Respiratory Syncytial Virus (RSV) Prevention Strategies and the Appropriate Identification of Vulnerable Populations

Based on an RSV Expert Panel, Aug. 18, 2008, Chicago

HIGHLIGHTS

- RSV in the Pediatric Population
- In the Trenches: A Pediatrician’s Perspective on Implementation, Prevention, and Treatment Strategies
- RSV in the Adult Population
- Medical Director Considerations
- Pharmacy Director Considerations
- RSV Issues and Solutions

This activity is sponsored by The Chatham Institute

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Respiratory syncytial virus (RSV) is a source of substantial morbidity in the very young and the very old. For children younger than 1 year, serious RSV infection of the lower respiratory tract may require hospitalization for bronchiolitis or pneumonia, and for premature infants, the services of a neonatal intensive care unit. Among the elderly, RSV often is active at the same time as influenza and appears to be responsible for some of the deaths attributed to influenza.

There is no treatment for RSV infection, so prophylactic measures are the key to protecting high-risk populations. For the elderly, common-sense precautions like washing hands and minimizing visits from small children can break the transmission of RSV. For infants, immunoprophylaxis with palivizumab (Synagis) is available. Palivizumab is a humanized monoclonal antibody that binds with a protein on the surface of the virus, effectively neutralizing it. The drug, however, does not elicit any immune response that confers lasting protection — palivizumab is the protection. To be effective, it must be administered prior to the beginning of an RSV season and every 30 days thereafter for the duration of the season. For high-risk infants, such as infants younger than 35 weeks gestational age, immunoprophylaxis with palivizumab should be administered before hospital discharge and then throughout the infant’s first RSV season.

These considerations raise several challenges for physicians and for medical directors and pharmacists in managed care organizations: Quickly identifying those infants at high risk for whom immunoprophylaxis is appropriate; knowing when the RSV season is likely to begin in a given locale; administering the first dose prior to the RSV season; and making sure that patients adhere to therapy.

These and related issues were addressed by an RSV Expert Panel convened by The Chatham Institute this past August in Chicago. The articles in this supplement are an outgrowth of that panel and present the perspectives of practicing physicians, a pediatrician, and managed care executives.
Respiratory Syncytial Virus (RSV)
Prevention Strategies and the Appropriate Identification of Vulnerable Populations

Based on an RSV Expert Panel, Aug. 18, 2008, Chicago
A Continuing Education Activity

INTRODUCTION
Managed Care Considerations: Vulnerable Populations and Prevention Strategies for Respiratory Syncytial Virus Disease
STEVEN R. PESKIN, MD, MBA

FACULTY PRESENTATIONS
RSV Disease in the Pediatric Population: Epidemiology, Seasonal Variability, and Long-Term Outcomes
ERIC A. F. SIMÕES, MD, DCH

In the Trenches: A Pediatrician’s Perspective on Prevention and Treatment Strategies for RSV Disease
MICHAEL P. FROGEL, MD

RSV Infection in the Adult Population
JULIO A. RAMIREZ, MD, FACP

Health Plan Medical Director: Considerations for Prevention and Management of RSV Disease
ALBERT TZEEL, MD, MHSA

Health Plan Pharmacy Director: Considerations for Treatment and Management of RSV Disease
DOUGLAS S. BURGOYNE, PHARM.D, RPH

ROUNDTABLE
RSV Issues and Solutions

CONTINUING EDUCATION
Continuing Education Objectives
Assessment/Evaluation/Certificate Request
Post-Test
SELF-STUDY CONTINUING EDUCATION ACTIVITY

Respiratory Syncytial Virus (RSV): Prevention Strategies and the Appropriate Identification of Vulnerable Populations

Overview/needs assessment
Respiratory syncytial virus (RSV) is a common and easily transmitted disease that affects young children and is the leading cause of hospitalization of infants younger than 1 year of age. It is estimated that in the United States, up to 126,000 infants are hospitalized each year because of severe RSV disease, and that close to 20 percent of these are premature infants. RSV disease is also a risk factor for the development of respiratory ailments and physician-diagnosed asthma in later life.

RSV is costly. A single hospitalization can cost more than $5,000 a day for a child in need of respiratory assistance, and the high cost of immunoprophylaxis limits its use to those infants at highest risk of complications from RSV infection. RSV infection also is common among the elderly and the immunocompromised and, together with influenza virus, is the most common cause of hospital admissions for adults with chronic cardiac and pulmonary disorders and acute respiratory failure.

This Continuing Medical Education program provides current information on our understanding of RSV seasonality, vulnerable populations, preventive strategies, and the therapeutic approaches available to manage RSV.

Target audience
This program is targeted to medical directors, physicians, and pharmacists in managed care organizations.

Educational objectives
After reading this publication, participants will be able to:

- Explain the epidemiology, burden of disease, and seasonal and regional variability of RSV.
- Discuss the economic impact of RSV on the health care system.
- Explain which populations are at high risk of RSV infection and why.
- Discuss current and new prophylactic options for managing RSV.
- Establish educational initiatives to raise the awareness of parents and health care professionals about the prevention and treatment of RSV.
- Assess best practices in a managed care setting for managing RSV, so as to improve outcomes.

Method of instruction
Participants should read the learning objectives and review the activity in its entirety. After reviewing this activity, submit a completed post-test and evaluation. Upon achieving a passing score of 70 percent or better on the post-test, a statement of credit will be awarded.

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This activity has been planned and implemented in accordance with the Essential Areas and policies of the Accreditation Council for Continuing Medical Education through the sponsorship of The Chatham Institute. The Chatham Institute is accredited by the ACCME to provide continuing medical education for physicians. The Chatham Institute designates this educational activity for a maximum of 1.50 AMA PRA Category 1 Credits. Physicians should claim credit commensurate with the extent of their participation in the activity.

The Chatham Institute is accredited by the Accreditation Council for Pharmacy Education (ACPE) as a provider of continuing pharmacy education. This program is approved for 1.50 contact hours (0.150 CEU) of continuing education for pharmacists.

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By the age of 2 years, most children will have acquired a respiratory syncytial virus (RSV) infection (Glezen 1986). For most of these children, the RSV infection will be unremarkable, but a subset of children, notably infants born prematurely or with congenital heart disease (CHD), is at an increased risk for severe RSV-associated lower respiratory tract infection (LRTI), particularly bronchiolitis. In the United States, up to 126,000 infants are hospitalized each year because of severe RSV disease (Shay 1999). Additionally, from 1990 through 1999, the estimated annual number of RSV-associated deaths was 235. Ninety-four percent of these deaths occurred in infants, accounting for 5.3 deaths per 100,000 person-years among infants and 0.2 deaths per 100,000 person-years among children aged 1 to 4 (Thompson 2003).

RSV seasonality

The RSV season in the United States, as acknowledged by the American Academy of Pediatrics (AAP), generally extends from November through March with a peak in January or February (AAP 2006), but considerable geographic and temporal variation in RSV seasonality exists. The Centers for Disease Control and Prevention define the onset of an RSV season as the first of 2 consecutive weeks during which the median percentage of specimens testing positive for RSV antigen is 10 percent or greater, and offset is the last of 2 consecutive weeks when the median percentage of positive specimens is 10 percent or greater (CDC 2007). When analyzed by these definitions in terms of the broad U.S. census regions (Northeast, South, Midwest, West), it has been found that the RSV season varies from region to region and within any given region from year to year (Panozzo 2007). The South has the earliest onset (median onset in late November [week 47], with a range from week 41 to week 51), and the longest duration (16 weeks; range, 13–20 weeks). The Midwest has the latest onset (median onset in early January [week 1], with a range from week 41 to week 51) and the shortest duration (13 weeks; range 10–16 weeks). The Figure on page 4 shows regional RSV trends from July 2000 through July 2006.

Analyses within states show substantial variations in RSV seasonality, which are lost in regional reports. In the southwest, northwest, and north regions of Florida, for example, RSV seasons range from 7 to 8 months, while in central and southeastern Florida, the RSV seasons last 11 or 12 months (Light 2008).

In Colorado, we have analyzed 10 years of RSV hospitalization data at the local level using ZIP code tabulation areas (ZCTAs), which are comparable to ZIP codes, and we have noticed considerable geographic and temporal variations (Zachariah 2008). In some locales, the RSV seasons lasted only 3 months, whereas in others, the seasons exceeded 5 months. For about one third of all Colorado children, the RSV season is less than 5 months, but for another third, the RSV season lasts 6 or 7 months, i.e., comparable to much of Florida. We also have found that local weather conditions affect RSV activity through complex interactions of temperature and humidity (Yusuf 2007), and we speculate that this might affect the stability of the virus in the large-particle aerosols or...
human secretions through which RSV is believed to be transmitted. We also have found that cyclical levels of maternal serum anti-RSV antibody, as reflected by cord blood RSV-neutralizing antibody, precede the onset and end of the RSV season for infants, suggesting a role for the decline of maternal RSV antibodies in the susceptibility of newborn infants to RSV and the increase in the levels that presage the end of the epidemic (Stensballe 2008).

**Risk factors**

Although most infants acquire an RSV infection during their first RSV season, and although most of those infections are relatively mild, certain infants are at increased risk for severe RSV disease (Welliver 2003). Those at high risk include premature infants, children with chronic lung disease (CLD) or CHD, and children who are immunosuppressed because of transplants or chemotherapy (Simões 2003, Welliver 2003). Environmental and demographic risk factors for severe RSV disease are: birth during the first half of the RSV season; a gestational age (GA) of 35 weeks or less; the first 6 weeks of life; male sex; household crowding (e.g., sharing a bedroom with siblings); and attending day care with five or more children (Simões 2003). There also is good evidence for exposure to indoor tobacco smoke (Carroll 2007, Simões 2007a) but equivocal evidence for breast feeding for less than 2 months, and no evidence that low maternal education or malnutrition are risk factors. In Colorado, we have found that living at a high altitude (above 2,500 m) increases the risk of RSV-associated hospitalization; the effect of altitude is more pronounced in children aged 1 to 4 years than in infants (Choudhuri 2006).

In the United States, 10 percent of premature infants are born at a GA of 28 completed weeks or less, 20 percent between 28 and 31 weeks, and 70 percent between 32 and 35 weeks (Ventura 1996). For preterm infants with underlying CLD, RSV-associated LRTIs are associated with increased morbidity and higher mortality rates and a higher reinfection rate (Navas 1992). In preterm infants without underlying CLD, RSV-associated LRTIs are associated with a hospitalization rate approaching 10 percent and increased morbidity (Simões 2002).

Using various risk factors, my colleagues and I have developed a model to predict which premature infants (33–35 weeks GA) are at highest risk for RSV hospitalization (Simões 2008). This model is intended to facilitate the effective and responsible use of palivizumab (Synagis), a humanized monoclonal antibody used for immunoprophylaxis in this population. We began with a set of 15 risk factors based on those identified in a Spanish case-control study (Figueras-Aloy 2004), but we were able to make the model easier to use by reducing the number of variables to eight without loss of sensitivity, specificity, or predictive value. This model has a sensitivity and specificity of 72 percent in predicting RSV hospitalization.

**Long-term outcomes**

Although hospitalization is a major outcome of severe RSV infections, it is not the only outcome. One important long-term outcome, which is largely unrecognized, is the development of wheezing later in life.

The relationship of early viral infection to specific wheezing phenotypes is a matter of some controversy, but it has raised these critical questions: Does severe RSV-associated LRTI cause the differences in pulmonary sequelae that have been observed in longitudinal stud-
ies? Do inherent abnormalities that predispose a child to wheeze later in life also predispose the child to develop a severe RSV LRTI?

The causal relationship of early RSV infection to later wheezing seemed to be supported by a study conducted by Stein (1999) in which a cohort of 207 children who had an RSV-associated lower respiratory tract illness during the first 3 years of life were prospectively followed for up to 13 years. Their risk for frequent or infrequent wheeze was increased up to the age of 11 years compared with children who had no lower respiratory tract illness during their first 3 years. For infrequent wheeze, the adjusted odds ratios were 3.2, 2.5, and 1.7 at age 3, 6, and 11 years, respectively, and for frequent wheeze, 4.3, 1.9, and 2.4 at the same time points. All these odds ratios were statistically significant (P < .05), except for frequent wheeze at 6 years.

Conflicting results emerged from a study conducted by Lemanske (2005) in which a cohort of newborns were followed for up to 3 years. To be enrolled in this study, an infant needed to have at least one parent with respiratory allergies, or a history of physician-diagnosed asthma, or both. After stratifying by the severity of RSV illness, the percentage of children wheezing in their third year of life was most strongly associated with the severity of rhinovirus wheezing illnesses during infancy rather than the severity of RSV illnesses. More recently, this association was found to exist up until the age of 6 years (Jackson 2008).

My colleagues and I conducted a nested (1:5) case-control study (Stensballe 2006) in Denmark of 2,564 children under 18 months of age with RSV hospitalization compared with 12,816 control children who had been prospectively followed from birth to 18 months of age without RSV hospitalization as participants in the Danish national birth cohort. The point estimates of the adjusted relative risk (RR) of RSV hospitalization were 1.11 for maternal atopic dermatitis, 1.72 for maternal asthma, and 1.23 for paternal asthma. Infrequent wheezing in the child was associated with an RR of subsequent hospitalization of 2.98 and recurrent wheezing with an RR of 5.90. We concluded that asthmatic disposition and wheezing were strong determents of subsequent RSV hospitalization in Danish children less than 18 months of age. In this study, up to a third of children had experienced wheezing prior to RSV hospitalization.

Our subsequent studies of RSV immunoprophylaxis have addressed the role of RSV in the causation of subsequent recurrent wheezing. These studies also provide insight into resolving this apparent conundrum. In one such study (Wenzel 2002), we evaluated pulmonary function and atopy in 13 children at high risk for respiratory disease 7 to 10 years after they had received immunoprophylaxis with RSV immunoglobulin. We compared them with 26 high-risk controls matched for age and GA. The children who had received RSV immunoprophylaxis had better lung function and less atopy than the control group. This small study suggests that preventing or blunting RSV infections might decrease the risk for asthma later in life, but larger prospective studies of children at high risk for asthma are warranted to confirm this association. Following that study, we conducted a multicentered study (Simões 2007b) in Europe and Canada using palivizumab. Beginning at a mean age of 19 months, we prospectively followed for 24 months a cohort of preterm infants who had received RSV immunoprophylaxis with 3 or more doses of palivizumab in infancy and who never had been hospitalized for RSV (n=191) and a cohort who never received palivizumab (n=230), including 76 who were hospitalized for RSV and 154 who were not. The mean GA in the palivizumab-treated and the untreated groups was 29.9 and 31.4 weeks, respectively. At follow up at 4 to 5 years of age, the proportion of children with recurrent wheezing was reduced by 49 percent in the palivizumab-treated group relative to the proportion in the untreated group (13 percent [25/191] versus 26 percent [59/230]; P=.001). Likewise, there was a relative reduction of 51 percent in the palivizumab-treated group in the proportion of children with physician-diagnosed recurrent wheezing (8 percent [15/191] versus 16 percent [37/230]; P=.011).

Taken together, our studies in Europe and in the United States have shown that in up to a third of children with RSV hospitalization, an atopic disposition may be responsible for the hospitalization. In preterm infants, we have shown that RSV infection may cause up to 50 percent of the recurrent wheezing seen at the age of 3 to 4 years. How long this wheezing continues is unknown; however, a study in Tucson, Ariz. (Stein 1999) suggests that in normal infants, RSV infection in the first 3 years of life predisposes them to recurrent wheezing up to 11 years of age but disappears by age 13. In children with a strong atopic background, rhinovirus rather than RSV may be a more important inciting factor for the development of asthma seen at 6 years of age (Jackson 2008).

Summary

Infants younger than 1 year, and especially premature infants, are susceptible to severe RSV disease, which accounts for up to 126,000 hospitalizations each year. In the United States, the RSV season generally extends from November through March, but varies considerably both temporally and geographically. Studies, such as the one we have conducted in Colorado, indicate that the RSV season can even vary among local communities. In addition to seasonal variability, other independent risk factors also have to be taken into consideration when considering RSV immunoprophylaxis. Among these are a GA of less than 33 weeks, infants with CLD or CHD or who are immunosuppressed, male sex, household crowding, and...
daycare attendance. Exposure to indoor tobacco smoke and abbreviated breast feeding (less than 2 months) also may be pertinent risk factors. The Colorado studies show that high altitude also increases the risk of RSV hospitalization.

Although hospitalization is a major outcome of severe RSV infections in infants, the development of wheezing and physician-diagnosed asthma later in life may be a long-term outcome that should be considered.

References


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Respiratory syncytial virus (RSV) bronchiolitis is the leading cause of hospitalization of infants younger than 1 year (Figure). Between 1980 and 1996, the rate of hospitalization for bronchiolitis in children younger than 6 months increased 2.4-fold (Shay 1999). More recent estimates place the rate of RSV hospitalization in infants younger than 1 year at 24.3 per 1,000, with annual RSV hospital costs exceeding $1.1 billion (McLaurin 2005).

Palivizumab (Synagis) is a U.S. Food and Drug Administration-approved monoclonal antibody that is administered intramuscularly to prevent severe RSV disease in high-risk infants. Although timely immunoprophylaxis with palivizumab can reduce RSV hospitalizations and morbidity in high-risk populations, pediatricians who provide immunoprophylaxis face numerous challenges, such as reimbursement obstacles and achieving continuity of care. In this article, I discuss those challenges from the perspective of a practicing pediatrician at a children’s hospital.

**Premature infants at high risk**

Children at high risk of RSV disease include infants born prematurely; children with chronic lung disease (CLD), also known as bronchopulmonary dysplasia (BPD); and children with hemodynamically significant congenital heart disease (CHD). There remains significant controversy concerning the appropriate criteria and need for immunoprophylaxis with palivizumab for premature infants born after 32 weeks gestational age (GA). Among premature infants, the severity of RSV infection intuitively would be greater in those born with a GA of 32 weeks or less; however, some data indicate that the severity of illness during hospitalization appears to be at

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**FIGURE**

RSV is the leading cause of hospitalization of infants aged 1 year or younger

![Graph showing hospitalization rates for different causes of respiratory illnesses from 1997 to 2002.](source: McLaurin 2005)
least as high, if not greater, in infants born 32 to 35 completed weeks of gestation (Horn 2003).

Prevention of RSV hospitalization through immunoprophylaxis is likely to have a positive economic impact beyond inpatient admissions, as it has been found that infants hospitalized for RSV also have greater subsequent health care utilization. In a comparison with a control group of 20,254 infants of 32 to 35 weeks GA but no RSV hospitalization during a mean follow-up of 1.66 years, a cohort of 2,415 infants hospitalized for RSV infection had not only more hospital stays (2.96 versus 1.28; \( P = .001 \)) and a longer mean length of stay (14.71 versus 5.04 days; \( P < .001 \)), but also more outpatient visits (18.4 versus 7.54; \( P = .001 \)) and greater mortality (8.1 versus 1.6 percent; \( P = .001 \)) (Sampalis 2003). In the IMPact-RSV trial (IMPact-RSV Study Group 1998), palivizumab immunoprophylaxis reduced hospitalization rates by 55 percent overall (10.6 versus 4.8 percent) compared with placebo, but by 80 percent in infants 32 to 35 weeks GA without CLD or CHD. Further study and analysis is needed, however, to define the severity and utilization risks for this subset of infants, and to establish better criteria for immunoprophylaxis.

RSV prevention

RSV immunoprophylaxis with palivizumab should be initiated just prior to the onset of the local RSV season and terminated at its end with intramuscular injections administered every 30 days. American Academy of Pediatrics (AAP) guidelines (AAP 2006) recommend, in general, five monthly doses from November to March. The AAP also states that any deviation from this recommendation requires careful consideration of the benefit and cost. Because of the geographical and seasonal variability of RSV, I recommend that pediatricians monitor local virology data in their respective communities along with historical virology data to prepare for timely, appropriate administration of immunoprophylaxis. If the RSV season should begin unexpectedly early, timely immunoprophylaxis may be difficult because of the logistical challenges involved in obtaining the necessary approvals and supply of palivizumab. Preparation for dosing should begin in advance of the start of the RSV season in the infant’s community. For example, if the season usually starts in November, pediatricians should begin to obtain insurance/health plan approvals during the first or second week of October and begin to schedule appointments to provide immunoprophylaxis during the last week of October, as it takes 48 to 72 hours to achieve protective levels with palivizumab. This approach will obviate any difficulty in receiving the necessary insurance approvals or in scheduling patient visits before the RSV season starts. High-risk infants will thereby receive their first injections just prior to the start of the RSV season and achieve appropriate prophylaxis levels to prevent hospitalization.

In my practice, we screen patients year-round to identify high-risk patients who are candidates for immunoprophylaxis. We maintain an ongoing, coordinated list of eligible patients discharged from our neonatal unit or otherwise entering my practice. In early October, my dedicated palivizumab nurse (a major impact on practice manpower) studies our roster of patients and begins to set up medical appointments and to contact insurers for coverage approval and to check if reimbursement policy has changed. Throughout the RSV season, we receive a report from our virology laboratory of all RSV specimens submitted. We then track the number of tests performed and the number of positive and negative results.

AAP guidelines

The AAP guidelines for RSV immunoprophylaxis have evolved over the past decade. Since 1998, the AAP guidelines consistently have recommended palivizumab immunoprophylaxis for children with severe CLD who are less than 2 years of age at the start of the RSV season (AAP 1998, 2003, 2006). For children with hemodynamically significant CHD who are younger than 2 years at the start of the season, the 2003 and 2006 guidelines recommend that monthly injections of palivizumab be considered during the RSV season. Current AAP guidelines (AAP 2006) state that immunoprophylaxis should be administered usually in five monthly injections during the RSV season and that immunoprophylaxis should be considered for premature infants who are born 32 weeks GA or earlier and for infants 32 to 35 weeks GA with two or more risk factors during their first RSV season (Table 1).

The AAP guidelines also mention five demonstrated risk factors drawn from epidemiological data that may point to an increased risk for severe RSV infection (Table 2). Other risk factors also have been identified (Table 2), some of which are supported by evidence in the literature, but most insurers will consider only those risk factors mentioned in the AAP guidelines.

Timing of Immunoprophylaxis

The question of when the first dose of palivizumab should be administered is a major issue confronting
MCOs. In 2003, the AAP (AAP 2003) recommended that the first dose of palivizumab be given to an infant before discharge from the neonatal intensive care unit (NICU); however, the 2006 guidelines (AAP 2006) do not address this issue. In a study by Speer (2005), only 43 percent of discharges from a NICU received the first palivizumab dose while still in the hospital; the other 57 percent received the first dose as an outpatient, and the average number of days between discharge and the time of that dose was 28 days (range, 0 to 122). The usual reason the first dose of palivizumab is not administered in the hospital is financial — the hospital does not want to absorb the cost if it is not going to be reimbursed. But deferring the first dose exposes high-risk, just-discharged patients to RSV infection. Immuno prophylaxis takes 48 to 72 hours to reach protective levels; therefore, palivizumab given at least 48 to 72 hours prior to hospital discharge should be the standard.

Even if a high-risk infant has already had an RSV infection, the AAP guidelines remind us that it is important that the infant continues to receive immunoprophylaxis, as the initial injection may not provide protection against recurrent infection. This recommendation is based on observations that high-risk infants may be hospitalized more than once during the same RSV season, and more than one RSV strain may be circulating in a community.

### Treatment of RSV bronchiolitis
The aim of treatment for RSV bronchiolitis is to relieve respiratory distress, overcome airway obstruction, enhance mucociliary clearance, and return the child to nor-

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**TABLE 1**

<table>
<thead>
<tr>
<th>AAP guidelines for RSV immunoprophylaxis</th>
<th>Recommendation</th>
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</thead>
<tbody>
<tr>
<td>Severe CLD* and less than 2 years of age at start of RSV season</td>
<td>Palivizumab immunoprophylaxis; patients benefit with second season of therapy</td>
</tr>
<tr>
<td>Hemodynamically significant CHD and 2 years of age or younger at start of RSV season</td>
<td>Palivizumab immunoprophylaxis — 5 monthly doses; re-administer after bypass surgery to maintain palivizumab levels</td>
</tr>
<tr>
<td>Immunocompromised children</td>
<td>No recommendations due to lack of data; however, severe combined or acquired immunodeficiency may benefit from immunoprophylaxis</td>
</tr>
<tr>
<td>Premature (28 weeks GA or less) and 12 months of age or younger at start of RSV season</td>
<td>Immunoprophylaxis — 5 monthly doses of palivizumab</td>
</tr>
<tr>
<td>Premature (29–32 weeks GA) and 6 months of age or younger at start of RSV season</td>
<td>Immunoprophylaxis — 5 monthly doses of palivizumab</td>
</tr>
<tr>
<td>Premature (32–35 weeks GA) and 6 months of age or younger at start of RSV season</td>
<td>Immunoprophylaxis if two or more risk factors are present — 5 monthly doses of palivizumab</td>
</tr>
</tbody>
</table>

*Requiring treatment in the past 6 months.
CHD=chronic heart disease, CLD=chronic lung disease, GA=gestational age.
Source: AAP 2006

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**TABLE 2**

<table>
<thead>
<tr>
<th>Risk factors for severe RSV infection</th>
<th>Other potential risk factors</th>
</tr>
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<tbody>
<tr>
<td>Child care attendance</td>
<td>Immune deficiency*</td>
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<tr>
<td>School-age siblings</td>
<td>Low birthweight*</td>
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<tr>
<td>Exposure to environmental air pollutants</td>
<td>Exposure to environmental/tobacco smoke*</td>
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<tr>
<td>Congenital airway abnormalities</td>
<td>Multiple births*</td>
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<tr>
<td>Severe neuromuscular disease</td>
<td>Family history of wheezing or asthma*</td>
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<td></td>
<td>Minimal breast feeding*</td>
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<tr>
<td></td>
<td>Chronological age ≤ 10 weeks at RSV season onset*</td>
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<tr>
<td></td>
<td>Crowded living conditions*</td>
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<tr>
<td></td>
<td>Male sex*</td>
</tr>
<tr>
<td></td>
<td>Black race*</td>
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<tr>
<td></td>
<td>Low socioeconomic status*</td>
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</table>

Pharmacologic options that have been studied as treatments for RSV bronchiolitis include bronchodilators, corticosteroids, antiviral agents, and leukotriene receptor antagonists. The vast majority of patients with RSV bronchiolitis should not receive bronchodilators, as they have not been shown to reduce the rate of hospitalization, and they provide only modest short-term clinical benefit in patients with mild or moderate bronchiolitis (Kellner 1996). However, there may be a subgroup of patients with reactive airway disease who will respond to a bronchodilator. Nebulized racemic epinephrine or albuterol are often used in the inpatient hospital or emergency room. For outpatients, albuterol would be preferred, because it produces less of a rebound effect than racemic epinephrine and is safer to use at home. Therefore, if there is a consideration of discharge from the ER or physician’s office, albuterol should be tried. Bronchodilators should be continued only if there is an objective response to therapy.

Systemic corticosteroids may provide minimal reductions in the length of stay in infants hospitalized with bronchiolitis (Garrison 2000); however, there is not sufficient evidence to support their use. Furthermore, data on potential harm are lacking. AAP guidelines (AAP 2006) state that corticosteroids are not effective and are not indicated in hospitalized infants with RSV bronchiolitis. Likewise, no data support the use of inhaled corticosteroids in RSV bronchiolitis (Viswanathan 2003).

Use of the antiviral agent ribavirin generally is not recommended because it is difficult to use, has a high cost, and confers potential risks to caregivers and marginal benefits. In the Pediatric Investigators Collaborative Network on Infections in Canada study (Law 1997), there was no statistically significant association with any outcome measure in ribavirin-treated ventilated subsets, regardless of risk group. In highly selected situations, AAP (2006) states that “a decision about ribavirin administration should be made on the basis of the particular clinical circumstances and experience of the physician.”

The rationale for using the leukotriene receptor antagonist montelukast is that leukotriene release may contribute to the development of reactive airway disease after RSV bronchiolitis. A pilot study (Bisgaard 2003) suggested that montelukast may be efficacious in treating recurrent respiratory symptoms in children post-RSV bronchiolitis, but a larger study (Bisgaard 2008) found that montelukast did not improve respiratory symptoms in this population. Because of insufficient data, this treatment is not recommended.

There is no indication for antibiotics in the treatment of RSV bronchiolitis because it is a viral disease; however, some patients develop bacterial pneumonia secondary to the RSV infection. If a patient has been doing well 3 or 4 days into the course of bronchiolitis but suddenly develops a high fever and more tachypnea, a secondary bacterial infection should be suspected. Otitis media can be treated with antibiotics (AAP 2006). In general, there is low risk for serious bacterial infections, and if present in young infants, they are usually from the urinary tract.

Improving compliance

The key to optimizing protection against serious RSV infections in high-risk patients is compliance. In a study of 10,390 infants receiving palivizumab (Berger 2003), noncompliant patients had a 2.2-fold increased risk of hospitalization (1.4 versus 3.1 percent; \( P < .001 \)). Compliance was defined as having, on average, 35 or fewer days between palivizumab doses. A strategy for improving compliance and outcomes through home-based delivery of palivizumab injections has been recently reported (Hand 2003, Golombek 2004). In a study of 236 infants (Hand 2003), home care was linked to a 20 percent increase in compliance rates, fewer hospitalizations, and fewer unscheduled medical visits. In a study of 1,446 infants (Golombek 2004), periodic nursing visits to a home, compared with a pediatrician’s office, resulted in greater completion of recommended doses (98 versus 89 percent; \( P < .001 \)) and a lower rate of hospitalizations (0.93 versus 3.57 percent; \( P < .001 \)).

At Schneider Children’s Hospital (SCH), we have had direct experience with home-based delivery of palivizumab immunoprophylaxis. Through an independent 5-year study (Frogel 2004) conducted between 1998 and 2003, we have demonstrated that the coordination of efforts between a NICU and a pediatric practice using

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**Keys to successful palivizumab immunoprophylaxis**

- Screen all patients to determine high-risk infants that require immunoprophylaxis
- Immunize with palivizumab before hospital discharge; provide parent education
- Secure approval of required doses from insurers/health plans before onset of the local RSV season
- Give subsequent doses monthly at home (intervals of 30 days from last dose)
- Track all patients for compliance
- Track patient outcomes regarding hospitalizations and any adverse events

Source: Based on author recommendations
home-based delivery of palivizumab can be a highly successful strategy for ensuring that immunoprophylaxis is provided to high-risk infants. SCH NICU gave our general pediatric practice a discharge summary and indications for palivizumab for all patients who would receive follow-up care in our practice. We then entered these patients into a database and tracked them from the beginning to the end of the RSV season. We also notified the insurance providers and the parents of the children who required immunoprophylaxis. We developed a screening tool for use with all other children coming to our practice, and we dedicated a nurse and a physician to track all the patients. We assigned office staff to resolve insurance and health care provider issues. Working with our home pharmacy provider, we started to obtain palivizumab 2 or 3 weeks before the anticipated start of the RSV season. We also worked closely with home care companies. Because MCOs were concerned about anaphylaxis, an anaphylaxis protocol for the home care nurses was put in place whereby nurses were supplied with epinephrine and a procedure to follow if a child developed anaphylaxis. As severe reactions with palivizumab are rare, we have had no cases of anaphylaxis. I would recommend that an anaphylaxis protocol be part of any home care program for palivizumab immunoprophylaxis.

During 5 RSV seasons, 401 patients received prophylaxis. Their distribution by GA was: Less than 29 weeks (36 percent), 29–32 weeks (29 percent), 32–35 weeks (25 percent), and greater than 35 weeks (9 percent). One third of this population had CLD. Because of RSV activity in our region, tracked locally, full protection required a series of five and sometimes up to seven palivizumab injections for each infant born at the start of the season, or less, depending on their date of birth within the season. Infants who had been admitted to the NICU received a first injection of palivizumab in the hospital. During five consecutive RSV seasons, the average number of injections per patient increased each year. Over the course of five seasons, there were only eight hospital admissions for RSV lower respiratory infection in the 395 patients available for follow-up. The hospitalization rate of 2 percent was well below the expected rate of 10.6 percent.

We believe this program, with a greater than 90 percent compliance rate in terms of number of injections administered in seasons 2 to 5 and with a significant numbers of patients receiving home care, establishes a workable, coordinated approach for palivizumab immunoprophylaxis that can be duplicated by other pediatric practices.

Real-world experience

A recent analysis of a nationwide palivizumab registry showed that palivizumab immunoprophylaxis is associated with reduced hospitalization rates (Frogel 2008). The registry enrolled 19,548 patients who received at least one dose of palivizumab during four RSV seasons at 256 pediatric sites in 41 states and the District of Columbia. Doses were administered at clinics, physician offices, or at home. Subjects receiving doses in more than one season were counted as separate enrollments.

Across all four seasons, 40 percent of patients were born at a GA less than 32 weeks, 48 percent between 32 and 35 weeks, and 12 percent after 35 weeks gestation. In addition to prematurity, common risk factors among the patients in the registry included childcare attendance, CLD, and CHD. Follow-up information was available for 19,474 patients. Over all four seasons, the confirmed RSV hospitalization rate was 1.3 percent. Higher hospitalization rates were associated with male gender, birth before 32 weeks gestation, a history of CLD or CHD, congenital airway abnormalities or neuromuscular disease, and the presence of two or more children in the household. In the fourth season, CHD was the most common reason listed for palivizumab immunoprophylaxis in children whose GA exceeded 35 weeks.

In terms of timely administration — receipt of a dose within 35 days of the previous one — and the number of doses administered, the compliance rate ranged from 65 to 69 percent, and 59 percent of patients were compliant with palivizumab immunoprophylaxis by both measures. Patients in the mixed group (office/home) had lower compliance than either group alone. In comparison with clinic- or office-based administration of palivizumab, home care improved compliance by both measures (number of doses, 88 versus 81 percent; P<.0001); timely administration, 76 versus 69 percent; P<.0001). The home care-only group admission rate was 0.4 percent versus 1.2 percent for the clinic office-only group.

Summary

Pharmacologic options in the treatment of RSV infection have no or minimal effectiveness. Therefore, for infants at high risk of RSV infection, proper hand hygiene, limiting exposure to infection, and immunoprophylaxis with palivizumab is paramount. The first injection of palivizumab must be given prior to the start of the local RSV season and subsequent injections should be administered every 30 days to provide protective levels until the end of the RSV season. Pediatricians should anticipate the start of the RSV season and attend to reimbursement issues and obtain all necessary approvals well in advance of the time when the first injections will be given. Compliance is the key to providing protection for high-risk infants. Compliance has a positive association with decreasing RSV hospitalization rates; however, it is difficult for pediatricians to achieve optimal compliance on their own. A collaborative effort involving the hospi-
tal and NICU, pediatrician, parent, home care provider, and insurer is necessary to achieve optimal compliance.

References


Disclosures: Michael P. Frogel, MD, has received grant and research support and consulting fees related to palivizumab from MedImmune, and serves on MedImmune’s speaker’s bureau.
Respiratory syncytial virus (RSV) is usually regarded as a concern of pediatricians, whereas, in fact, RSV is a significant and unrecognized cause of seasonal respiratory tract infections (RTIs) in adults as well.

RSV may be responsible for as much as 25 percent of excess wintertime mortality usually attributed to influenza. For all age groups, the RSV-associated mortality rate in the category of underlying respiratory and circulatory deaths (a group that includes pneumonia and influenza deaths but excludes the accidental deaths that would be captured by the commonly used metric of all-cause mortality) has been estimated at 4.3 per 100,000 person-years. Among persons aged 65 and older, the mortality rate rises to 26.5 per 100,000 person-years, and 78 percent of RSV-associated underlying respiratory and circulatory deaths occur in this group (Thompson 2003).

One of the best studies showing the effects of RSV on morbidity and mortality in adults in the United States appeared in the *New England Journal of Medicine* (Falsey 2005). The study followed 680 healthy elderly patients and 540 high-risk adults1, and 1,388 patients hospitalized during the winter with cardiopulmonary illnesses (Figure, page 14). Over the course of four winters, 2,514 respiratory tract infections occurred among these patients. Using reverse transcriptase-polymerase chain reaction (PCR) technology, 102 RSV infections and 44 influenza infections were found among the ambulatory patients (the healthy elderly and the high-risk adults), and 142 RSV and 154 influenza infections were found in the hospitalized patients. None of the healthy elderly or high-risk patients with influenza infections died. Among the healthy elderly with an RSV infection, no deaths were recorded, but 4 percent of the high-risk patients with an RSV infection died. Among the hospitalized patients, 8 percent of those with an RSV infection died, as did 7 percent of those with an influenza infection. On a nationwide basis, this RSV mortality rate was estimated to translate into 14,000 deaths annually. The authors also estimated that RSV would account for about 180,000 hospital admissions each year at a cost exceeding $1 billion.

**Clinical manifestation of RSV**

Clinical manifestation of RSV will vary with the patient’s age and immune status, and whether the infection is primary or secondary. The depth to which the virus descends into the respiratory tract may be regarded as an indication of the degree to which a patient is immunocompromised, owing to age or illness or both. At both extremes of age, when the immune system either is undeveloped or decreasing, RSV can gain a foothold deep in the respiratory tract.

In an RSV infection, virus particles attach to airway epithelium, which leads to destruction of the epithelial cells and damage to cilia, similar to the way the mucociliary mechanism is damaged by the influenza virus. In severe influenza pneumonia or severe RSV pneumonia, the tissue damage is a consequence of the release of cytokines and chemokines. The virulence of the virus depends upon its ability to provoke an immune response

1 Patients aged 21 years or older with physician-diagnosed heart failure [New York Heart Association class II or higher] or chronic pulmonary disease severe enough to restrict activities or require the use of long-term medication.
that unleashes a cytokine storm in the respiratory tract.

**RSV in the upper respiratory tract.** Except for the nasopharynx, the respiratory tract is sterile. The normal respiratory flora in the nasopharynx constitute an important defense mechanisms against infection. Viral rhinitis — the common cold — is the most common upper respiratory infection during the winter. Viral rhinitis often results in edema of the mucosa that predisposes the patient to sinusitis. PCR technology also has confirmed that RSV is a cause of viral sinusitis (Louie 2005, Ramadan 1997).

An issue clouding the treatment of adults with RTIs in clinical practice is the inappropriate use of antibiotics, which is a primary driver for the development of multidrug-resistant organisms. RTIs are the leading reason antibiotics are prescribed, but about one third of RTIs are viral and do not require antibiotics. Lacking diagnostic tests to determine whether an RTI is viral or bacterial, primary care physicians sometimes prescribe antibiotics just in case the infection is bacterial. In the outpatient setting, the common cold and viral sinusitis are primary indications for inappropriate use of antibiotics. The problem confronting the clinician is how to know whether maxillary sinusitis is due to a virus or a bacterial pathogen such as *S. pneumoniae*. Physicians should consider that if the infection is viral, the patient will start to improve in 3 to 5 days, but if a viral infection is superimposed with a bacterial infection, in 3 to 5 days the patient’s condition will worsen. If this is true, sinusitis therapy can be withheld during the first 3 to 5 days while the patient’s clinical response is monitored. One strat- egy for reducing the inappropriate use of antibiotics while meeting patients’ expectations is to give patients a prescription for antibiotics but instruct them not to fill it for 3 to 5 days, depending on the course the disease follows. This strategy would not be advisable for children, however, because persistent rhinitis often lasts for weeks in children with viral illness who lack bacterial sinusitis.

**RSV in the lower respiratory tract.** In the lower respiratory tract, acute bronchitis is one of the few infectious diseases in otherwise healthy adults that always has a viral etiology, including RSV. Acute bronchitis thus represents another RTI associated with the inappropriate use of antibiotics. In adults with acute bronchitis who cough for 2 or 3 weeks, atypical pathogens such as *Mycoplasma* or *Chlamydia* should be suspected, in which case the patient would be a candidate for an antibiotic, such as a macrolide. RSV also is an important cause of viral pneumonia in adults. Until recently, *S. pneumoniae*, *H. influenza*, *Moraxella*, and atypical pathogens were the pathogens identified in community-acquired pneumonia series, but now influenza and RSV are recognized as the two primary viruses that cause pneumonia in adults.

**RSV management**

There is no evidence-based literature to define the best treatment approach for RSV infections. At the University of Louisville Hospital, we use corticosteroids and ribavirin whenever we see cases of RSV in bone marrow transplant patients, but these therapies are controversial. Because there is no treatment for RSV infections in adults, the institution of preventive measures is paramount, especially in hospitals and nursing homes where many immunocompromised patients live. The simple expedient of hand washing is the key to breaking the chain of transmission. When RSV is circulating, it also may be helpful to minimize contact between children and patients who are hospitalized or at high risk.

**Summary**

RSV is a significant and unrecognized cause of seasonal RTIs in adults, accounting for as much as 25 percent of excess wintertime mortality usually attributed to influenza. Nearly 80 percent of RSV-associated underlying respiratory and circulatory deaths occur among the elderly, and RSV is estimated to account for about
180,000 hospital admissions each year at a cost exceeding $1 billion. RSV also is recognized as an important cause of viral pneumonia in adults.

Preventive measures, such as hand washing, are paramount, especially in hospitals and nursing homes where many immunocompromised patients reside. When RSV is circulating, it is advisable to minimize contact between high-risk patients and children.

References

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Health Plan Medical Director:
Considerations for Prevention and Management of RSV Disease

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Health plans play an important role in the management of respiratory syncytial virus (RSV) disease. Joseph Juran, the great pioneer in quality control who passed away last March, always talked about the cost of poor quality in manufacturing, and said that the cost of prevention is less than the cost of inspection and less than the cost of internal and external failure. Certainly the cost of preventing a disease is going to be less than the cost of the disease itself. Humana’s intent is to make sure that all our members who are candidates for RSV immunoprophylaxis do, in fact, receive it.

At Humana, RSV management is guided by the three I’s: Integration of data, Identification of individuals who should receive immunoprophylaxis, and Interaction with both plan members and physicians. Successful outreach begins with candidate identification. To that end, we continuously mine our patient/physician database, which contains about 4 terabytes of data (by comparison, the Library of Congress’s data warehouse contains about 20 terabytes). These data are fed into CareHub, the largest information technology investment in Humana’s history. CareHub is a collaborative guidance model that engages both plan members and their health care providers by leveraging technology to share information among members, physicians, and Humana’s internal nurses, who work with our disease management vendors to improve medical outcomes. CareHub identifies pediatric members by mining claims received. It does not identify adult members, because there currently is no indication for the use of RSV immunoprophylaxis in adults.

The heart of CareHub is an evidence-based rules engine. This tool applies accepted clinical guidelines to an algorithm that helps us identify specific candidates for clinical engagement. By mining members’ clinical profiles and analyzing their individual data, we can identify and evaluate potential candidates for appropriate interventions and then route those candidates to those interventions. CareHub also enables us to conduct personalized interactive communication campaigns via multiple channels.

Creating a clinical profile
The clinical profile generated with CareHub provides a unique view of every plan member. The profile incorporates data from medical claims (diagnoses, using ICD-
9 codes; types of services; and procedures) and pharmacy claims (NDC codes; medication classes; and J codes for office-administered medications). A clinical profile, which, for example, includes a diagnosis of prematurity in a child, would denote that child as a potential candidate for RSV immunoprophylaxis. These claims also can be used in predictive modeling. Centralizing and integrating all the available data for each of our members greatly increases our ability to target outreach and communications.

Gathering additional data from other sources helps us to improve the sensitivity and specificity of our database, enabling us to identify (and predict) the cohort at greatest need for obtaining case management due to a risk of RSV infection; therefore, the clinical profile also incorporates registry data and self-generated information. Registry data useful in RSV management are available by diagnosis (e.g., prematurity or heart murmur), age cohort (e.g., children and elderly [if it were to become applicable]), and history (e.g., employer demographics). Self-generated information comes from the patient’s health risk assessment, which might reveal helpful information about smoking in the household or daycare arrangements; the patient’s medical history, which would incorporate information from a previous carrier; and external vendors. In summary, the clinical profile provides myriad ways in which we can identify those children most at RSV risk who would benefit from case management.

Engaging patients and helping physicians
A substantial percentage of our members live in the southern United States (Florida, Louisiana, Texas), so we know that the annual RSV season in those geographical areas extends beyond the five months of November through March. We have developed several “rules of engagement” for managing RSV risk, all of which depend on access to the patient’s database. First, the patient’s parents (member) must be continually provided with timely, accurate information about palivizumab immunoprophylaxis, but the method of contact must be one with which the member is most comfortable, whether it be by regular mail, secured e-mail, or telephone. Second, external partners (e.g., palivizumab vendor) must be aware of and willing to accommodate the member’s delivery preferences (home or physician’s office). Third, physicians must compile lists for all their patients who may require palivizumab (their list may be identical to ours) and make preparations to administer the medication. We try to complement physicians’ efforts by sending them visual aids, such as stickers for charts, and notifying them when palivizumab is sent to their office or the patient’s home. On behalf of the physician, we send e-mails and other reminders to the parent to make an appointment (e.g., telephone calls utilizing voice application technology) for administration of the drug.

Immunoprophylaxis guidelines
Although the RSV season in many locales is limited in duration, at Humana, preparing for the RSV season is a year-round event. Identification of patients requiring immunoprophylaxis is an ongoing process, and contacts have to be made prior to the RSV season.

Because Humana relies on evidence-based medicine, we stay consistent with the recommendations of the American Academy of Pediatrics (AAP) for palivizumab immunoprophylaxis. The AAP recommends that palivizumab immunoprophylaxis be considered for infants born between 32 and 35 weeks gestational age if two or more of the following risk factors are present: child care attendance, school-aged siblings, exposure to environmental air pollutants, congenital abnormalities of the airways, and severe neuromuscular disease (AAP 2006).

We are amenable to speaking with physicians to address eligibility criteria. We review all of our coverage issues on a regular basis, but if important new information about RSV should become available between regularly scheduled reviews, we will take that information to our Technology Assessment Forum for a possible update of our coverage policy.

Continuous quality improvement
Humana embraces continuous quality improvement (CQI) for its RSV risk management programs. The first step in the CQI process is to define what we expect to see and then to measure it — were the right candidates receiving RSV immunoprophylaxis? Unfortunately, analysis of our data suggests that about 20 percent of patients who should have received immunoprophylaxis may not have received it, so how can we work with physicians to improve that number? The second step is outcomes analysis — did we achieve what we expected to achieve? Third, was quality of care balanced with the cost of care? Fourth, we tie outcomes analysis into claims analysis — did we see an impact on utilization metrics (e.g., hospital admissions per thousand patients, length of stay, readmissions)? The final step is to ask how can we optimize our services for this population.

Summary
At Humana, our intent is to provide RSV immunoprophylaxis to all our members who need it quickly and efficiently. Humana’s CareHub is a collaborative guidance model that fully engages our members and their health care providers, and allows us to leverage technology to develop a comprehensive clinical profile for each member and to share information.

This clinical profile provides many ways in which we can identify those children who are at high risk of severe RSV infection, allowing us to implement RSV treatment and management quickly and effectively before the RSV season begins.
Along with human growth hormone and factor VIII, palivizumab (Synagis), an approved humanized monoclonal antibody to prevent respiratory syncytial virus (RSV) infection, was among the first drugs to be managed by health plans as a specialty drug. Specialty drugs are the high-cost biologics and injectables that often can blur the line between a medical benefit and a pharmacy benefit. Because of their high cost, health plan pharmacy directors want to be certain that specialty drugs are used at the right time by the right population.

Preparing for the RSV season

The RSV season usually begins in November and extends through March, although there is great geographical variability (AAP 2006). For a health plan pharmacy director, the challenge is to budget for the inevitability of the RSV season on the basis of historical data. We at Scrip World rigorously review prior authorization (PA) requests, especially at the beginning of an RSV season, to allow for the very real possibility that the season may last longer than usual. If we fail to keep palivizumab utilization within budget during the first RSV season, we will be even more constrained during the following season. For example, if historical data for the previous 5 years show that the RSV season in a given geographical area begins Nov. 15,

I recommend that physicians notify payers of the number of patients for whom they expect to provide palivizumab immunoprophylaxis and precertify the PAs for those patients well before the anticipated start of the season. This practice will allow both the MCO and the physicians to be prepared for the oncoming RSV season.

The Centers for Disease Control and Prevention (CDC) defines the onset of the RSV season as the first of two consecutive weeks in which the median percentage of positive tests for RSV antigen is 10 percent or greater (CDC 2007). In some locales in Utah, we use a threshold of five confirmed cases within seven consecutive days to determine season onset. However, even if local historical data show that the RSV season usually does not begin until December, and even if the threshold for season onset has not been reached by then, some payers have agreed with physicians that immunoprophylaxis should be initiated in November. Initiating therapy in November, even without meeting the threshold criteria, recognizes an agreement between the payer and the physician that immunoprophylaxis will occur eventually, and that it is better to set a definite start date for reimbursement rather than to wait until physicians are inundated with cold and flu season patients, not to mention the increased risk of exposure to RSV associated with the holidays. Physicians need time to prepare and to schedule and effectively deliver RSV immunoprophylaxis to their patients and not expose their patients unnecessarily to RSV infection.

Need for RSV guidelines

When an infant is in a neonatal intensive care unit (NICU), it is critical for the hospital to work with the payer to make certain that the PA for immunoprophylaxis is received before the infant is discharged. A difficult situation for an MCO arises when an infant has re-
ceived its first dose of palivizumab in the NICU, but is a borderline candidate for immunoprophylaxis, such as an infant born at a gestational age of 34 weeks who is relatively healthy but has only one risk factor for serious RSV infection. If we were to evaluate this case independently, we probably would deny coverage, yet the NICU has initiated treatment. At this point, it becomes difficult to deny further immunoprophylaxis because of the parents’ and the physician’s expectations. Establishing regional guidelines for RSV immunoprophylaxis prior to the onset of an RSV season and working collaboratively with NICUs to make them aware of reimbursement policies might help eliminate this kind of conflict.

Among general practitioners, there seems to be some confusion about palivizumab. Some physicians equate it with a standard vaccine that requires only one or two injections. They seem unaware that palivizumab immunoprophylaxis usually involves a total of five or six injections, administered monthly starting prior to the onset of the RSV season and continuing for its duration. In terms of cost, the most expensive patient is the one who receives only one or two doses and, thus, fails to receive the long-term benefit of the drug. Sporadic administration of palivizumab is ineffective — an initial dose in November followed by a second one in January is suboptimal. Therefore, MCOs stress compliance. An MCO can put PA in place and provide access to the drug, and issue reminders and incentives to parents and physicians to get immunoprophylaxis, but in the end, successful immunoprophylaxis depends on a collaborative relationship between the parents or caregivers and their physician.

Cost-savings through home care
Palivizumab presents a new challenge for specialty pharmacy, because sometimes it is provided through home care. When a physician administers the drug in the office, the price at which the physician acquired it is usually marked up by some percentage that the MCO must then absorb. To counter this practice, it is very likely that MCOs will turn to home care more and more for palivizumab immunoprophylaxis, because it provides an opportunity for specialty pharmacy to contract for the drug at a volume discount and bypass the physician markup. This savings would more than offset the cost of a home care visit (often $70 or more). Another cost-reduction strategy is to have the pharmacy deliver the drug to the patient’s house, which the patient would then take to the physician’s office for administration.

Summary
RSV immunoprophylaxis presents a challenge for MCOs. Despite its demonstrated ability to protect high-risk infants against serious RSV infection and to reduce morbidity, immunoprophylaxis with palivizumab incurs high costs that MCOs must grapple with every year. If MCOs, physicians, and professional organizations can agree on common guidelines for RSV management, then MCOs will be able to provide affordable treatment for those children at high risk.

References

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ROUNDTABLE DISCUSSION
RSV Issues and Solutions

RETURN ON INVESTMENT
MICHAEL FROGEL, MD: The key message from Dr. Simões’s presentation is that you can’t just look at hospitalization as an endpoint. Managed care entities need to realize there is an association between RSV infections and recurrent wheezing later in life, so there may be more downstream costs if RSV immunoprophylaxis is not provided. That’s a key issue that has not been addressed well.

STEVEN PESKIN, MD, MBA: For payers, what makes the kind of information Dr. Simões provided valuable?

ALBERT TZEEL, MD, MHSA: There are two ways to look at it. I agree with what Eric [Simões] is saying in terms of the predictive value of a tool like the one he described. That is very helpful, because cost ultimately is where the rubber meets the road. Philosophically, I agree with the idea of looking further down the road in terms of the potential decrease in the risk of asthma. Given the amount of turnover in managed care, however, we are reduced to arguing in favor of paying for a treatment now rather than for one that will provide a return for some other MCO later.
FROGEL: If there are a limited number of insurance companies and a limited number of patients, and they are all flipping back and forth, it doesn’t matter. You’ll benefit if they provide immunoprophylaxis, and they’ll benefit if you provide it.

TZEEL: We’ve bought into that argument with cardiovascular disease and asthma in adults. The difference between those two areas and RSV immunoprophylaxis is cost. You can’t say that you are going to spend $20,000 and not have any return until 4 or 5 years from now. You can spend $200 a month on cardiac medications and inhalers and nearly everyone agrees it’s worth the cost. But when a drug costs well over $1,000 per month, and there is still some controversy about appropriate populations, it’s too big a financial risk.

FROGEL: I would argue that with adults you spend billions of dollars on some procedures that aren’t proven to be effective. Expenditures for children versus adults are horrendously disproportionate. A lot of the treatments provided for adults may not be evidence-based and may lack good outcomes. Yes, palivizumab is costly, but there is nothing as safe and as effective as it is.

TZEEL: There are other issues to take into account. We analyzed our national data, using the current criteria for utilization of immunoprophylaxis. We found that, especially in the 32- to 35-week gestational age population, we questioned about 40 percent of the requests on the basis of whether the children met the criteria, but their medication was authorized nevertheless. Our bigger concern is that we believe that about 20 percent of children who should be getting palivizumab immunoprophylaxis are not receiving it.

DISEASE TRANSMISSION

FROGEL: In the prevention of viral infections, hand washing and sterile technique are always important. When you’re talking about hospital-acquired infections and nursing homes and high-risk patients, then hand washing, hand washing, hand washing is the key element to preventing nosocomial infection. Another important measure is to prevent the transmission of the virus to high-risk adults and to not allow children to visit grandpa who is ill and laying in a bed at home. We also recommend keeping high-risk kids away from day care during the RSV season, and to do the same thing with the elderly — keep them away from exposure to RSV.

TZEEL: From a managed care perspective, we have done a lot of outreach to our members reminding them about simple measures like the ones you have mentioned.

JULIO A. RAMIREZ, MD: The general public doesn’t recognize that most of our immunocompromised patients are at home — the grandfather with cardiovascular disease or the newborn.

FROGEL: Children are the reservoir of infection. Universal influenza vaccination for children could decrease the burden of influenza in the adult population, because the kids are the ones who spread it like wildfire.

PESKIN: It would seem that education about RSV prevention is important, because RSV appears to present a more significant burden in the adult and senior populations than has been generally thought.

COORDINATION WITH NICU

PESKIN: Doug, are you saying that a conundrum for an MCO is created when palivizumab immunoprophylaxis is initiated in the neonatal intensive care unit (NICU) for a child who would not have met the MCO’s criteria for palivizumab?

DOUGLAS S. BURGOYNE, PHARMD, RPH: Correct.

ERIC A.F. SIMÕES, MD: I’ve seen that, and when that happens, what do you do?

BURGOYNE: It depends. We often have to explain to the NICU that although the patient doesn’t fit our guidelines, we will cover the cost of the drug because the NICU has initiated treatment, and the family and their physician are now expecting to receive it. But this can create an antagonistic relationship between the hospital and the payer.

TZEEL: You don’t want to strain the relationship with the hospital, especially if there is only one NICU in the area.

FROGEL: Part of the problem is that the MCO isn’t providing the product for the hospital, so there is no interaction between them. You need to tell the NICUs that you want to work collaboratively with them and possibly save them some money.

BURGOYNE: Absolutely. I’m all for interaction and collaboration.

TZEEL: It depends on contracting and how the NICU gets paid.

FROGEL: This is something that has fallen through the cracks. Whether it’s the payer or the hospital, this issue needs to be resolved. It’s not as though the hospital should just pay out of pocket for a drug, but hospitals are being remiss if they do not renegotiate their contracts and include palivizumab for these patients. Contracts should set up prior-to-discharge administration of palivizumab.

SIMÕES: Our hospital did build it into its contracts with the health plans. The problem with providing palivizumab on the day of discharge is that palivizumab levels don’t go up for 48 hours.

FROGEL: What Dr. Simões and I are saying is that the child who is indicated to receive palivizumab should not leave the NICU without administration at least 48 to 72 hours before discharge.
CONTINUING MEDICAL EDUCATION ASSESSMENT/EVALUATION/CERTIFICATE REQUEST

Respiratory Syncytial Virus (RSV):
Prevention Strategies and the Appropriate Identification of Vulnerable Populations

CE Credit for Physicians/Pharmacists

I certify that I have completed this educational activity and post-test and claim (please check one):
☐ Physician credit hours
☐ Pharmacist contact hours

Signature: _______________________________

PLEASE PRINT CLEARLY

First name, MI _______________________

Last name, degree _____________________

Title ________________________________

Affiliation ___________________________

Mailing address __________________________

City____________________ State ____ ZIP______

Daytime telephone (____) __________

Fax (_____) _____________________

E-mail __________________________

Physicians — This activity is designated for a maximum of 1.50 AMA PRA Category 1 Credit(s).™

Pharmacists — This activity is approved for 1.50 contact hours (0.150 CEU).

ACPE Universal Program Number (UPN): 812-000-08-024-H01-P

Release Date: Nov. 20, 2008

Expiration Date: Nov. 20, 2009

To receive a statement of credit, complete the assessment/evaluation form and mail or fax the completed form to:

The Chatham Institute
26 Main Street, Suite 350
Chatham, NJ 07928
Fax: (973) 701-2515

Allow 6–8 weeks for processing.

This activity is sponsored by The Chatham Institute and is provided at no cost to the participant through an educational grant from MedImmune.

EXAMINATION: Place an X through the box of the letter that represents the best answer to each question on page 21. There is only ONE correct answer per question. Place all answers on this form.

A. B. C. D.

1. ☐ ☐ ☐ ☐
2. ☐ ☐ ☐ ☐
3. ☐ ☐ ☐ ☐
4. ☐ ☐ ☐ ☐
5. ☐ ☐ ☐ ☐
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8. ☐ ☐ ☐ ☐
9. ☐ ☐ ☐ ☐
10. ☐ ☐ ☐ ☐
11. ☐ ☐ ☐ ☐
12. ☐ ☐ ☐ ☐

PROGRAM EVALUATION

So that we may assess the value of this self-study program, we ask that you please fill out this evaluation form.

Have the objectives for the activity been met?

1. Explain the epidemiology, burden of disease, and seasonal and regional variability of RSV. ☐ Yes ☐ No
2. Discuss the economic impact of RSV on the health care system. ☐ Yes ☐ No
3. Explain which populations are at high risk of RSV infection and why. ☐ Yes ☐ No
4. Discuss current and new prophylactic options for managing RSV. ☐ Yes ☐ No
5. Establish educational initiatives to raise the awareness of parents and health care professionals about the prevention and treatment of RSV. ☐ Yes ☐ No
6. Assess best practices in a managed care setting for managing RSV, so as to improve outcomes. ☐ Yes ☐ No

Was this publication fair, balanced, and free of commercial bias? ☐ Yes ☐ No

If no, please explain: ____________________________________________

Please use the following scale to answer the next four questions:

Strongly Agree ................. 5
Agree .............................. 4
Neutral .......................... 3
Disagree ........................ 2
Strongly Disagree ............. 1

Did this educational activity meet my needs, contribute to my personal effectiveness, and improve my ability to:

Treat/manage patients? 5 4 3 2 1 N/A

Communicate with patients? 5 4 3 2 1 N/A

Manage my medical practice? 5 4 3 2 1 N/A

Other _________________________________________________________

5 4 3 2 1 N/A

Effectiveness of this method of presentation:

Excellent Very good Good Fair Poor

5 4 3 2 1

What other topics would you like to see addressed? ____________________________

Comments: ____________________________________________________________
CONTINUING EDUCATION POST-TEST
Respiratory Syncytial Virus (RSV):
Prevention Strategies and the Appropriate Identification of Vulnerable Populations

Please tear out the assessment/evaluation form on page 20. On the answer sheet, place an X through the box of the letter corresponding to the correct response for each question. There is only ONE correct answer to each question.

1. In the United States, how many infants are hospitalized each year because of severe RSV disease?
   a. 150,000.
   b. 50,000.
   c. 126,000.
   d. 74,000.

2. In the United States, the RSV season always begins in November and ends in March of each year.
   a. True.
   b. False.

3. Which of the following is not a risk factor for severe RSV disease in infants:
   a. A gestational age (GA) of 28 weeks or less.
   b. Household crowding.
   c. School-age siblings.
   d. Malnutrition.

4. A long-term outcome of RSV in infancy may be:
   a. Chronic lung disease.
   b. Physician-diagnosed asthma.
   c. Allergies.

5. Palivizumab is an FDA-approved _____ that is administered _____ to prevent severe RSV disease in _____ infants.
   a. Monoclonal antibody, intramuscularly, high-risk.
   b. Monoclonal antibody, orally, all.
   c. Polyclonal globulin, intravenously, high-risk.

6. Current AAP guidelines recommend that at the start of an RSV season, palivizumab immunoprophylaxis should be considered for children less than 2 years of age with severe chronic lung disease or congenital heart disease, and also for:
   a. Infants born 32 weeks GA or less.
   b. All infants younger than 1 year.
   c. All infants who are not breastfeeding.

7. According to Frogel, for optimal value, RSV immunoprophylaxis should be given _____ the RSV season begins, terminated _____ after the season, with intramuscular injections of palivizumab administered _____:
   a. 2 months before; 1 month after; every 45 days.
   b. 1 month before; 1 month after; every 30 days.
   c. 1 week before; at the end of the season; every 30 days.

8. According to Frogel, compliance with immunoprophylaxis for high-risk infants can best be maintained by:
   a. Better coordination between the neonatal intensive care unit and pediatricians and home-based delivery of palivizumab.
   b. Parent education.
   c. Better tracking of high-risk infants to determine adherence to immunoprophylaxis.
   d. All of the above.

9. Among persons 65 years and older, what percent of deaths can be attributed to RSV-associated underlying respiratory and circulatory diagnoses?
   a. 65 percent.
   b. 78 percent.
   c. Less than 50 percent.

10. The most effective treatment for RSV infections in both the upper and lower respiratory tract in adults is:
    a. Corticosteroid therapy.
    b. Antibiotic therapy.
    c. Good hygiene practices.

11. A primary advantage of Humana’s CareHub information technology program is its ability to:
    a. Identify specific candidates for RSV case management.
    b. Keep an accurate record of all medical and pharmacy claims.
    c. Develop clinical guidelines for RSV immunoprophylaxis.

12. In the management of RSV, Scrip World uses prior authorization as a way to:
    a. Identify specific candidates for RSV case management.
    b. Keep an accurate record of all medical and pharmacy claims.
    c. Develop clinical guidelines for RSV immunoprophylaxis.