

# Respiratory Syncytial Virus Infection and Bronchiolitis

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## Practice Gaps

1. Respiratory syncytial virus (RSV) is the most common respiratory pathogen in infants and young children worldwide. Although the most effective management of this infection remains supportive care, many patients continue to be managed with therapies that lack the support of scientific evidence.
2. Although the quest for a safe and effective vaccine remains unsuccessful, the more vulnerable patients can be protected with passive prophylaxis. Because of limited clinical benefits and high costs, RSV prophylaxis should be limited to high-risk infants as directed by the most current evidence-based guidelines that, however, are not consistently followed.
3. The acute phase of this infection is often followed by episodes of wheezing that recur for months or years and usually lead to a physician diagnosis of asthma. The phenotype of post-RSV wheezing is different from atopic asthma, yet it is usually managed using the same pharmacologic therapy with often ineffective results.

## Objectives After reading this article, readers should be able to:

1. Understand the microbiology, epidemiology, pathophysiology, and clinical manifestations of RSV bronchiolitis in infants and children.
2. Know the scientific evidence relevant to prophylactic and therapeutic strategies currently available and recognize the lack of evidence concerning several pharmacologic agents commonly used in the management of bronchiolitis.
3. Be aware of alternative pharmacologic strategies currently being evaluated.
4. Learn the epidemiologic and experimental information suggesting the existence of a link between early-life infection with RSV and the subsequent development of recurrent wheezing and asthma in childhood and adolescence.

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### ABBREVIATIONS

|      |                                   |
|------|-----------------------------------|
| AAP  | American Academy of Pediatrics    |
| DBPC | double-blind, placebo-controlled  |
| FDA  | Food and Drug Administration      |
| LRTI | lower respiratory tract infection |
| RSV  | respiratory syncytial virus       |

## VIROLOGY

Human respiratory syncytial virus (RSV) is a single-stranded RNA virus of the Paramyxoviridae family whose genome includes 10 genes that encode 11 proteins (Figure 1). Two surface proteins, the F (fusion) protein and the G (attachment glycoprotein) protein, are the major viral antigens and play a critical role in the virulence of RSV. The G protein mediates RSV attachment to the host cell, after which the F protein enables fusion of the host and viral plasma membranes to permit virus passage into the host cell. The F protein also promotes the aggregation of multinucleated cells through fusion of their plasma membranes, producing the syncytia for which the virus is named and allows the transmission of virus from cell to cell. RSV has 2 distinct antigenic subtypes, A and B, which are usually present in the communities during seasonal outbreaks. It remains controversial whether subtype A is more strongly associated with severe disease.

## EPIDEMIOLOGY

RSV is the most frequent cause of bronchiolitis in infants and young children and accounts in the United States alone for approximately 125,000 hospitalizations and 250 infant deaths every year. Global estimates by the World Health Organization indicate that RSV accounts overall for more than 60% of acute respiratory infections in children. Furthermore, RSV is responsible for more than 80% of lower respiratory tract infections (LRTIs) in infants younger than 1 year and annually during the peak of viral season. In summary, RSV is by far the most frequent cause of pediatric bronchiolitis and pneumonia (Figure 2).

Nearly all children are infected at least once by the time they are age 2 years, but peak incidence occurs between ages 2 and 3 months and corresponds to nadir

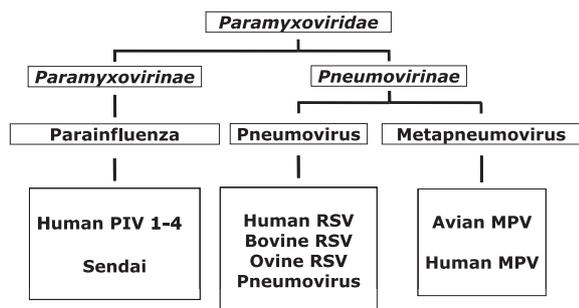


Figure 1. Respiratory syncytial virus (RSV) classification. Human RSV is an enveloped, nonsegmented, negative-strand RNA virus of the Paramyxoviridae family, genus *Pneumovirus*. The closely related *Metapneumovirus* genus was considered an exclusively avian virus until the discovery of a human strain in 2001.

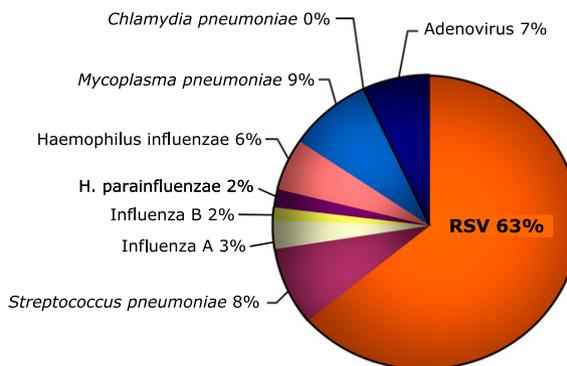


Figure 2. Etiology of acute respiratory infections in children. The World Health Organization estimates indicate that respiratory syncytial virus (RSV) accounts worldwide for more than 60% of acute respiratory infections in children and more than 80% in infants younger than 1 year and at the peak of viral season. Therefore, RSV is by far the most frequent cause of pediatric bronchiolitis and pneumonia.

concentrations of protective maternal IgG transferred to the fetus through the placenta. Seasonal outbreaks occur each year throughout the world, although onset, peak, and duration vary from one year to the next. In the United States, the annual epidemics usually begin in November, peak in January or February, and end in May.

However, the epidemiology of RSV differs widely across latitudes and meteorologic conditions. For example, at sites with persistently warm temperatures and high humidity, RSV activity tends to be continuous throughout the year, peaking in summer and early autumn. In temperate climates, RSV activity is maximal during winter and correlates with lower temperatures. In areas where temperatures remain colder throughout the year, RSV activity again becomes nearly continuous. Thus, RSV activity in communities is affected by both ambient temperature and absolute humidity, perhaps reflecting meteorologic combinations that allow greater stability of RSV in aerosols.

Morbidity and mortality of RSV disease are higher in premature infants and in infants with chronic lung disease (eg, bronchopulmonary dysplasia, cystic fibrosis, and interstitial lung diseases) or hemodynamically significant congenital heart disease. Because preterm infants miss, in part or completely, the third trimester window during which the placenta expresses Fc receptors mediating the transfer of maternal IgG to the fetus, they are born with reduced humoral protection against infection and reach lower nadir concentrations of maternal IgG. This is compounded by T-cell-mediated responses that are inefficient because T cells also mature primarily during the last trimester of pregnancy.

Development of bronchopulmonary dysplasia or other chronic respiratory conditions amplifies the risk of severe

infections by limiting pulmonary functional reserve, distorting airway architecture, and promoting a proinflammatory milieu. Additional risk factors for severe disease include age younger than 12 weeks, history of prematurity, male sex, crowding, lack of breastfeeding, congenital heart disease, and any immunodeficiency. Despite numerous studies that have explored whether environmental tobacco smoke exposure affects RSV morbidity, definitive evidence of this association is lacking, and its clinical significance remains controversial. Nevertheless, physicians should inquire about tobacco smoke exposure when assessing infants and children for bronchiolitis and advise caregivers about smoke cessation.

Previous infection with RSV does not convey persistent immunity even in the presence of significant antibody titers, although higher titers may attenuate the course of the disease. Consequently, subsequent infection is common, can recur within the same viral season, and occurs across all age groups. The first episodes of infection typically occur in the first 2 years after birth and tend to be the most severe because of the limited immunologic protection discussed above, smaller airway size, and unique structural and functional features of the developing respiratory tract (eg, lack of interalveolar pores and channels and different innervation patterns).

Most subsequent infections remain confined to the upper respiratory tract and run a milder course, although the illness may still progress to an LRTI, especially in elderly and immunodeficient patients, usually characterized by more severe symptoms. The clinical manifestations of RSV pneumonia in immunocompromised patients vary, depending on the extent and severity of the underlying deficit, ranging from substantial morbidity and mortality in the first 3 months after bone marrow transplantation to a usually milder course in patients with AIDS.

## **PATHOGENESIS AND PATHOPHYSIOLOGY**

Transmission of RSV infection occurs through inoculation of the nasopharyngeal or conjunctival mucosa with respiratory secretions from infected individuals. The virus remains viable on hard surfaces for up to 6 hours, on rubber gloves for 90 minutes, and on skin for 20 minutes. This prolonged survival highlights the need for hand washing and contact precautions as an essential (and cost-effective) practice to limit the spread of infection, especially in clinic settings. The incubation period ranges from 2 to 8 days, and immunocompetent individuals can shed the virus for up to 3 weeks, although on average this is limited to approximately 8 days. However, viral shedding from

immunocompromised individuals can continue for several months because intracellular replication is not effectively contained by specific cell-mediated immunity.

RSV infection starts in the nasopharyngeal epithelium but then spreads rapidly by intercellular transmission through the lower airways, reaching the terminal bronchioles, where the replication of this virus is most efficient. Direct pathologic consequences of lytic viral replication include sloughing of necrotic epithelial cells, which exposes the dense subepithelial network of nociceptive nerve fibers, forming the afferent limb for the cough reflex. The initial influx of polymorphonuclear neutrophils into the airways is rapidly replaced by predominantly lymphomononuclear infiltration of peribronchiolar tissues and increased microvascular permeability, leading to submucosal edema and swelling. Mucous secretions increase in quantity and viscosity and tend to pool because of the loss of ciliated epithelium, resulting in widespread mucous plugging.

This constellation of acute inflammatory changes that form the immediate response to exponential viral replication in the bronchioles leads to airway obstruction and air trapping, producing the classic clinical triad of polyphonic wheezing, patchy atelectasis, and bilateral hyperinflation. However, disease severity and duration are primarily a function of the immune response mounted by the host. Innate immune mechanisms provide the respiratory tract with a first barrier against the establishment of a productive infection. Subsequently, specific humoral and cell-mediated immunity play a critical role in clearing the infection and attenuating its course.

Although this response does not result in complete protection against subsequent infection, it decreases their severity. In infants, higher titers of maternally derived RSV-neutralizing antibody are associated with a much lower risk of hospitalization due to RSV, and this protective effect can be replaced or enhanced in high-risk infants by passive prophylaxis. Cytotoxic T lymphocytes are central in the control of active infection and viral clearance, which explains why immunocompromised individuals with deficient cell-mediated immunity experience more severe and prolonged RSV disease and shed the virus much longer.

## **CLINICAL MANIFESTATIONS**

RSV infection in children almost always causes clinical manifestations, but these manifestations can vary widely in severity, depending on the patient's age, comorbidities, environmental exposures, and history of previous infections. Typically, the infection starts with signs and symptoms

of mucosal inflammation and irritation of the upper respiratory tract (congestion, rhinorrhea, and sneezing). In the next few days, the clinical status evolves with involvement of the lower respiratory tract manifested by cough and increased work of breathing with use of accessory respiratory muscles to overcome the increased resistance of obstructed airways. As noted above, many of the clinical manifestations of airway obstruction are driven by the immune response against the virus rather than by viral replication and direct cytotoxicity. Therefore, wheezing and other typical signs of bronchiolitis may be reduced or even absent in immunosuppressed patients and be replaced by rapidly evolving parenchymal infiltrates that can lead to acute respiratory distress syndrome.

Inspection reveals respiratory distress ranging from minimal to profound respiratory failure associated with a variable degree of nasal flaring and intercostal retractions. Auscultation reflects the vibration of conducting airways generated by turbulent airflow and is remarkable for a prolonged expiratory phase, diffuse polyphonic wheezing, and coarse crackles (rales) scattered throughout the lung fields. Pulse oxymetry and arterial blood gas analysis detect moderate to severe hypoxemia derived primarily from the perfusion of respiratory units that are poorly ventilated because of mucous plugging (ventilation-perfusion mismatch). Progressive carbon dioxide retention and respiratory acidosis signal the development of respiratory muscle fatigue and evolving respiratory failure that require ventilatory assistance.

Infants are usually more severely affected and may also develop lethargy, fever, poor feeding, and otitis media, whereas older children typically manifest symptoms of the upper respiratory tract but may also develop tracheobronchitis. Apnea is a well-known complication of RSV infection in infants, and its incidence is as high as 20% in infants younger than 6 months who require hospitalization. When present, apnea usually is an early event that precedes lower respiratory tract signs and symptoms, suggesting the involvement of reflex neural activity triggered in the upper airways. The highest incidence of apnea occurs in premature infants and in infants younger than 1 month, probably because of the relative immaturity of ventilatory control. In most cases, however, apnea is self-limited and does not recur with subsequent infections.

The diagnosis of acute bronchiolitis should be based exclusively on the history and physical examination findings and does not require radiographic or laboratory studies. The specific cause can be confirmed by antigen detection tests, currently being replaced by more sensitive polymerase chain reaction-based assays. Arguably, this step is not essential

because, especially during the epidemic peak and in the first year after birth, RSV is responsible for most cases of bronchiolitis and other pathogens are much less common. However, confirming the viral origin strengthens the rationale for withholding therapies known to be ineffective and provides prognostic clues concerning complications, such as recurrent wheezing and asthma, based on robust epidemiologic data.

Correct etiologic diagnosis is also important to rule out rare conditions that could be worsened by the management commonly used for bronchiolitis. For example, infants with dilated cardiomyopathy and congestive heart failure may present with symptoms of wheezing that mimic an acute respiratory infection, but these patients are at risk of developing supraventricular tachycardia and even cardiopulmonary collapse after administration of  $\beta$ -agonist agents. In cases of suspected cardiac disease, chest radiography will reveal cardiomegaly, suggesting a different diagnosis and therapy, and thereby might avoid significant complications or even death.

Other laboratory and imaging studies also add little information, although it is advisable to determine the complete and differential blood cell counts and C-reactive protein level to assess the risk of bacterial superinfection in febrile children, as well as electrolyte serum concentrations to monitor



**Figure 3.** Clinical manifestations of respiratory syncytial virus (RSV). Chest radiography performed in a child with RSV bronchiolitis revealed bilateral hyperinflation from air trapping, patchy atelectasis from airway plugging, and peribronchial thickening from lymphomonocytic infiltration. Patients with severe disease may also have features more consistent with pneumonia, with areas of interstitial parenchymal infiltration.

hydration status and electrolyte imbalance. If chest radiography is performed, findings typically include bilateral hyperinflation, patchy atelectasis, and peribronchial thickening, but patients with severe lower respiratory tract involvement have radiologic features more consistent with pneumonia and areas of interstitial parenchymal infiltration (Figure 3).

## THERAPY

### Supportive Care

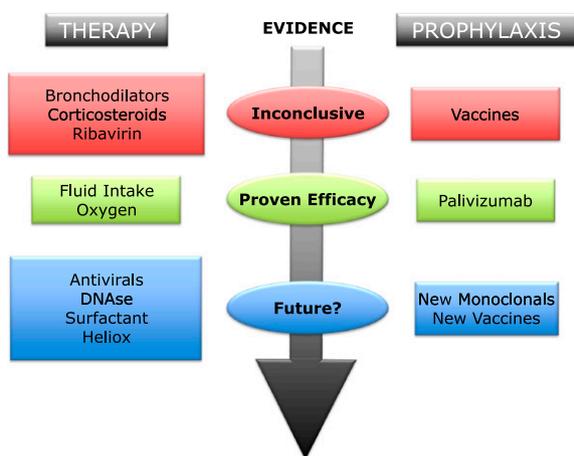
Most infants with RSV infection develop a mild, self-limited illness, which is usually managed in outpatient settings but still requires close follow-up with special attention to respiratory distress, oxygen requirement, and hydration. Those infants with difficulty feeding, pronounced respiratory distress, or need for supplemental oxygen require hospital admission for more aggressive management and monitoring. Regardless of the setting in which the patient is treated, the mainstay of therapy remains supportive care, which includes respiratory support combined with appropriate fluid and nutrition management (Figure 4).

Nasal obstruction is a common problem in young infants who are obligate nose breathers and often improves significantly after nasal toilet with saline drops and a suction bulb. Chest physiotherapy is often provided in an effort to mobilize secretions and reexpand atelectatic segments, but a recent Cochrane systematic review found no evidence to support its

use, which, combined with the unnecessarily increased hospitalization costs, should discourage this practice.

Children with oxygen saturations of 90% or less should receive warm, humidified oxygen. Infants with hypoxemia refractory to supplemental oxygen, persistent respiratory distress, or evolving respiratory failure require either non-invasive support with nasal continuous positive airway pressure or endotracheal intubation. Positive pressure mechanical ventilation has been used for decades in the management of infants with severe RSV bronchiolitis and is probably one of the most important factors that lead to the progressive decrease in mortality. A few infants with particularly severe disease may require escalation of mechanical ventilation to high-frequency oscillatory ventilation or extracorporeal membrane oxygenation.

Infants hospitalized with RSV bronchiolitis often have decreased nutritional intake due to respiratory distress and tachypnea with increased insensible losses and will need fluid and nutritional support. Continued oral feeding in the presence of significant tachypnea and respiratory distress is known to increase the risk of aspiration. Indeed, aspiration has been revealed with the use of barium contrast in a significant proportion of infants hospitalized with RSV bronchiolitis. Thus, in patients who are unable to tolerate oral feeds, adequate fluid intake and nutrition should be maintained by placement of a nasogastric or orogastric feeding tube or with parenteral fluids when enteral nutrition is deemed unsafe.



**Figure 4.** Evidence-based management of bronchiolitis. Passive prophylaxis is a safe and effective way of protecting infants at risk for severe respiratory syncytial virus (RSV) disease but is not cost-efficient. Once the infection is established, the mainstay of current therapy remains supportive care because no solid scientific evidence supporting the use of any conventional or experimental pharmacologic agent currently exists. For the future, promising antiviral molecules and new-generation humanized monoclonal antibodies are being investigated, and structural biology may overcome the challenges that have so far prevented the development of a safe and effective RSV vaccine.

### Pharmacologic Therapy

Despite relentless attempts to identify pharmacologic strategies to improve the clinical course and outcomes of this infection, the most effective management remains limited to the supportive care measures discussed above. There is no solid scientific evidence supporting the use of any pharmacologic agent currently available.

**Bronchodilators.** Albuterol does not provide consistent benefit in the treatment of RSV infection and should not be administered to infants and children diagnosed as having bronchiolitis. A brief trial with objective evaluation of the response may be warranted, but this therapy should be discontinued if no improvement occurs because of the significant adverse effects, including tachycardia, tremor, hypokalemia, and hyperglycemia. These adverse effects can be amplified and become life-threatening in patients with underlying lung or heart disease, also due to the interaction with other commonly used therapies (eg, diuretics).

Other inhaled selective  $\beta$ -agonists, such as levalbuterol, have no demonstrable advantage over albuterol in humans despite preliminary data in rodent models that suggest

potential benefits. Epinephrine does not provide consistent benefit in the inpatient setting, and although some studies suggest that it may produce a modest improvement in the outpatient setting, it is not deemed safe for use at home or other settings where cardiorespiratory monitoring is not available. Oral or parenteral adrenergic agonists have no advantages over nebulized ones but have much stronger adverse effects that contraindicate their use in any obstructive airway disease, including bronchiolitis. Finally, there is no evidence supporting the use of anticholinergic agents, such as atropine or any of its synthetic derivatives, which may also have significant untoward effects by predisposing patients to more extensive mucous plugging.

**Hypertonic Saline.** Nebulization of 3% saline improves mucociliary clearance and is increasingly being used in airway diseases that involve mucous plugging (eg, cystic fibrosis). It has also been reported to reduce length of hospital stay and provide symptomatic relief in patients with bronchiolitis, but its use remains controversial. In particular, it is not effective in reducing hospitalization when used in emergency settings. Therefore, on the basis of current evidence, the administration of hypertonic saline for bronchiolitis should be limited to hospitalized infant and children.

**Corticosteroids.** Neither systemic nor inhaled corticosteroids have consistent benefit in the treatment of acute RSV disease or in the prevention of post-RSV wheezing. In particular, a systematic review of 13 trials of corticosteroid therapy in 1,198 children with viral wheezing ages 0 to 30 months concluded that this therapy lacks any significant clinical benefit compared with placebo and is not indicated for this patient group. The findings of this meta-analysis have been complemented by a number of more recent individual studies that have reached more or less the same conclusions.

Another area of concern derives from safety considerations. In fact, viral bronchiolitis typically occurs during the first year after birth and coincides with a critical phase of rapid lung growth. The safety of corticosteroids during this developmental window is virtually unknown, and corticosteroids are not approved by the Food and Drug Administration (FDA) for use in the treatment of bronchiolitis or asthma in the first year after birth. Therefore, on the basis of current and extensive scientific evidence, corticosteroids are not recommended for routine use in the treatment of acute bronchiolitis.

It has been argued that virus-induced wheezing in infants and young children could be the early manifestation of persistent asthma and therefore warrant the use of corticosteroids for the secondary prevention and control of asthma.

However, in general young children without an atopic phenotype who wheeze in response to viral infections show a poor response to corticosteroids, and even children who will ultimately develop chronic asthma are usually unresponsive to this therapy when they develop virus-induced wheezing during their first years after birth.

**Antimicrobials.** The only antiviral agent ever licensed by the FDA for the therapy of severe RSV infections is ribavirin, a synthetic nucleoside analog with broad *in vitro* virustatic activity. Unfortunately, by the time the infection manifests clinically *in vivo*, most of the viral load has already been cleared, and the disease process is driven primarily by inflammatory mechanisms largely independent from viral replication. After some initial encouraging data from industry-sponsored studies, a series of randomized trials were unable to demonstrate any short- or long-term improvement in the clinical course of bronchiolitis, leading to a rapid decline and virtual disappearance of ribavirin use in this setting. Therefore, inhaled ribavirin is no longer recommended for routine treatment of RSV infection, although it may be considered in select immunocompromised individuals, who can continue to shed virus for several months because replication is not limited by host defenses.

Antibiotics should be used in patients with bronchiolitis only when specific evidence of coexistent bacterial infection is present. Such coinfections are uncommon, perhaps with the exception of bacterial otitis media that can be managed with oral antibiotics no differently than in the absence of bronchiolitis.

**Experimental Agents.** A variety of other experimental therapeutic interventions has been tested, but none have been approved by, or even submitted to, the FDA, and currently the evidence supporting clinical use of any of them is largely insufficient. Starting with aerosol-delivered drugs, DNase does not provide consistent benefit in the treatment of RSV infection, and although neutrophils, the primary source of extracellular DNA, are indeed recruited in the airways during the early stage of the infection, they are not predominant in RSV-infected airways as they are in cystic fibrosis, which remains the only accepted indication for this therapy. Surfactant and Heliox may provide some benefit in the treatment of this infection, but again the available data are far from conclusive.

Concerning oral drugs, antileukotrienes used during the acute phase of RSV bronchiolitis improve postbronchiolitis respiratory symptoms, especially in younger patients with high urinary leukotriene E<sub>4</sub> levels. However, a large, multicenter, randomized, double blind, placebo-controlled (DBPC) trial with montelukast did not find statistically significant clinical improvement. Post hoc analysis of data

collected during this trial revealed that children with persistent respiratory symptoms after the acute phase of the infection may indeed benefit from montelukast, but the manufacturer (Merck & Co) is no longer pursuing this indication. We have elected to not include in this review the extensive pipeline of antiviral compounds currently being developed because they are not likely to become available for clinical use in the foreseeable future.

## PREVENTION

Disinfection with alcohol-based rubs and hand washing with alcohol-based rubs or soap and water are highly effective in reducing the spread of RSV, and it is invaluable in preventing nosocomial infections. The use of gloves and gowns can help in limiting transmission, but the use of masks is controversial because RSV is mostly transmitted by direct contact with infected secretions and rarely by aerosolization. Our own data obtained with air-sampling devices provided by the National Institute of Occupational Safety and Health have confirmed that it is rare to detect airborne RSV around infected infants (G.P., unpublished data, 2014). This observation, combined with the mounting efforts to contain health care costs through evidence-based practices, prevents us from recommending the use of masks to limit RSV transmission.

### Active Prophylaxis

No vaccine exists today for active prophylaxis against RSV. A formalin-inactivated vaccine marketed in the United States in the 1960s had to be withdrawn because, in addition to being poorly immunogenic, it predisposed children to aberrant T<sub>H</sub>2-type immune responses and life-threatening disease on subsequent exposure to wild-type virus. Since then, a vast array of experimental approaches, ranging from purified capsid proteins to attenuated or inactivated virus, have failed to deliver a safe and effective vaccine. Only recently has new hope been sparked by the use of cutting-edge structural biology to engineer a stabilized and customized version of the RSV surface F protein (immunogen) that binds highly protective antibodies and triggers a potent RSV-specific neutralizing response when injected into animals.

### Passive Prophylaxis

Perhaps the most important success in the war against RSV so far has been the development of safe and effective passive prophylaxis, first with polyclonal intravenous immunoglobulin and later with monoclonal antibodies for intramuscular administration. Palivizumab is a humanized

IgG1 monoclonal antibody developed by MedImmune Inc and licensed by the FDA since 1998 for the prophylaxis of children at high risk for severe RSV disease. With this technology, murine-derived sequences complementary to the A antigenic site of the RSV F protein were grafted into a human IgG frame, resulting in a protein that is minimally immunogenic.

Palivizumab is administered monthly during the RSV season as an intramuscular dose of 15 mg/kg, which has consistently had an excellent safety profile. American Academy of Pediatrics (AAP) guidelines providing a better definition of high risk for severe RSV disease were originally published a few months after FDA approval and have been subsequently revised 4 times to account for new evidence from postmarketing studies and to balance the limited clinical benefits with the high costs of this expensive biological agent (currently approximately \$3,000 per vial). The most recent AAP Policy Statement, published in 2014 to replace the recommendations found in the 2012 *Red Book* and in the 2006 AAP guidelines for the diagnosis and management of bronchiolitis, is significantly more restrictive than the previous revisions (Table 1). (1)

Palivizumab prophylaxis with a maximum of 5 monthly doses is now recommended only in the first year after birth for otherwise healthy infants born before 29 weeks' gestation and for infants born before 32 weeks' gestation with chronic lung disease of prematurity defined as a requirement for supplemental oxygen for at least 28 days after birth. Prophylaxis is no longer recommended in the second year after birth, except for infants with chronic lung disease of prematurity still requiring oxygen, corticosteroids, or diuretics. Palivizumab prophylaxis should be discontinued after a breakthrough RSV hospitalization because the likelihood of a second RSV hospitalization in the same season is low. Palivizumab should be considered also for children with hemodynamically significant congenital heart defects, profound immunodeficiency, and pulmonary or neuromuscular diseases that impair airway clearance, but no formal recommendation was made for patients with Down syndrome or cystic fibrosis because of insufficient data.

As shown in preclinical studies in cotton rats, palivizumab provides optimal protection with blood levels above 40 µg/mL. Unfortunately, by using the recommended dosage, trough concentrations after the first monthly injection decrease below the protective level in more than half of the patients. Subsequently, trough levels increase after each monthly injection because of progressive accumulation. This finding explains why almost half of all breakthrough RSV hospitalizations in infants receiving prophylaxis occur after the first injection, whereas less than one-third occur

**TABLE 1. Current American Academy of Pediatrics Guidance for RSV Prophylaxis (1)**

Prophylaxis (palivizumab, 15 mg/kg IM, for a maximum of 5 monthly doses) is recommended for:

1. Infants born at <29 weeks 0 days of gestation without chronic lung disease of prematurity who are younger than 12 months at the onset of RSV season.
2. Infants with chronic lung disease of prematurity younger than 24 months who continue to require medical therapy within 6 months of the onset of RSV season.

Prophylaxis may be considered for:

1. Infants younger than 12 months with hemodynamically significant heart disease or children younger than 24 months who undergo cardiac transplantation during RSV season.
2. Infants younger than 12 months with airway abnormalities or neuromuscular disorder impairing cough.
3. Children younger than 24 months old severely immunocompromised during RSV season.

Prophylaxis is not recommended for:

1. Infants born at ≥29 weeks 0 days of gestation without chronic lung disease.
2. Infants with chronic lung disease of prematurity 12 months or older who no longer require medical therapy.
3. Children who experience a breakthrough RSV hospitalization while taking palivizumab.
4. Children with Down syndrome or cystic fibrosis.
5. Children exposed to RSV in a health care facility.

**Additional recommendations**

- Careful hand hygiene.
- Breastfeeding.
- Elimination of tobacco smoke exposure.
- Avoidance of crowded environments.
- Limitation of group daycare activities.

IM=intramuscular; RSV=respiratory syncytial virus.

after the first 2 injections. Furthermore, palivizumab dosage is not sufficient to reach protective levels in the nasal mucosa and therefore does not prevent infection of the upper airways or middle ear.

To address these limitations, a second-generation IgG1 monoclonal antibody (motavizumab) was synthesized based on computer modeling, studied in a variety of preclinical models, and tested clinically up to a large, multicenter phase 3 trial. The new monoclonal antibody had 70-fold higher affinity for the RSV F protein and was fully humanized. However, the FDA Advisory Committee voted not to recommend

approval of motavizumab, justifying this decision based on questionable evidence that the new antibody provided additional benefit compared with palivizumab (nonsuperiority) and on concerns about the rare (2%–3%) but statistically significant increase in serious adverse events that involve the skin of infants.

## PROGNOSIS

In general, RSV bronchiolitis is a self-limiting disease with excellent long-term prognosis. However, the existence of a causative relationship between RSV infection in infancy and the inception of childhood asthma has been debated for decades. There is certainly an increased risk of subsequent wheezing in children who have had RSV infection in early life, especially if the primary infection was severe enough to warrant hospitalization, but the question remains whether RSV is indeed a causative factor or rather a simple marker or trigger of a preexisting intrinsic predisposition to develop asthma.

Prospective epidemiologic studies published in the past 2 decades by Sigurs et al and Stein et al, among others, collectively suggest a 20% to 40% likelihood of recurrent asthma-like episodes after RSV LRTI in infancy. There is also general consensus that a nonatopic wheezing phenotype heralded by early RSV infections is often less responsive to corticosteroid therapy and usually resolves before adolescence. This information can be summarized in a model of asthma pathogenesis in which a genetic predisposition inherited from parents is not necessary or sufficient for the manifestation of this disease in childhood, whereas early respiratory infections, especially if severe and driven by specific viral pathogens, not only can lead to recurrent childhood wheezing even in the absence of genetic predisposition but also can amplify the risk deriving from such predisposition.

Nevertheless, epidemiologic studies are not suitable to resolve whether early-life RSV LRTIs are truly causal for subsequent asthma or more simply precipitate wheezing in children already predisposed because of their genetic or epigenetic makeup. Only carefully randomized controlled trials with specific prophylaxis can conclusively determine whether preventing or delaying the first RSV infection lessens the incidence and/or severity of asthma later in life. This is the major contribution of a recent industry-sponsored, multicenter, randomized DBPC trial by Blanken and coworkers investigating the causal role of RSV infection in the pathogenesis of wheezing illness during the first year after birth. This trial included 429 otherwise healthy infants born at 33 to 35 weeks'

gestational age, who were randomized to receive either monthly palivizumab injections or placebo during the RSV season. The primary end point was the total number of parent-reported wheezing days in the first year after birth. Consistent with previous nonrandomized data, RSV prophylaxis resulted in a relative reduction of 61% in the total number of wheezing days during the first year after birth and a statistically significant decrease in the proportion of infants with recurrent wheeze, regardless of whether there was a family history of atopy.

The data published so far provide robust preliminary evidence that RSV infection is an important mechanism in the pathogenesis of recurrent wheezing during the first years after birth. However, they are still limited to preterm children, who are at higher risk for recurrent episodes of wheezing because of intrinsic hyperreactivity and immaturity of their airways, and therefore cannot be generalized to healthy term infants, who constitute most patients who develop bronchiolitis and asthma. Thus, before a formal recommendation can be made concerning large-scale RSV prophylaxis to reduce the incidence of postviral wheeze in childhood, it will be essential to conduct independently funded, randomized, DBPC trials in large samples that include full-term infants.

Once these data are available, it will also become necessary to recalculate the clinical benefits and cost-effectiveness of palivizumab prophylaxis, which continue to be the most controversial aspects of its use. As pressures to reduce the unsustainable costs of health care continue to mount and value-based care becomes the standard model to follow, long-term cost-benefit analysis will be a predominant force shaping the use of biological agents in standard clinical protocols. Current analyses overwhelmingly argue that palivizumab is not cost-effective for the prevention of bronchiolitis, but this might change rapidly if rigorous evidence supports the notion that protection against RSV reduces the ever-growing direct and indirect costs of the asthma epidemic in industrialized countries.

## Summary

- On the basis of strong research evidence, respiratory syncytial virus (RSV) is the most frequent cause of bronchiolitis and pneumonia in infants and young children and a source of significant morbidity, mortality, and financial burden worldwide. (2)
- On the basis of some research evidence and consensus, transmission occurs through inoculation of the nasopharyngeal or conjunctival mucosa with respiratory secretions from infected individuals. Viral shedding persists for approximately 1 week but

can be significantly prolonged in immunocompromised individuals. (3)

- On the basis of expert opinion, infants with RSV infection typically present with upper respiratory tract symptoms that frequently progress to involve the lower respiratory tract with cough, wheeze, and increased work of breathing. Chest radiography typically reveals hyperinflation, patchy infiltrates, and atelectasis. Apnea can be the presenting manifestation, especially in young infants. The diagnosis of RSV bronchiolitis should be based on history and physical examination and does not require radiographic or laboratory studies.
- On the basis of expert opinion, supportive care is the mainstay of therapy for RSV disease and is directed at ensuring adequate oxygenation, improving respiratory toilet, and meeting fluid and nutrition requirements. Chest physiotherapy should not be used. Severe respiratory failure requires mechanical ventilatory support and occasionally high-frequency oscillatory ventilation or extracorporeal membrane oxygenation.
- Adrenergic  $\alpha$ - and  $\beta$ -agonists do not provide consistent benefit in the treatment of RSV infection. Similarly, neither systemic nor inhaled corticosteroids have been found to provide clear advantages in this setting. Therefore, these pharmacologic agents should not be used in infants and children diagnosed as having RSV bronchiolitis. Hypertonic saline may be used in hospitalized patients but not in the emergency setting.
- On the basis of some research evidence and consensus, the antiviral drug ribavirin is also not recommended for routine treatment of RSV infection but may be considered in select immunocompromised individuals. Antibiotics should not be used in infants and children diagnosed as having RSV bronchiolitis, unless there is evidence or suspicion of a concomitant bacterial infection. (4)(5)(6)
- On the basis of strong research evidence, hand washing or disinfection by all caregivers and contact isolation of patients are highly effective in preventing the spread of RSV infection. The humanized monoclonal antibody palivizumab is a safe option for passive RSV prophylaxis, but its use should be limited to infants at high risk for severe disease because of limited clinical benefits and high costs. (7)
- On the basis of some research evidence, solid epidemiologic data suggest that early RSV bronchiolitis predisposes patients to recurrent wheezing and asthma during the first decade after birth. This hypothesis has been confirmed recently by a randomized double-blind, placebo-controlled study indicating that palivizumab significantly reduces the frequency of wheezing in infancy. However, this evidence is still limited to prematurely born infants and cannot be generalized yet to otherwise healthy children born at full term. (8)(9)(10)

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## Respiratory Syncytial Virus and Bronchiolitis

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## Parent Resources from the AAP at HealthyChildren.org

- English: <http://www.healthychildren.org/English/health-issues/conditions/chest-lungs/Pages/Protecting-Your-Baby-from-RSV.aspx>
- Spanish: <http://www.healthychildren.org/spanish/health-issues/conditions/chest-lungs/paginas/protecting-your-baby-from-rsv.aspx>
- English: <http://www.healthychildren.org/English/health-issues/conditions/chest-lungs/Pages/Respiratory-Syncytial-Virus-RSV.aspx>
- Spanish: <http://www.healthychildren.org/spanish/health-issues/conditions/chest-lungs/Paginas/Respiratory-Syncytial-Virus-RSV.aspx>
- English: <http://www.healthychildren.org/English/health-issues/conditions/chest-lungs/Pages/Bronchiolitis.aspx>
- Spanish: <http://www.healthychildren.org/spanish/health-issues/conditions/chest-lungs/Paginas/Bronchiolitis.aspx>

## PIR Quiz

1. A 2-month-old, former full-term infant presents to your office in January with audible wheezing, use of accessory muscles, rhinorrhea, and a low-grade fever. Vital signs include a temperature of 100.4°F (38.0°C), a respiratory rate of 45 breaths per minute, a heart rate of 150 beats per minute, and oxygen saturation of 88% on room air. A trial of inhaled albuterol did not change her symptoms. The most appropriate next step in management of this infant is:
  - A. Oral prednisone.
  - B. Continuous inhaled albuterol administration.
  - C. Oxygen by nasal prongs.
  - D. Inhaled corticosteroid.
  - E. Oral amoxicillin.
2. You are seeing a 4-month-old, former 28-week premature infant in your office for his first well-child visit since being discharged from the neonatal intensive care unit. The mother has some questions about the use of palivizumab, the humanized IgG1 monoclonal antibody vaccine given to premature infants to help prevent respiratory syncytial virus (RSV) infection. Of the following, the best response would be:
  - A. Palivizumab is administered monthly during the RSV season as an intramuscular dose to those infants who are at high risk.
  - B. Palivizumab is administered only at the 2-month well-child visit as an intramuscular dose to all infants.
  - C. Palivizumab is only indicated for infants with underlying cardiac or pulmonary disease.
  - D. Palivizumab is administered monthly for the first year after birth as an intranasal vaccine.
  - E. Palivizumab is only indicated for infants with an underlying immunodeficiency.
3. You and your team are discussing RSV during rounds in the hospital. One of the medical students asks what measures are taken in the hospital to prevent the spread of nosocomial RSV. Of the following, the BEST response is:
  - A. Use of airborne precautions and N95 masks help in preventing nosocomial RSV infections.
  - B. Hand washing is highly effective in reducing the spread of RSV.
  - C. Active vaccination of all health care workers is helpful in the preventing RSV infections.
  - D. Passive prophylaxis is highly effective in preventing spread of RSV.
  - E. Use of negative pressure patient care rooms reduces the spread of nosocomial RSV infections.
4. A 5-month-old boy comes to your office after being hospitalized for RSV bronchiolitis and hypoxia. His current vital signs are stable, and his physical examination findings are benign. His parents are worried about the potential for him to develop asthma in the future. Of the following, the BEST response is:
  - A. There is an increased risk of wheezing with subsequent respiratory infections only if there is a strong family history of asthma.
  - B. Palivizumab is cost-effective in preventing future wheezing episodes in healthy, term infants.
  - C. Use of daily inhaled  $\beta$ -agonists is effective in preventing future wheezing episodes in infants who have a history of RSV bronchiolitis.
  - D. Children who have a nonatopic wheezing phenotype are often responsive to corticosteroid therapy.
  - E. There is likely an increased risk of subsequent wheezing in children who have had RSV infection in early life.

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5. In early February, a 3-week-old infant is hospitalized because of tachypnea, hypoxia, and difficulty feeding. Vital signs include a temperature of 100.0°F (37.8°C), respiratory rate of 50 breaths per minute, heart rate of 160 beats per minute, and oxygen saturation of 86% on room air. Chest radiography reveals bilateral hyperinflation and patchy atelectasis. You suspect RSV bronchiolitis. Of the following, the risk factor that is associated with more severe RSV disease is:
- A. Second-hand tobacco smoke exposure.
  - B. Underlying bronchopulmonary dysplasia.
  - C. Degree of hypoxia on presentation.
  - D. Exclusive breastfeeding.
  - E. A sibling with recent RSV infection.

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children from East Harlem and the South Bronx with levels greater than 100  $\mu\text{g}/\text{dL}$  (4.8  $\mu\text{mol}/\text{L}$ ). We know now that no level of lead is really acceptable, but in the 1970s the mean lead level of preschool-aged children in the United States was 15  $\mu\text{g}/\text{dL}$  (0.7  $\mu\text{mol}/\text{L}$ ), and it is now less than 2  $\mu\text{g}/\text{dL}$  (0.1  $\mu\text{mol}/\text{L}$ ).

Yes, we still see too many children in our emergency departments who have ingested drugs and other toxins, and

too many children are losing IQ points from lead that persists in the environment. However, regulatory measures have made a huge difference and remain, despite too many cries to the contrary, an effective tool in improving our public health.

– Henry M. Adam, MD  
Editor, *In Brief*

## Parent Resources from the AAP at HealthyChildren.org

- <http://www.healthychildren.org/English/news/Pages/Tips-for-Poison-Prevention-and-Treatment.aspx>
- Spanish: <http://www.healthychildren.org/spanish/news/paginas/tips-for-poison-prevention-and-treatment.aspx>

### Correction

In the December 2014 article “Respiratory Syncytial Virus Infection and Bronchiolitis” (Piedimonte G and Perez MK. *Pediatrics in Review*. 2014;35(12):519-530, doi: 10.1542/pir.35-12-519), an error occurred that changed the meaning of the last sentence on page 520, column 1. The sentence should read: “Nearly all children are infected at least once by the time they are age 2 years, but peak incidence occurs between ages 2 and 3 months and corresponds to nadir concentrations of protective maternal IgG transferred to the fetus through the placenta.” The online article was resupplied to correct the text. The journal regrets the error.



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