

AMERICAN ACADEMY OF PEDIATRICS

POLICY STATEMENT

Organizational Principles to Guide and Define the Child Health Care System and/or Improve the Health of All Children

Committee on Infectious Diseases and Committee on Fetus and Newborn

Revised Indications for the Use of Palivizumab and Respiratory Syncytial Virus Immune Globulin Intravenous for the Prevention of Respiratory Syncytial Virus Infections

ABSTRACT. Palivizumab and Respiratory Syncytial Virus Immune Globulin Intravenous (RSV-IGIV) are licensed by the Food and Drug Administration for use in preventing severe lower respiratory tract infections caused by respiratory syncytial virus (RSV) in high-risk infants, children younger than 24 months with chronic lung disease (formerly called bronchopulmonary dysplasia), and certain preterm infants. This statement provides revised recommendations for administering RSV prophylaxis to infants and children with congenital heart disease, for identifying infants with a history of preterm birth and chronic lung disease who are most likely to benefit from immunoprophylaxis, and for reducing the risk of RSV exposure and infection in high-risk children. On the basis of results of a recently completed clinical trial, prophylaxis with palivizumab is appropriate for infants and young children with hemodynamically significant congenital heart disease. RSV-IGIV should not be used in children with hemodynamically significant heart disease. Palivizumab is preferred for most high-risk infants and children because of ease of intramuscular administration. Monthly administration of palivizumab during the RSV season results in a 45% to 55% decrease in the rate of hospitalization attributable to RSV. Because of the large number of infants born after 32 to 35 weeks' gestation and because of the high cost, immunoprophylaxis should be considered for this category of preterm infants only if 2 or more risk factors are present. High-risk infants should not attend child care during the RSV season when feasible, and exposure to tobacco smoke should be eliminated.

ABBREVIATIONS. RSV, respiratory syncytial virus; RSV-IGIV, Respiratory Syncytial Virus Immune Globulin Intravenous; CLD, chronic lung disease; CHD, congenital heart disease.

Currently, there are 2 options for immunoprophylaxis for preventing respiratory syncytial virus (RSV) infection in high-risk infants. Respiratory Syncytial Virus Immune Globulin Intravenous (RSV-IGIV) is a polyclonal hyperimmune globulin prepared from donors selected for having high serum titers of RSV neutralizing antibody. Palivizumab is a humanized murine monoclonal anti-F glycoprotein immunoglobulin G1 antibody with

neutralizing and fusion inhibitory activity against RSV. Both preparations have been licensed for prevention of RSV disease in selected infants and children younger than 24 months with chronic lung disease (CLD [formerly called bronchopulmonary dysplasia]) or with a history of preterm birth (≤ 35 weeks' gestation). Only palivizumab is indicated for use in children with hemodynamically significant congenital heart disease (CHD). Choosing which product to use in a patient will depend on the nature of the underlying disease, the preferred route of administration, and other factors. However, in all instances immunoprophylaxis should be reserved for use in infants and children at greatest risk of RSV infection because of the high cost of this intervention.

Recommendations for use of both products have been summarized by the American Academy of Pediatrics.^{1,2} The purpose of this statement is to update clinicians on the appropriate use of RSV-IGIV and palivizumab on the basis of data from 5 clinical trials. Details regarding the results of clinical trials with RSV-IGIV and palivizumab are available in the accompanying technical report³ (also available online).

OVERALL CONSIDERATIONS

A critical aspect of RSV prevention in high-risk infants is the education of parents and other caregivers about the importance of decreasing infants' exposure to and acquisition of RSV. Preventive measures include eliminating exposure to cigarette smoke and settings where RSV or other respiratory viruses may be transmitted (eg, child care centers). Emphasis on hand hygiene also is important in all settings including the home, especially during periods when contacts of high-risk children have respiratory tract infections or when infants are at risk of exposure to respiratory infections from siblings who are in child care or who attend school.

Both palivizumab and RSV-IGIV have been shown to decrease the risk of severe RSV disease in high-risk infants and children. No direct studies have been conducted to compare the relative efficacy of the 2 interventions. Because of its ease of administration, monthly palivizumab, an intramuscular injection, generally is favored over RSV-IGIV, a 4-hour intravenous infusion.

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Limited data are available regarding the use of palivizumab for 2 consecutive seasons. No difference was noted between incidence of adverse events among children who received palivizumab prophylaxis for a second season and children receiving prophylaxis for only 1 season. In addition, limited experience from postmarketing data suggests that adverse events occurring after more than 5 doses in a single season are no different from adverse events occurring after the initial 5 doses.

Postmarketing surveys indicate that the effect of palivizumab prophylaxis on the rate of hospitalization for RSV is similar to that found in controlled clinical trials. Rare cases of severe hypersensitivity reactions (<1 case per 100 000 recipients) have been described after an initial dose as well as after reexposure to palivizumab.

Palivizumab attaches to a well-conserved epitope in the A-antigenic site of the F protein of RSV. Although resistant RSV strains can be generated in laboratory experiments, naturally occurring escape mutants (ie, resistant viruses) to palivizumab have not been identified after the administration of this product. Ongoing surveillance of RSV isolates has failed to identify any decrease in sensitivity to palivizumab.

CLINICAL SELECTION OF PALIVIZUMAB OVER RSV-IGIV

Although palivizumab provides effective protection against RSV for eligible infants and has greater ease of administration and fewer adverse effects than RSV-IGIV, there are other minor differences between the 2 products to be considered. In the RSV-IGIV trial, immunoprophylaxis decreased the overall rate of hospitalization for non-RSV respiratory infections. This may be of value for infants younger than 6 months who are not eligible for influenza immunization and for infants and children with severe pulmonary disease for whom respiratory tract infections in addition to RSV may be important. However, the concentration of antibodies against viruses other than RSV is not monitored in RSV-IGIV lots and is likely to vary from lot to lot, making this an unreliable basis for selecting RSV-IGIV. In addition, in the RSV-IGIV trial, immunoprophylaxis significantly decreased the frequency of otitis media, although this benefit alone does not justify its use. Palivizumab does not affect the rate of hospitalization for non-RSV respiratory disease or the incidence of otitis media. RSV-IGIV should not be administered to children with hemodynamically significant CHD.

ADMINISTRATION

Palivizumab is administered intramuscularly at a dosage of 15 mg/kg. Palivizumab is packaged in 100- and 50-mg vials, and opened vials must be used within 6 hours. Currently, palivizumab for intramuscular injection is available only as a lyophilized powder that is reconstituted with sterile water (that does not contain a preservative); a liquid formulation of palivizumab for intramuscular injection may be available in the future. RSV-IGIV is administered intravenously at a dosage of 750 mg/kg (15 mL/kg).

Either RSV-IGIV or palivizumab is administered once per month (eg, every 30 days) beginning just before the onset of the RSV season, which typically occurs in November but may vary by region. In general, 4 subsequent monthly doses (for a total of 5 doses) are sufficient to provide protection during the entire RSV season. Hospitalized infants determined to be at risk of severe RSV disease should receive RSV-IGIV or palivizumab 48 to 72 hours before discharge home from the hospital during the respiratory virus season and then every 30 days until the end of the season.

RSV IMMUNOPROPHYLAXIS AND VACCINE ADMINISTRATION

Palivizumab does not interfere with vaccine administration. For infants and children receiving RSV-IGIV prophylaxis, immunization with measles-mumps-rubella and varicella vaccines should be deferred for 9 months after the last dose. (see table 3.33 on p. 423 of the 2003 *Red Book*⁴). No data exist on the use of RSV-IGIV and the response to hepatitis B vaccine, but there is no reason to anticipate interference. RSV-IGIV use should not alter the primary immunization schedule for inactivated vaccines (eg, diphtheria and tetanus toxoids and acellular pertussis, *Haemophilus influenzae* type b conjugate, and inactivated poliovirus vaccines). The manufacturer of RSV-IGIV has suggested that an additional dose of vaccine might be needed to ensure an adequate immune response to diphtheria and tetanus toxoids and acellular pertussis, *H influenzae* type b, and oral poliovirus vaccines (refer to the RespiGam package insert), but available data do not support the need for supplemental doses of routinely administered vaccines.

COST-BENEFIT ANALYSES

Several economic analyses of RSV immunoprophylaxis have been published and reviewed. The primary benefit of immunoprophylaxis with either agent is a decrease in the rate of RSV-associated hospitalization. None of the 5 randomized, controlled clinical trials have demonstrated a significant decrease in rate of mortality attributable to RSV infection in infants who receive prophylaxis. Most of the economic analyses fail to demonstrate overall savings in health care dollars because of the high cost if all at-risk children were to receive prophylaxis. Estimates of cost per hospitalization prevented have been inconsistent because of considerable variation in the baseline rate of hospitalization attributable to RSV in different high-risk groups. Other considerations that will influence results include the effect of prophylaxis on outpatient costs and a resolution of the question of whether prevention of RSV infection in infancy decreases wheezing and lower respiratory tract problems later in childhood.

Factors other than degree of prematurity, CHD, and CLD that may influence the decision regarding prophylaxis include presence of other underlying conditions that predispose to respiratory complications (eg, neurologic disease in very low birth weight infants), number of young siblings, child care center

attendance, anticipation of cardiac surgery, and distance to and availability of hospital care for severe respiratory illness. For many infants who qualify for the approved indications, risk of hospitalization for serious respiratory illness will be low, and the cost and logistic difficulties associated with prophylaxis may outweigh potential benefits.

UPDATED RECOMMENDATIONS FOR RSV PROPHYLAXIS

1. Palivizumab or RSV-IGIV prophylaxis should be considered for infants and children younger than 2 years with CLD who have required medical therapy (supplemental oxygen, bronchodilator, diuretic or corticosteroid therapy) for CLD within 6 months before the anticipated start of the RSV season. Palivizumab is preferred over RSV-IGIV for most high-risk children because of its ease of administration, safety, and effectiveness. (Evidence grade I*.)
 - Patients with more severe CLD may benefit from prophylaxis during a second RSV season if they continue to require medical therapy for pulmonary or cardiac dysfunction. Individual patients may benefit from decisions made in consultation with neonatologists, pediatric intensivists, pulmonologists, or infectious disease specialists. There are limited data regarding the effectiveness of palivizumab during the second year of life, although children with CLD or CHD who require ongoing medical therapy may experience severe RSV infections.
2. Infants born at 32 weeks' gestation or earlier may benefit from RSV prophylaxis even if they do not have CLD. For these infants, major risk factors to consider include their gestational age and chronological age at the start of the RSV season. (Evidence grade I.)
 - Infants born at 28 weeks' gestation or earlier may benefit from prophylaxis during their first RSV season whenever that occurs during the first 12 months of life. Infants born at 29 to 32 weeks' gestation may benefit most from prophylaxis up to 6 months of age. For the purpose of this recommendation, 32 weeks' gestation refers to an infant born on or before the 32nd week of gestation (ie, 32 weeks, 0 days). Once a child qualifies for initiation of prophylaxis at the start of the RSV season, administration should continue throughout the season and not stop at the point an infant reaches either 6 or 12 months of age.
3. Although palivizumab and RSV-IGIV have been shown to decrease the likelihood of hospitaliza-

* Evidence grade I: evidence obtained from at least one properly designed, randomized, controlled trial.

Evidence grade II-1: evidence obtained from well-designed controlled trials without randomization; Evidence grade II-2: evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one center or research group; Evidence grade II-3: evidence obtained from multiple time series with or without the intervention, or dramatic results in uncontrolled experiments.

Evidence grade III: opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.

tion for infants born between 32 and 35 weeks of gestation (ie, between 32 weeks, 1 day, and 35 weeks, 0 days) (Evidence grade I), the cost of administering prophylaxis to this large group of infants must be considered carefully.

- Most experts recommend that prophylaxis be reserved for infants in this group who are at greatest risk of severe infection and who are younger than 6 months at the start of the RSV season. Epidemiologic data suggest that RSV infection is more likely to lead to hospitalization for these infants when the following risk factors are present: child care attendance, school-aged siblings, exposure to environmental air pollutants, congenital abnormalities of the airways, or severe neuromuscular disease. However, no single risk factor causes a very large increase in the rate of hospitalization, and the risk is additive as the number of risk factors for an individual infant increases. Therefore, prophylaxis should be considered for infants between 32 and 35 weeks' gestation only if 2 or more of these risk factors are present.
 - Exposure to tobacco smoke is a risk factor that can be controlled by the family of an infant at increased risk of RSV disease, and tobacco smoke control measures will be far less costly than palivizumab prophylaxis. High-risk infants never should be exposed to tobacco smoke. High-risk infants should be kept away from crowds and from situations where exposure to infected individuals cannot be controlled.
 - Participation in child care should be restricted during the RSV season for high-risk infants whenever feasible. Parents should be instructed on the importance of careful hand hygiene.
 - All high-risk infants and their contacts should be immunized against influenza beginning at 6 months of age.
4. Prophylaxis against RSV should be initiated just before the onset of the RSV season and terminated at the end of the RSV season. In most seasons and in most regions of the Northern Hemisphere, the first dose of palivizumab should be administered at the beginning of November, and the last dose should be administered at the beginning of March, which will provide protection into April.⁵ (Evidence grade III.)
 - To understand the epidemiology of RSV in their area, physicians should consult with local health departments or diagnostic virology laboratories or the Centers for Disease Control and Prevention if such information is not available locally. Decisions about the specific duration of prophylaxis should be individualized according to the duration of the RSV season. Pediatricians may wish to use RSV hospitalization data from their own region to assist in the decision-making process.
 5. Children who are 24 months or younger with hemodynamically significant cyanotic and acya-

notic CHD will benefit from 5 monthly intramuscular injections of palivizumab (15 mg/kg). (Evidence grade I.)

- Decisions regarding prophylaxis with palivizumab in children with CHD should be made on the basis of the degree of physiologic cardiovascular compromise. Infants younger than 12 months with CHD who are most likely to benefit from immunoprophylaxis include:
 - i. infants who are receiving medication to control congestive heart failure;
 - ii. infants with moderate to severe pulmonary hypertension; and
 - iii. infants with cyanotic heart disease.
- Because a mean decrease in palivizumab serum concentration of 58% was observed after surgical procedures that use cardiopulmonary bypass, for children who still require prophylaxis, a postoperative dose of palivizumab (15 mg/kg) should be considered as soon as the patient is medically stable.

The following groups of infants are not at increased risk from RSV and generally should not receive immunoprophylaxis:

- infants and children with hemodynamically insignificant heart disease (eg, secundum atrial septal defect, small ventricular septal defect, pulmonic stenosis, uncomplicated aortic stenosis, mild coarctation of the aorta and patent ductus arteriosus)
- infants with lesions adequately corrected by surgery unless they continue to require medication for congestive heart failure
- infants with mild cardiomyopathy who are not receiving medical therapy

Dates for initiation and termination of prophylaxis should be based on the same considerations as for high-risk preterm infants. Unlike palivizumab, RSV-IGIV is contraindicated in children with cyanotic CHD.

6. Palivizumab or RSV-IGIV prophylaxis has not been evaluated in randomized trials in immunocompromised children. Although specific recommendations for immunocompromised patients cannot be made, children with severe immunodeficiencies (eg, severe combined immunodeficiency or severe acquired immunodeficiency syndrome) may benefit from prophylaxis. If these infants and children are receiving standard IGIV monthly, physicians may consider substitution of RSV-IGIV during the RSV season. (Evidence grade III.)
7. Because RSV-IGIV and palivizumab are not effective in the treatment of RSV disease, neither is licensed for this indication. (Evidence grade I.)
8. Limited studies suggest that some patients with cystic fibrosis may be at increased risk of RSV infection. However, there are insufficient data to determine the effectiveness of palivizumab use in this patient population.
9. If an infant or child who is receiving immunoprophylaxis experiences a breakthrough RSV infection, prophylaxis should continue through the RSV season. (Evidence grade III.)

- This recommendation is based on the observation that high-risk infants may be hospitalized more than once in the same season with RSV lower respiratory tract disease and the fact that more than one RSV strain often cocirculates in a community.
10. Physicians should arrange for drug administration within 6 hours after opening a vial, because this product does not contain a preservative.
 11. Recommendations cannot be made regarding the use of palivizumab as a means of prevention of nosocomial RSV disease.
 - RSV is known to be transmitted in the hospital setting and to cause serious disease in high-risk infants. In high-risk hospitalized infants, the major means to prevent RSV disease is strict observance of infection control practices including the use of rapid means to identify and isolate RSV-infected infants. If an RSV outbreak is documented in a high-risk unit (eg, pediatric intensive care unit), primary emphasis should be placed on proper infection control practices, especially hand hygiene.
 12. Palivizumab does not interfere with the response to vaccines. Infants and children receiving prophylaxis with RSV-IGIV should have immunization with measles-mumps-rubella and varicella vaccines deferred for 9 months after the last dose of RSV-IGIV.
 - The use of RSV-IGIV should not alter the primary immunization schedule for other recommended immunizations. Available data at this time do not support the need for supplemental doses of any of these routinely administered vaccines.

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