Respiratory syncytial virus (RSV) was initially isolated in the late 1950s and quickly became established as the leading cause of bronchiolitis and lower respiratory tract infection (LRTI) in infants and young children \[1,2\]. Recent epidemiologic studies emphasize the impact of this virus \[3,4\]. RSV is a ubiquitous pathogen infecting virtually all children at least once by their third birthday. Initial RSV infection in infants is associated with LRTI (bronchiolitis and pneumonia) in 25–40% of cases and hospitalization rates of 0.5–3% (highest in infants <6 months of age) \[4,101\]. This translates to more than 100,000 hospitalizations per year in the USA. Worldwide, RSV is associated with 160,000–600,000 deaths per year in children \[5,6\]. Additionally, groups of children with certain underlying conditions are at increased risk for severe RSV infection (Box 1). Premature infants make up the largest segment of these high-risk infants with upwards of 500,000 babies born at 36 weeks or less gestational age (GA) in the USA annually \[102\]. Among these infants, the risk of hospitalization from RSV infection is more than double that for full-term infants and is fairly equal for all infants with a GA 35 weeks or less. \[7,4\]. Approximately two of every three premature infants is born at 32–35 weeks GA.

Reinfection with RSV occurs throughout one’s lifetime although subsequent infections are more limited to the upper respiratory tract. Still RSV causes significant morbidity in adult populations and has been identified as a major problem for certain immunosuppressed patients and in geriatrics \[9,10\]. Despite the recognition of severe RSV disease in adults, present pharmacologic approaches to treatment have only focused on infants. Very limited studies of the treatment of RSV infection with the antiviral drug ribavirin and the monoclonal antibody palivizumab have included older children and adults on bone marrow transplant units.

In addition to the short-term morbidity associated with RSV infection, numerous studies have documented increased rates of subsequent wheezing over a number of years after hospitalization for RSV LRTI in infancy \[11–13\]. Whether RSV contributes to the development of future wheezing episodes or is a reflection of an abnormal airway that was destined to develop reactive airway disease is unknown at present.
Structurally, RSV is a ssRNA virus and a member of the Paramyxoviridae genera. The two major surface glycoproteins G (glycoprotein) and F (fusion) are responsible for viral attachment and cell membrane fusion, and appear to be the principle targets of host humoral immune response following infection. Despite the development of neutralizing antibodies, reinfection occurs throughout life although, as noted earlier, recurrences are more limited. Two subgroups of RSV (A and B) have been identified based on variations in the G protein but their importance in severity of disease or reinfection is uncertain [14,15].

Given the frequency and morbidity of RSV infections, treatment of this disease is an important issue. This article will address the present status of treatment and prevention of RSV disease and comment briefly on approaches for therapy currently in development.

Current treatment

Present treatments for infants hospitalized with RSV are primarily supportive and aimed at maintaining adequate oxygenation and ventilatory support, and attention to hydration status with administration of intravenous fluids, if necessary. More specific therapies aimed at controlling the inflammatory responses triggered by the virus and/or inhibiting the virus directly have not demonstrated significant benefit to date, although as discussed in the following sections, a number of modalities are frequently used in infants with symptomatic RSV infection.

Acute bronchiolitis presents with diffuse small airway broncho spasms and wheezing suggestive of features of reactive airway disease. As a result, therapies for reactive airway disease have been employed in the management of RSV LRTI. Despite being used frequently, clinical trials have not clearly demonstrated benefit from these agents in the treatment of RSV LRTI or bronchiolitis [16].

Bronchodilators have been assessed in a number of studies conducted in emergency room and inpatient settings. Although some studies have suggested limited transient improvements in responses to β-adrenergic agents (e.g., albuterol and salbutamol), clinical benefit in preventing hospitalization, shortening hospital stay or other long-term benefit argue against routine use of these agents [17–21]. Since these studies have not defined which subsets of patients may possibly benefit from such therapies, a trial of bronchodilators may be considered. However, if bronchodilators are employed in the treatment of acute RSV infection, the response to treatments should be monitored and if benefits are not confirmed they should be abandoned [16].

α-adrenergic agents (e.g., epinephrine and adrenaline) have demonstrated potential short-term improvement in clinical score, oxygenation saturation and heart rate 60–90 min after treatment, but again these findings have not demonstrated a significant enough impact on the disease course to recommend their routine use [22–24].

Corticosteroids have also been frequently used in the management of acute RSV LRTIs. Again, however, there has not been sufficient clinical benefit demonstrated to justify their routine use in these infections. This observation is substantiated by a meta-analysis of multiple studies of children 30 months of age or less who received systemic corticosteroids (vs placebo) for acute bronchiolitis. In 13 trials totaling 1200 children, there was no significant effect on hospitalization, length of stay if hospitalized, clinical score or hospital re-admission demonstrated in steroid recipients [16,25]. An exception to this might be older children, children with chronic lung disease or those with a history of recurrent wheezing [16,26].

In an attempt to address airway inflammatory responses as a component of acute bronchiolitis, the leukotriene antagonist montelukast has been evaluated in the treatment of bronchiolitis. Assessments of short-term responses [27] and for up to 8 weeks after hospitalization for bronchiolitis have failed to demonstrate clinical benefit from such therapy [28].

Ribavirin is the only specific antiviral agent that has been approved for the treatment of acute RSV LRTI. The drug is a guanosine analog that interferes with RSV replication and is administered by prolonged aerosol via a small-particle aerosol generator. Owing to a combination of marginal clinical benefits from ribavirin treatment, high acquisition cost, the cumbersome route of delivery and concerns about potential secondary exposure and risk to caretakers, ribavirin use is extremely limited at present [29]. It may have a place in treatment of RSV infection in severely immunocompromised hosts where significant mortality exists [30].

The observation that the level of cord blood neutralizing antibody titers correlates with time to initial RSV infection, and animal data on protective levels of antibody for preventing RSV infection, led to the development of polyclonal antibodies and subsequently a monoclonal antibody against RSV for prophylaxis against severe RSV disease in high-risk babies [31,32].

Palivizumab is a humanized monoclonal antibody with neutralizing activity against the F protein of RSV. Given intramuscularly on a monthly basis at a dose of 15 mg/kg throughout a single RSV season, palivizumab has demonstrated significant benefit in protecting against RSV hospitalization in premature infants with underlying prematurity, chronic lung disease of infancy and congenital heart disease [32,33]. Based on these trials, palivizumab was approved by the US FDA for prevention of RSV disease in high-risk infants in 1998. Subsequent observations have continued to demonstrate benefit and safety with palivizumab prophylaxis. Cost considerations, however, have led to recommendations for more restrictive guidelines for selecting high-risk infants for palivizumab preventive therapy. The Committee on Infectious Disease (COID) of the American Academy of Pediatrics (AAP)
has published guidelines for consideration of palivizumab use. In their 2009 statement, the COID suggested further restrictions in these indications compared with those published in 2006 based on cost considerations (Table 1) [34,35]. The main focus of the restrictions is for infants born at 32–35 weeks GA, mainly because approximately two of three infants from this group were born premature. As noted earlier, however, the risk for RSV hospitalization is fairly equal across all degrees of prematurity [8]. Furthermore, there are no available data to support limiting palivizumab administration in 32–35-week GA infants to a maximum of three doses and stopping their prophylaxis at 90 days of chronological age as recommended in the 2009 COID statement [36]. Additionally, although a course of palivizumab prophylaxis is expensive (US$6000–7000 per child), when this course is distributed over a healthcare plan, given the limited number of high-risk infants in a given group, expanding the eligibility criteria for these infants may have only a low budget impact [37].

In one retrospective small study, 32–35-week GA infants who received palivizumab prophylaxis had less subsequent wheezing episodes over several years of follow-up than a matched group of infants who did not receive prophylaxis [38]. However, this observation needs verification before suggesting a long-term benefit from palivizumab prophylaxis.

A trial of a single dose of palivizumab given intravenously early in the course of RSV infection in infants demonstrated a significant decrease in RSV titers in nasal secretions but no impact on the course of illness in treated infants [39]. Potential explanations for this discrepancy include failure to obtain adequate palivizumab levels in the lung and/or the persistence of the inflammatory responses already triggered by the virus.

A second-generation monoclonal antibody, motavizumab, developed by affinity maturation of palivizumab and with a much higher affinity for RSV was recently evaluated in comparison to palivizumab for prevention of severe RSV infection in premature infants. Motavizumab demonstrated noninferiority in preventing RSV hospitalization (1.4% in the motavizumab group vs 1.9% with palivizumab) and a statistically significant decrease in outpatient medically attended RSV-specific LRTIs (2.0 vs 3.9% with palivizumab) in the motavizumab recipients [40,41]. There was an increase in cutaneous reactions with motavizumab (7.2 vs 5.1% with palivizumab) but most were considered mild with 0.3% discontinuing participation due to these reactions. The FDA has requested additional safety and efficacy data on motavizumab before considering it for approval. A trial of treatment of acute RSV infection with motavizumab is currently in progress [42]. Given motavizumab’s higher affinity for RSV it may reach neutralizing titers in upper airway tissue as well as in the lung but it remains to be seen whether this will translate into clinical efficacy for treating established RSV infection.

Expert commentary

In this article, the present state of treatment and prevention of severe RSV disease in infants has been summarized. Clearly, improved modalities are needed to help control this important virus. Additionally, given the ubiquity of this virus and the increasingly recognized importance of the disease in adults, attention to management and prevention in these settings is also needed. Furthermore, a better understanding of the role of RSV in long-term recurrent wheezing is also important.

As a second-generation monoclonal antibody, motavizumab may offer potential advantages for prevention of severe RSV disease in high-risk infants and may even have a role in treatment of severe infection. Additional treatment modalities are in development as recently reviewed by Olszewska and Openshaw [43] and Empey and colleagues [44]. Newer approaches to RSV treatment include small interfering RNA particles that interfere with viral protein synthesis, anti-RSV agents with greater potency than ribavirin and development of focal immunomodulatory agents that may target aspects of the inflammatory responses seen in severe RSV disease. Combination approaches that address both viral replication and inflammatory responses may also be considered.

Table 1. Comparison of 2006 and 2009 Committee on Infectious Disease of the American Academy of Pediatrics Guidelines for palivizumab†.

<table>
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<tbody>
<tr>
<td>Chronic lung disease of infancy</td>
<td>Consider ≤24 months of age; five doses</td>
</tr>
<tr>
<td>Congenital heart disease</td>
<td>Consider ≤24 months of age; five doses</td>
</tr>
<tr>
<td>≤28 weeks GA</td>
<td>During first RSV season (≤12 months of age)</td>
</tr>
<tr>
<td>29–32 weeks GA</td>
<td>29 weeks, 0 days to 32 weeks, 0 days; up to 6 months of age at start of RSV season</td>
</tr>
<tr>
<td>32–35 weeks GA</td>
<td>32 weeks, 1 day through 35 weeks, 0 days; ≤6 months at start of RSV season AND two of five risk factors (childcare attendance, school-aged siblings, exposure to environmental air pollutants, congenital airway abnormalities and severe neuromuscular disease)</td>
</tr>
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*2009 changes in bold.

GA: Gestational age; RSV: Respiratory syncytial virus.
A review of the challenges faced in the development of an RSV vaccine is beyond the scope of this article, but the development of a safe and effective RSV vaccine would be the optimal approach to controlling RSV disease. Although progress has been made in this regard and a number of candidate vaccines are in early stages of clinical evaluation [45], it will be at least a number of years before prevention of RSV LRTI via immunization becomes a reality. Therefore, continued advancing approaches to treat and prevent this infection remain an important priority for the wellbeing of our children.

Five-year view
Over the next 5 years, I certainly expect further understanding of the epidemiology of RSV and risk factors, which should allow better definition of candidates for RSV prophylaxis, and that motavizumab will likely replace palivizumab in the treatment of RSV infection. Further understanding of genetic polymorphisms affecting susceptibility to severe RSV disease will likely help predict those at greatest risk for severe RSV infection [46].

I believe it is likely that additional treatment modalities will become available for treatment of RSV-infected infants during this time. At present, small interfering RNAs that interfere with viral protein synthesis are furthest along in clinical development, although problems of particle stability, effective delivery to the lower respiratory tract and issues of cost still need to be overcome to enable them to be introduced into clinical practice. Other antiviral drugs and immunomodulatory agents will hopefully also proceed to development during this time to help improve the management of this important infection. Unfortunately, I do not anticipate successful introduction of an RSV vaccine during this time frame but hopefully in the next report on this subject, significant advance in RSV vaccine development will be reported, because, ultimately, I believe control of severe RSV disease will only be achieved through immunization.

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The author has received clinical research grant support and has been a consultant to MedImmune (the manufacturer of palivizumab [Synagis]). He is also on their speakers' bureau. The author has no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed. No writing assistance was utilized in the production of this manuscript.

Key issues
- Respiratory syncytial virus (RSV) infection is a major cause of morbidity in infants and young children.
- Infants at increased risk for severe RSV disease include those born prematurely, and infants with congenital heart disease, chronic lung disease, neuromuscular disease, anomalies of the airway and immunodeficiency.
- Infants who have severe RSV disease are at increased risk for subsequent wheezing episodes over a number of years.
- Treatment of RSV disease remains primarily supportive (e.g., supplemental oxygen, respiratory support and fluid support).
- Bronchodilators and corticosteroids are frequently used in the treatment of RSV disease, although available data have not shown clear clinical benefit.
- The antiviral drug ribavirin is licensed for aerosol administration in the treatment of RSV disease, although again clinical benefit is marginal and issues of cost and route of administration have contributed to very restrictive use of ribavirin.
- Palivizumab is a monoclonal antibody against RSV that is approved for prophylaxis against severe RSV disease in high-risk infants.
- Improved therapies against RSV are clearly needed. A second-generation monoclonal antibody, motavizumab, is presently under evaluation by the US FDA. Newer antiviral agents and anti-inflammatory drugs are also in development.

References
Papers of special note have been highlighted as:
• of interest
•• of considerable interest
8 Law BJ, MacDonald NE, Langley JM et al. Analysis of RSV hospitalizations in a Medicaid population demonstrating the increased risk in all premature infants of 35 weeks or less gestational age.


• Long-term and well-controlled study of the increased rate of asthma in infants hospitalized in infancy for RSV infection.


• Detailed review of aspects of RSV infection and its current management based on critical assessments of published data.


• Recent, large, double-blind, randomized, placebo-controlled trial that failed to demonstrate a benefit from steroid treatment in the emergency department in preventing hospitalization for acute bronchiolitis.


• The definitive palivizumab study in premature infants demonstrating safety and efficacy of seasonal prophylaxis in premature infants in preventing RSV hospitalizations.


• Similar trial to [32] of palivizumab demonstrating efficacy and safety in infants with hemodynamically significant congenital heart disease.


• Most recent statement of the Committee on Infectious Disease of the American Academy of Pediatrics on RSV disease with guidelines for treatment and prevention.


• Evidence-based commentary questioning aspects of the 2009 American Academy of Pediatrics guidelines for palivizumab use in premature infants.


- **Large clinical trial comparing motavizumab with palivizumab in preventing RSV disease in premature infants.**


**Websites**
