Respiratory Syncytial Virus Prophylaxis
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Objectives After completing this article, readers should be able to:

1. Identify risk factors for severe respiratory syncytial virus (RSV) lower respiratory tract disease in children.
2. Identify strategies for prevention of severe RSV disease among high-risk infants and children.
3. Know the recommendations for prophylaxis of RSV disease with palivizumab.

Introduction
RSV is the leading viral pathogen responsible for bronchiolitis and pneumonia in infants and young children worldwide. Preterm infants and children who have bronchopulmonary dysplasia (BPD) (otherwise known as chronic lung disease of prematurity) or congenital heart disease are at increased risk for severe RSV disease that requires hospitalization (Table 1).

Prophylactic Strategies
Education of parents and other caregivers about methods to decrease the infant’s exposure to RSV and to factors that may contribute to the severity of the RSV infection must form the basis of any RSV prophylaxis program. Because RSV is transmitted by direct or close contact with contaminated secretions and the virus is known to persist for hours on environmental surfaces and for 30 minutes or longer on hands, emphasis on hand hygiene is crucial. High-risk infants and children should not be exposed to individuals who have respiratory infections, and if at all possible, they should not be in settings (eg, child care centers) where such exposures are likely. Exposure to tobacco smoke must be eliminated because it has been associated with more severe RSV disease. These measures have the added benefit of decreasing transmission of other respiratory pathogens. In addition, all high-risk children older than 6 months of age and their contacts must receive influenza vaccine.

Passive immunoprophylaxis of high-risk children with RSV immune globulin intravenous (RSV-IGIV) and palivizumab has been shown to prevent RSV hospitalization, the surrogate marker for severe RSV lower respiratory tract disease in clinical trials.

RSV-IGIV
RSV-IGIV is a hyperimmune polyclonal human intravenous antibody preparation that is prepared from multiple donors. It was licensed by the United States Food and Drug Administration (FDA) in 1996. Two multicenter, randomized clinical trials demonstrated that monthly RSV-IGIV infusions of 750 mg/kg in children who had either prematurity (≤35 weeks of gestation, <6 months of age) or BPD (age ≤24 months of age) resulted in a 41% to 63% reduction in RSV hospitalization. (1)(2) An additional multicenter trial of RSV-IGIV in children younger than 48 months of age who had congenital heart disease showed a nonsignificant 31% decrease in RSV hospitalization. A significant increase in cyanotic episodes and cardiac surgery-related deaths occurred among children who had cyanotic congenital heart disease and right-to-left shunt. Accordingly, RSV-IGIV should not be administered to children who have congenital heart disease. Other disadvantages of RSV-IGIV prophylaxis include the need for intravenous access, the fluid load (15 mL/kg) required to deliver the drug, the potential for transmission of blood-borne pathogens, and
the interference with the antibody response to live-virus vaccines. RSV-IGIV no longer is marketed in the United States; its use has been replaced by palivizumab.

Palivizumab

Palivizumab is a neutralizing humanized mouse IgG1 monoclonal antibody directed against a well-conserved epitope in the antigenic site of the RSV-F (fusion) glycoprotein that blocks fusion of the virus to the host epithelial cell. Palivizumab is engineered completely in the laboratory, being 95% of human origin and only 5% murine. It was licensed by the FDA in 1998 (3) for prevention of severe RSV disease in preterm infants and children who have BPD. More recently, palivizumab was approved for use in children who have hemodynamically significant congenital heart disease.

The IMpact Trial assessed the safety and efficacy of intramuscular palivizumab at a dose of 15 mg/kg provided every 30 days during the RSV season for prevention of RSV hospitalization. (1) This international, randomized, double-blind, placebo-controlled study enrolled 1,502 children who were either 1) 35 or fewer weeks of gestation and 6 months of age or younger, or 2) 24 months of age or younger and had BPD that required medical treatment (ie, supplemental oxygen, steroids, bronchodilators, or diuretics) within the previous 6 months. Palivizumab significantly reduced RSV hospitalization by 55% (Table 2). Subgroup analyses by degree of prematurity and by absence of BPD also yielded significant reductions in RSV hospitalization. Data obtained from the Palivizumab Outcomes Registry, a prospective nationwide registry of 2,116 high-risk children who received palivizumab after its FDA licensure, demonstrated similar RSV hospitalization rates as in the IMpact trial. (4) Most of the RSV hospitalizations reported to the Registry occurred between the first and second doses, possibly reflecting lower trough concentrations of palivizumab following a single dose.

Palivizumab also has shown benefit in children who have congenital heart disease. From 1998 to 2002, an international, multicenter, randomized, double-blind, placebo-controlled study evaluated the safety and efficacy of palivizumab for prevention of RSV hospitalization in 1,287 children who were at least 24 months of age and had hemodynamically significant congenital heart disease.
disease. This study demonstrated the safety of palivizumab in children who had cardiac disease and that its use resulted in a 45% decrease in the rate of RSV hospitalization (Table 2). (5) Among children who had cyanotic congenital heart disease, RSV hospitalization was reduced by only 29% (P=0.285); among children who had acyanotic lesions, there was a significant reduction of 58% (P=0.003). In addition, among all study children, there was a 56% decrease in total days of RSV-associated hospitalization per 100 children (P=0.003) and a 73% decrease in total RSV-associated hospital days with supplemental oxygen per 100 children (P=0.014). The percentage of children who died was similar in both the palivizumab (3.3%) and placebo (3.7%) groups. None of the fatalities were attributed to the study drug. Because palivizumab serum concentrations decreased by 58% after cardiopulmonary bypass, it is recommended that a postoperative dose of palivizumab be administered to children who continue to require prophylaxis after such surgery.

Palivizumab has not been associated with an increased risk of localized or systemic adverse events. Specifically, there has been no significant difference in hematologic, renal, or hepatic abnormalities between palivizumab and placebo recipients, even with repeated dosing during a second season of prophylaxis. In the IMpact trial, fever and mild injection site erythema, induration, or swelling occurred in 3% of recipients. Antibodies to palivizumab have been seen transiently among both drug and placebo recipients, but this has not been associated with adverse reactions. Following licensure of palivizumab, anaphylaxis after re-exposure and acute hypersensitivity reactions on initial and re-exposure to palivizumab have been reported rarely.

Palivizumab is an expensive drug, and its use should be reserved for children at the highest risk of severe RSV disease. It has been estimated that approximately 16 patients would have to receive palivizumab to prevent one hospital admission. Economic analyses of RSV immunoprophylaxis, however, have been inconsistent because of considerable variation in the baseline rate of hospitalization attributable to RSV among high-risk groups. Factors such as outpatient and emergency department visits and family costs during a child’s RSV hospitalization also need to be considered. There also may be potential savings from prevention of long-term sequelae such as recurrent wheezing and asthma. In an animal model, palivizumab prophylaxis prevented the development of airway hyperresponsiveness. (6)

**Recommendations for Palivizumab Prophylaxis**

Palivizumab is administered intramuscularly at a dose of 15 mg/kg monthly (every 30 d) during the RSV season, which typically in the United States starts in November and ends in March or April. A maximum of five doses generally is sufficient prophylaxis during one season. This recommended dose and schedule assures the maintenance of serum palivizumab concentrations of at least 40 mcg/mL, a concentration that decreases pulmonary RSV replication in the cotton rat model by more than 100-fold. To date, no palivizumab-resistant RSV mutants have been identified in children hospitalized with RSV infection. (7) High-risk infants and children should receive palivizumab before hospital discharge. Once a child qualifies for prophylaxis, administration should continue throughout the RSV season and not stop at the point he or she reaches any certain age. Because some children experience more than one RSV infection during a given season, infants and children who develop an RSV infection while receiving palivizumab should continue to receive prophylaxis after recovery from the acute infection. Palivizumab is not approved or recommended for treatment of RSV disease. Palivizumab can be given with routine immunizations because it does not interfere with the immunologic response to vaccines.

Palivizumab has been marketed as a lyophilized product that requires reconstitution with sterile water to a concentration of 50 or 100 mg/mL, a process that requires approximately 20 minutes. The drug is supplied as a single-dose vial, and because it lacks a preservative, it must be used within 6 hours after reconstitution. In actuality, many nurseries and clinics provide palivizumab to several infants from the same vial after it is prepared by aseptic technique to minimize cost and wastage of unused drug. In July 2004, the FDA approved a new liquid formulation of palivizumab that differs from the lyophilized product by not containing mannitol. Liquid palivizumab has been shown to have the same pharmacokinetics as the lyophilized formulation, and it is similarly nonimmunogenic. The manufacturer plans to discontinue production of the current lyophilized preparation in October 2004, with liquid palivizumab becoming available for intramuscular administration in the United States in the 2005 to 2006 RSV season.

Palivizumab has been administered intravenously (IV). Lyophilized palivizumab (15 to 30 mg/kg) is reconstituted using sterile water to achieve a concentration of 10 to 20 mg/mL. A 0.2-micron filter is used to withdraw the reconstituted palivizumab into a syringe. The drug then is infused through an inline 0.2-micron filter at a rate of 1 to 2 mL/min. This IV preparation has...
not been approved by the FDA, even though it has been shown to be safe and well tolerated and attained the desired protective antibody titers. (8)

The American Academy of Pediatrics (AAP) has issued recommendations for the use of palivizumab in high-risk children (Figure). (9) For infants born between 32 weeks, 1 day and 35 weeks, 0 days of gestation, the AAP recommends that prophylaxis be considered only if two or more risk factors are present. Although palivizumab has been shown to decrease RSV hospitalization in these infants, and infants between 33 to 35 weeks of gestation may have adverse hospital outcomes due to RSV, (10) the health care expenditures of prophylaxis makes routine administration of palivizumab problematic in this group of infants. Local data regarding RSV hospitalization rates among high-risk children can be used to develop guidelines for palivizumab prophylaxis.

Not all children who have congenital heart disease are candidates for prophylaxis. The degree of physiologic cardiovascular compromise must be assessed. Children who have the following cardiac lesions are not at increased risk from RSV and generally should not receive immunoprophylaxis: 1) hemodynamically insignificant congenital heart disease such as secundum atrial septal defect, small ventricular septal defect, pulmonic stenosis, uncomplicated aortic stenosis, mild coarctation of the aorta, and patent ductus arteriosus; 2) lesions adequately corrected by surgery unless there is continued requirement of medication for congestive heart failure; and 3) mild cardiomyopathy not requiring medical therapy.

Data are insufficient to recommend the routine use of palivizumab for children who have cystic fibrosis. Results are pending of a phase IV multicenter, randomized, double-blind, placebo-controlled study on the safety and tolerance of palivizumab in children 24 months of age and younger who have cystic fibrosis. Palivizumab should not be administered routinely to all high-risk infants in the neonatal intensive care unit.

Figure. Recommendations for RSV prophylaxis in high-risk children. (9)
The optimal and cost-effective means to prevent nosocomial RSV disease is strict adherence to infection control practices, such as hand hygiene, contact precautions, cohorting of infected infants and staff, and exclusion of visitors and staff who have respiratory illness from contact with susceptible infants. A single dose of palivizumab, however, could be provided to uninfected infants who are cared for by the same nurse or are in close proximity to an infant who develops RSV disease.

Use of home health care services to provide palivizumab to high-risk patients significantly improves adherence to the monthly schedule. (11) This strategy has the added advantage of not exposing these children to individuals who have RSV and other respiratory infections while in physician waiting areas.

Future Considerations
A new, enhanced-potency, humanized RSV monoclonal antibody that is derived from palivizumab has been developed. In the cotton rat model, it has demonstrated 50 to 100 times greater neutralizing activity against RSV than palivizumab in the lower respiratory tract. A phase III trial comparing the new agent with palivizumab is being conducted during the 2004 to 2006 RSV seasons to determine the safety and efficacy in reducing RSV hospitalization in high-risk children. The new agent may have the added advantage of preventing upper respiratory tract RSV infection.

Research on the development of an RSV vaccine that can provide safe and long-term protective immunity is ongoing in several laboratories worldwide. RSV vaccination of pregnant women and young infants is the future of RSV prophylaxis, but it remains an elusive goal.

References
NeoReviews Quiz

3. Respiratory syncytial virus (RSV) is the leading viral pathogen for bronchiolitis and pneumonia in infants and children. Of the following, the strongest risk factor for RSV-related illness in infants is:

   A. Bronchopulmonary dysplasia.
   B. Congenital heart disease.
   C. Multiple congenital anomalies.
   D. Neonatal sepsis.
   E. Prematurity.

4. Palivizumab, a neutralizing humanized monoclonal antibody directed against RSV fusion glycoprotein, is being used for prevention of RSV-related illness among high-risk infants. Of the following, the most accurate statement regarding the use of palivizumab for prevention of RSV-related illness in infants is that:

   A. A maximum of three doses of palivizumab is sufficient for RSV prophylaxis during one season.
   B. Combining palivizumab with other vaccines during immunization interferes with the immunologic response.
   C. The desired serum concentration of palivizumab against RSV replication is 40 mcg/mL or greater.
   D. The lyophilized preparation of palivizumab must be used within 30 minutes of reconstitution with sterile water.
   E. The number of patients who would have to receive palivizumab to prevent one hospital admission related to RSV illness is 10.
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