use of bronchodilator treatment, particularly the use of albuterol. If a patient was wheezing, most centers conducted a trial of albuterol and/or racemic epinephrine. The guidelines recommended stopping treatment if no response was evident after 1 or 2 treatments. Most studies reported that though bronchodilator treatments frequency decreased, substantial numbers of ineffective treatments were still ordered.

Most guidelines recommend against the use of routine RSV diagnostic testing. Although the RSV immunoassay does represent a cost, a positive diagnosis of RSV obviates antibiotics and ensures that patients will be placed in appropriate isolation as soon as possible. However, the one study that examined changes in nosocomial RSV infection rate found no change even though use of RSV diagnostic testing was decreased.[212]

Conclusion

The overwhelming impression from the approximately 2,000 studies that have been published on various aspects of RSV is that much of this disease remains a mystery. It is ubiquitous, and its unique infectious nature partially protects it from the human immune system and prevents complete immunity from forming. This makes development of an effective vaccine extremely difficult, and it

guarantees that there will always be an abundance of susceptible hosts in the community.

The biology of the disease is slowly but steadily being elucidated in the laboratory, but results from the vast array of clinical studies are contradictory and inconclusive for nearly every topic addressed. Given the level of effort expended by scientists and clinicians throughout the world to develop effective treatment and prophylaxis, we have remarkably little to show for it.

The most consistent theme running through all of the clinical research published to date is that we need better, larger, and more tightly controlled studies to determine the effectiveness of various treatments. Yet the vast majority of published clinical studies, especially those published within the last 15 years, are well designed, randomized, double-blind studies. Also, the more tightly clinical study conditions are defined, the less generalizable they are to everyday clinical practice. Therefore, more rigorous clinical studies may not be the answer; rather the answer lies in acknowledging that the treatments we are testing are for the most part minimally effective.

In spite of the difficulties, development of a vaccine is proceeding with reasonable progress on a number of fronts. Until this vaccine comes on line, however, evidence-based clinical practice guidelines should be used to avoid squandering increasingly tight medical resources. Clinical practice guidelines are clearly very effective, and once they have been put in place, they can be sustained and the gains achieved can be continued.[213,214]

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Discussion

Salyer: In Salt Lake City we had a 6-year campaign to standardize the treatment of RSV, and I have data on some 2,500 patients. We've recently published some abstracts showing the association between nasopharyngeal suctioning and the use of albuterol, and nasopharyngeal suctioning and the use of radiographs.[1–6] These were not systematic, prospective studies; they were process-oriented measures. But we were pretty convinced that there was a salutary effect from a systematic approach to using nasopharyngeal suctioning with catheters into the hypopharynx. We were called "protocol Nazis" by the nursing staff, but we effected and sustained a 38–40% drop in albuterol use. We use chest physiotherapy in maybe less than 2% of these patients. I've heard of plenty of places where 60–70% of admitted bronchiolitic infants receive chest physiotherapy.

Finally, what really impressed us was that in the early 1990s two thirds to three quarters of admitted bronchiolitics less than 2 years old were mild to moderate in severity of illness. That's changed tremendously since then. The proportion of bronchiolitics who are mild to moderate is down to 40–50%. There are now a number of published trials and reports on the effect of guidelines on RSV treatment,[7–11] and a lot of progress has been made in minimizing over-treatment of RSV patients.

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Anderson: My question also concerns protocols, and it may actually be more philosophical than scientific. You and Dr Kercsmar and my colleagues from Seattle have provided some telling evidence in favor of protocol treatment of various diseases, including asthma, seizures, gastroenteritis, and RSV. What I, as an educator, struggle with is how do we resolve the fact that we also want to teach our students to *think*—to think through disease states and to think outside the box, if you will. Sometimes residents

just give me a blank stare and say, "Well, he's in the bronchiolitis care path." And I ask, "Well, yeah, but does he have an element of heart failure?" How do you resolve the fact that, while we're implementing protocols for many aspects of pediatric care, we still want to train intelligent, hard-thinking clinicians?

Black: Well, obviously, with protocols, if the pendulum swings too far in one direction, you can get to the point of "robotics," and clearly that's not where we want to go. As an educator, I can tell you that when I teach the more advanced students, we teach protocols in both the clinical setting and the classroom setting, and there's nothing that substitutes for a good assessment. The standard thing that the medical student is told is that 95% of all diseases are diagnosed by the end of the history, and 99% by the end of the physical examination and history. Clearly, because house officers and respiratory therapists are being pressed so hard right now with increased workloads, there is a strong temptation to fall back on the protocol.

From a philosophical standpoint, those of us who teach have to insist that our patients be rigorously assessed on a regular basis. One of the most positive things about the protocols that we've seen today is that there are regular assessment periods. We may not necessarily have a treatment, but there is a regular assessment period. I can tell you that the protocols we use in pediatrics at Saint Vincent/Mercy Medical Center involve that same thing.

Kercsmar: Concerning RSV bronchiolitis, the airway pathophysiology (profound inflammation) suggests that steroids should help, but none of the trials have indicated that they do, until a recent study indicated that emergency room pediatric patients who received dexamethasone had fewer hospital admissions and more rapid improvement.[1] Would anyone like to comment on why that study flies in the face of every previous study?

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Black: Well, as you say, steroids should help. This is primarily an inflammatory/destructive process, and the destruction comes about via inflammatory mechanisms, so anything we can do to reduce inflammation obviously should help. I think part of the problem might be that by the time we see a severe RSV infection in the hospital setting, so much damage has already been done that a relatively short course of steroids such as dexamethasone probably just isn't going to make that much difference. It's the same with acute respiratory distress syndrome. Steroids should help there, but I think they've been shown not to.

Wagener: I will propose 2 reasons that steroids will not help early in RSV either. One is that steroids don't get rid of the virus, and 50% of patients will have positive viral cultures for up to 9 days. The second is that early on in this disease the airway inflammation is primarily neutrophilic. Steroids have a relatively weak effect on neutrophils. That brings up another question. You mentioned that mucolytics such as hypertonic saline and Mucomyst are not effective. Since in the early part of RSV the inflammation is primarily neutrophilic, would drugs such as dornase alfa (Pulmozyme) be of benefit?

Black: That's an interesting question. Mucomyst attacks the protein molecule of the mucus directly by cleaving the disulfide bonds, whereas Pulmozyme is a deoxyribonoclease, and if there isn't a lot of DNA in the sputum causing the increased viscosity, then Pulmozyme is not going to be helpful. But if there is a lot of cellular debris, and obviously there should be, then Pulmozyme should be effective. I'm not aware of any trials on this subject, and we certainly don't use it in our hospital setting, because it's so expensive.

Kercsmar: There is one published trial that had a fair number of non-intensive care unit patients, but the only outcome showing improvement was chest radiograph scores.[1] Dornase alfa is pretty expensive, and it seems that maybe it should work, but it also seems that it should work in adults with chronic obstructive pulmonary disease and chronic bronchitis, but it doesn't. Just another vexing point about RSV.

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Cheifetz: My question concerns the use of albuterol for infants with bronchiolitis. In your presentation you played down the role of albuterol, but the available data indicate that a subset of infants with RSV bronchiolitis will respond to bronchodilator therapy.[1,2] Do you have clinical data that would help to predict which infants will respond to albuterol? Or do you recommend that all patients who are admitted with RSV bronchiolitis and respiratory distress receive a trial of albuterol and then only those patients who clinically respond continue to receive it?

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Black: Probably. And the same is true with racemic epinephrine. It's certainly worthwhile having a trial. Many protocols involve a trial of 1 or 2 doses of albuterol and/or racemic epinephrine. If you see a positive response, presumably decreased wheezing, decreased dyspnea, or whatever scoring system you're using, then that might be helpful. As I said, there are some patients who will respond to albuterol, but it's probably going to be those who have reactive airway disease superimposed on top of the RSV infection.

Salyer: Let me address that. We use a "score/suction/score/treat/score" protocol, using a clinically-driven symptom score. We score the patient, suction, and if there is improvement we stop. If there is no improvement, we treat with albuterol. If the albuterol causes improvement, we continue the albuterol. So essentially we had a system in which albuterol was trialed in patients who did not respond to suctioning the upper airway. You're absolutely correct. About 40–50% of patients who responded never got treated. We were up to 60–70% of patients who never got an albuterol treatment outside the emergency room.

Wiswell: In an earlier [unrecorded] conversation here, you mentioned parents who had premature twins, and you recommended isolating the babies for a year, or at least relatively isolating, which has been extremely controversial. I'm not aware of any data that show that's helpful. Think of the im-

practicalities of such isolation. If there are any other siblings in the household, RSV is going to come in. Parents will bring it in from going out in public, especially if they come from a health care professional's office RSV's going to come home with them. I've never seen any data showing that isolation has worked. I realize where your heart is, but I'm not sure of the practicalities.

Black: You're absolutely right; we're never going to completely avoid RSV infection in these kids. But if you can get them through the first season, then the likelihood of a severe infection is diminished tremendously. Those parents spent 2 years and a lot of money trying to get that pregnancy, so it seems to me that attempting isolation ought to be worth it.

Wiswell: My other comment relates to the degree of prematurity, and I'm making a presumption that they have little or no respiratory distress. They're not the micro-preemie, and they're not the chronic-lung-disease babies that we're most worried about, so I think the chances are less likely. Maybe I'm playing devil's advocate, but in the Synagis (palivizumab) studies, although there were statistically significant differences in the occurrence and severity of RSV, clinically there wasn't really that big of a difference. So although it helps some, we're all going to still see RSV.

The vaccines to date are not the panacea that we'd love to have. I don't think RSV is going to go away. We in neonatology and high-risk newborn follow-up care, as well as anyone who sees kids during the first year of life, are all being pushed by the drug company to get all premature infants treated with Synagis, but I am not yet

convinced that's the appropriate thing. The highest-risk babies, the micro-preemies and those with chronic lung disease, need it, I'm sure, but for other groups I'm not convinced it is a proven therapy.

Black: All I know is that I've seen "normal" newborns come in with bad RSV, wind up on a ventilator, and even die. So, although it obviously happens much more frequently in the high-risk infants, it certainly does happen in all infants. Clearly, any time you're giving an antibody, that is a less-than-ideal situation. What you want is an antigen that will promote the body to produce its own antibodies, but we're clearly still a very long way from that.

Rodriguez: A little bit has to do with what Tom Wiswell was saying. In the existing studies the reduction in hospitalizations was statistically significant, but the absolute reduction was very small, so the number-to-treat to prevent one hospitalization is rather large. Have you seen Deshpande's comment on cost-analysis, which suggests that Synagis is not effective in reducing the incidence of RSV or is not any better than a good education program?[1]

REFERENCE

1. Deshpande S. RSV prevention (letter). Arch Dis Child 2000;82(1):88.

Black: Yes I have, and the emphasis was very strongly on a good education program there. Clearly that's the low-tech, low-cost way to go. The other thing is that the more this drug is used, hopefully, the more the cost will come down, and that will make it more cost-effective.