Respiratory syncytial virus (RSV) immune globulin and palivizumab for prevention of RSV infection

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The treatment and prevention of viral infections is a significant public health issue. Respiratory syncytial virus (RSV), an enveloped RNA virus, is responsible for most upper and lower respiratory-tract infections, such as bronchiolitis and pneumonia, in infants and children less than two years of age. Transmission of the virus occurs through direct contact with contaminated air particles and through contact with secretions or contaminated surfaces. Exposure is often underestimated, since viral shedding may occur one to two days before the onset of symptoms and persists for up to two weeks thereafter. Emphasis on hand washing and preventive measures, such as elimination of passive smoke exposure, limiting exposure to infected individuals, and avoiding crowded conditions, may decrease transmission of the virus.

Although RSV infection is generally a mild self-limiting disease in most populations, certain populations are at increased risk of developing severe debilitating disease. Patients at increased risk include those with bronchopulmonary dysplasia, those with congenital heart disease, those with a history of apnea or respiratory arrest, immunocompromised patients, those with pulmonary consolidation on chest radiography, and those born prematurely. American Academy of Pediatrics guidelines do not preferentially recommend use of either agent; each has advantages and disadvantages. Prophylactic therapy with RSV-IGIV or palivizumab may reduce the likelihood of RSV infection in high-risk patients.

Abstract. The efficacy, safety, administration, and advantages and disadvantages of respiratory syncytial virus (RSV) immune globulin and palivizumab for preventing RSV infection are discussed.

Prevention of RSV infection has attracted considerable attention because of its clinical and economic impact. Studies have shown respiratory syncytial virus immune globulin intravenous (RSV-IGIV) and palivizumab to be effective in decreasing the number of hospitalizations and hospital days attributable to RSV. The number of intensive-care-unit admissions and the severity of RSV infection in high-risk children decreased with the use of these agents. Both agents have been well tolerated, with few adverse effects; however, their high cost necessitates strict guidelines on use. The patient populations at greatest risk are those with bronchopulmonary dysplasia, those with congenital heart disease, those with a history of apnea or respiratory arrest, immunocompromised patients, those with pulmonary consolidation on chest radiography, and those born prematurely. American Academy of Pediatrics guidelines do not preferentially recommend use of either agent; each has advantages and disadvantages.
Infections during RSV season are increased because of illness in the hospital staff and may be reduced by appropriate infection-control measures.

The clinical and economic impact of RSV worldwide has led to considerable research on its prevention and treatment. Vaccine development has been complicated by the limited ability of infants to develop an immune response and by the presence of maternal neutralizing antibodies, which may attenuate an active immune response in a vaccinated infant. In the 1960s, a formalin-inactivated vaccine was developed to combat RSV, but the vaccine resulted in increased mortality and morbidity in infants because of a reaction to the formalin component. Studies in infants unaffected by RSV showed that infants acquiring high titer of serum neutralizing antibody transplacentally remained free from RSV infection for longer intervals than infants acquiring lower titers. The subsequent pursuit of passive immunization led to the development of two medications, respiratory syncytial virus immune globulin intravenous (RSV-IGIV; RespiGam, Massachusetts Public Health Biologic Laboratories and M edimmune, Inc., Gaithersburg, MD) and palivizumab (Synagis, M edimmune). It is important to note that these agents have not been effective in the treatment of RSV infection and are not labeled for that indication.

**RSV-IGIV**

RSV-IGIV received marketing approval by FDA in January 1996 for the prevention of RSV infections. It is a sterile human immunoglobulin derived from pooled adult plasma containing high titers of neutralizing antibodies to RSV and has a low risk of transmission of known blood-borne pathogens because of solvent detergent viral inactivation.

The RSV-neutralizing antibodies of RSV-IGIV are directed mainly against two RSV surface glycoproteins, F and G, that protrude from the RSV envelope. These glycoproteins are responsible for adherence of RSV to the respiratory lining and subsequently cause infection.

**Efficacy and safety.** Numerous trials have evaluated the safety and efficacy of RSV-IGIV for the prophylaxis of RSV infection. Two of the most prominent studies are discussed below.

The PREVENT Study Group conducted a randomized, double-blind, placebo-controlled, multicenter trial that evaluated the safety and efficacy of RSV-IGIV prophylaxis in 510 patients with BPD (diagnosed by a neonatologist or pulmonologist) requiring supplemental oxygen in the past six months or premature delivery (<35 weeks of gestation). Patients were excluded if they were being treated with mechanical ventilation at the time of randomization, had an active or recent RSV infection, had known immunoglobulin A (IgA) deficiency or immunodeficiency, had suffered a reaction to blood products within two months, or had a known renal impairment.

The investigators found that, compared with the placebo group, the RSV-IGIV group had 41% fewer hospitalizations related to RSV infection (p = 0.047) and 53% fewer days of hospitalization (p = 0.045). The difference in costs related to these outcomes was not reported. Differences between groups in total days of intensive-care-unit (ICU) care or mechanical ventilation for RSV infection were not significant. Correlations between RSV-IGIV administration and improved outcomes in patients with BPD and age greater than six months and in infants weighing less than 4.3 kg were noted. Compliance, defined as patients receiving four or five infusions during the 1994–95 season, was similar for the placebo and RSV-IGIV groups (94% and 95%, respectively). Occurrences of rash and otitis media in the two groups were comparable, but patients receiving RSV-IGIV had fever more frequently, and 13% of patients with BPD required diuretics to treat fluid accumulation in the lungs.

The other trial, by Groothuis et al., was a placebo-controlled, randomized, multicenter study of the frequency and severity of RSV infection in 249 children and infants less than 48 months of age with (1) congenital heart disease or cardiomyopathy, (2) BPD, or (3) premature delivery (≤35 weeks of gestation) and a chronological age of less than 6 months. Patients were excluded if they had poorly controlled heart disease or renal failure, were ventilator dependent, were expected to survive less than six months, or were immunodeficient. Enrollment of patients was unblinded; however, a separate blinded team was responsible for weekly monitoring and surveillance. Patients were randomized to receive RSV-IGIV (high dose = 750 mg/kg via two-hour infusion monthly, low dose = 150 mg/kg via one-hour infusion monthly) or no RSV-IGIV (placebo) during the 1992–93 RSV season.

Compared with the control group, RSV-IGIV recipients had 48% fewer lower-respiratory-tract infections of any type, and moderate to severe infections were reduced by 62%. Reductions in the frequency of RSV lower-respiratory-tract infections and hospitalizations related to RSV were greatest in RSV-IGIV recipients with BPD and those who were born prematurely. The study did not have the statistical power to identify significant risk factors for RSV infection, but study center, male sex, number of people in the household, and recent RSV infection were related to RSV infection frequency and severity.

Adverse effects reported by Groothuis et al. were minor (e.g., mild fluid accumulation in 3% of patients and decreases in oxygen saturation, which responded to reducing the in-
fusion rate). Diuretics may reduce the frequency of respiratory distress related to fluid overload. As with other immunoglobulin preparations, RSV-IGIV may interfere with the immune response to live virus vaccines; thus, readministration of such vaccines is recommended by the manufacturer. Other reactions associated with RSV-IGIV have included fever and rash.

Administration. RSV-IGIV is available as a multidose vial (50 mg of immune globulin per milliliter) containing mainly IgG and trace amounts of IgA and IgM. A dose of 750 mg/kg (15 mL/kg) is administered every month by intravenous infusion throughout the RSV season, which is dependent on geographic location. Initiation of prophylaxis should begin by October or November at the latest in most locations in the Northern Hemisphere. Administration of RSV-IGIV requires an infusion lasting three to four hours, as well as concurrent monitoring of vital signs and oxyhemoglobin saturation to ensure tolerance and safety.

Palivizumab

Palivizumab, the humanized monoclonal antibody genetically engineered from mouse monoclonal antibodies, was approved for marketing by the FDA in June 1998 and addresses the administration and safety concerns noted with RSV-IGIV. This agent recognizes the F glycoprotein of RSV, decreases fusion to the host cell, and thus neutralizes viral activity. The F glycoprotein is conserved among the two major strains of RSV, A and B. This conservation is believed to decrease the development of resistant strains seen with RSV-IGIV; however, further study is required.

Efficacy and safety. IM pAct-RSV, a randomized, double-blind, placebo-controlled trial, was conducted at various centers throughout the United States, the United Kingdom, and Canada to determine the safety and efficacy of palivizumab for patients at increased risk of RSV infection. The 1502 patients who participated in the study were (1) born at ≤35 weeks of gestation and were ≤6 months of age or (2) ≤24 months old with a diagnosis of BPD. Patients were excluded if they were presently hospitalized and had an expected hospitalization time of ≥30 days or if they required mechanical ventilation at the time of entry. Patients who suffered from hepatic or renal dysfunction, seizure disorder, or immunodeficiency or who received immunoglobulins within the past three months were excluded from the study. In addition, those patients who previously received monoclonal antibodies, were exposed to experimental drugs, or were afflicted by a condition that decreased life expectancy to six months or less were excluded.

Compared with the control group, the palivizumab recipients had 55% fewer hospitalizations caused by RSV (p = 0.00004) and fewer total hospital days per 100 children (p = 0.005). The supplemental oxygen needs, number of days with moderate to severe illness, and number of ICU admissions were smaller in the palivizumab than in the placebo group (all p < 0.001). The study also established that palivizumab protected against serious RSV infection regardless of BPD status, gestational age, or weight of a child at high risk. However, unlike RSV-IGIV therapy, palivizumab was not found to have any effect on hospitalizations due to non-RSV-related respiratory disease. Adverse effects associated with palivizumab included slight increases in erythema at the injection site and mild to moderate elevations in aspartate transaminase; however, these were not clinically significant because of their transient nature and did not occur significantly less frequently in the control group. Examination of the possible development of anti-palivizumab antibodies has been investigated, but further long-term and second-season studies are necessary.

Administration. Palivizumab is supplied as a sterile lyophilized powder. This powder is reconstituted with 1 mL of sterile water to produce a 100-mg/mL solution. No shaking should be performed during reconstitution, and at least 120 minutes should be allowed before drawing up the dose. The solution must be administered intramuscularly (i.m.) in the anterolateral area of the thigh within six hours of reconstitution. A dose of 15 mg/kg (0.15 mL/kg) is administered i.m. every 28 days during the RSV season. The dose should be administered at least 48 hours before hospital discharge to achieve a serum concentration adequate to provide protection outside of the institution.

Guidelines for clinical use

In November 1998, the American Academy of Pediatrics (AAP) published guidelines reviewing the indications for which prophylaxis with RSV-IGIV or palivizumab should be considered. The guidelines should be supplemented by clinical judgment and consideration of patient-specific risk factors, such as BPD, gestational age of the patient and chronological age at start of RSV season,4 and underlying illness. In addition, social issues, such as passive smoke exposure, and environmental conditions, such as number of individuals residing in the household, may place patients at increased risk.

Listed below are the AAP guidelines for determining which patients may benefit from RSV prophylaxis with palivizumab or RSV-IGIV.

1. Patients less than two years of age whose chronic lung disease has required treatment within six months before RSV season should be considered candidates for prophylaxis. Those with more severe chronic lung disease requiring medical intervention may require therapy for two seasons.
2. It is recommended that infants born...
at <29 weeks of gestation receive prophylaxis up to 12 months of age and that those born at 29–32 weeks of gestation receive prophylaxis up to 6 months of age. Institution-specific data on RSV hospitalizations should be taken into account when determining length of therapy.

3. Initiation of prophylaxis in patients born between 32 and 35 weeks of gestation is advocated only in the presence of additional risk factors, such as those listed above, because of the questionable cost:benefit ratio in other situations.

4. Prophylaxis is contraindicated in patients with cyanotic congenital heart disease. However, patients with acyanotic congenital heart disease (patent ductus arteriosus and ventricular septal defect) who meet one of the above criteria may benefit from prophylaxis.

5. At this time, explicit recommendations for prophylaxis in immunocompromised patients cannot be made from the available literature. The substitution of RSV-IGIV for IGIV monthly injections may be of benefit in this population, in particular among those suffering from myelosuppression secondary to chemotherapy or immunosuppression from therapy for organ transplantation. However, further studies are necessary before definitive recommendations can be given.

6. Initiation and termination of prophylaxis should be based on the virology data available at the county health department specific to the patient’s geographic location.

7. The use of prophylaxis in high-risk hospitalized infants has not been studied, so recommendations for routine prophylaxis should not be implemented. Emphasis should be placed on other preventive measures.

8. Lastly, special attention to the scheduling of immunizations is required if RSV-IGIV is chosen for prophylaxis.

**Therapeutic considerations**

The AAP guidelines do not preferentially recommend use of either agent. The high cost of prophylaxis has led to debate over the optimal agent and its role in the prophylaxis of RSV infection. To assist in the individualization of therapy, the advantages and disadvantages of using each agent are presented below.

**Advantages of RSV-IGIV.** Patients with immunosuppression secondary to chemotherapy or transplantation are at increased risk of severe RSV infection. Replacement of IGIV monthly with RSV-IGIV in the immunocompromised population during RSV season may provide the added benefit of respiratory pathogen coverage without an increase in administration time; however, there is a significant increase in costs.

It has been estimated that 9.3 million episodes of acute otitis media (AOM) occur among U.S. children during the first two years of life. RSV may be responsible for AOM infections. RSV-IGIV contains antibodies to RSV and provides protection against other pathogens implicated in AOM, as well as against non-RSV respiratory illness caused by organisms like Haemophilus influenzae and Streptococcus pneumoniae. Investigators have noted that high doses of RSV-IGIV appear to decrease the frequency of AOM in patients at increased risk of RSV by decreasing the prevalence of both RSV-related and non-RSV-related AOM. A decrease in the frequency of hospitalizations for non-RSV respiratory illness has been observed in patients receiving RSV-IGIV. Thus, patients at high risk of RSV infection may benefit from additional coverage against other respiratory pathogens. However, prospective studies are necessary to evaluate the effect of RSV-IGIV on the frequency of AOM.

**Disadvantages of RSV-IGIV.** Ease of administration is a primary consideration in the selection of prophylactic therapy. RSV-IGIV must be given by slow (about three hours) intravenous infusion. Thus, intravenous access and the time and cost of giving the infusions pose difficulties. The fluid volume required for administering the dose and the cost of any additional measures, such as diuretics and slowing of infusion, that may be necessary in patients with pre-existing lung disease, should be considered. Difficulty of administration may lead to decreased compliance and, eventually, increased health care costs.

Because production of RSV-IGIV depends on the availability of donors, shortages in the supply may result in an insufficient reserve to satisfy the demand and may ultimately affect patient care.

There are no reports of transmission of blood-borne pathogens with RSV-IGIV. However, products derived from pooled human plasma may place patients at increased risk of transmission of yet unidentified blood-borne pathogens. Procedures to inactivate blood-borne pathogens, such as precipitation and solvent detergent procedures, have been implemented to reduce such risk.

RSV-neutralizing antibodies are directed mainly against two RSV surface glycoproteins, F and G, that protrude from the RSV envelope. The G glycoprotein may not be well conserved over time between RSV strains A and B, and thus resistance may develop.

In one study, increased morbidity and mortality were found in patients with cyanotic congenital heart disease who received RSV-IGIV. It is believed that the increased viscosity of the blood due to the higher hemoglobin concentrations compromised cardiac function. FDA has not approved either agent for the prophylaxis of RSV infection in patients with cyanotic congenital heart disease.

Finally, altering the immunization schedule and requirements must be considered when administering RSV-IGIV. Administration of mumps-
measles–rubella and varicella vaccines should be deferred for nine months after the last dose of RSV-IGIV. An additional dose may be necessary for adequate coverage with diphtheria and tetanus toxoids, whole-cell or acellular pertussis, H. influenzae type b, and poliovirus vaccines (inactivated or oral poliovirus) to ensure adequate response.11

Advantages of palivizumab. The availability of an i.m. injection decreases administration time and personnel needs, eliminates the requirement of i.v. access, and decreases the amount of fluid to be administered.18 Ease of administration would increase availability at office, clinic, and home and make monthly administration more convenient to patients and caregivers during RSV season.

Palivizumab does not interfere with vaccine administration schedules or alter published recommendations for vaccine administration. Through the initiation of administration clinics and the use of single vials for multiple patients, waste could be decreased and the costs of therapy thus reduced. Many institutions have established such administration measures; however, present packaging does not conduce re entry of the vial.12

Palivizumab is a humanized monoclonal antibody; thus, the risk of transmission of unidentified blood-borne pathogens is eliminated.

Supply is not influenced by donor accessibility.

Disadvantages of palivizumab. The use of palivizumab for second-season prophylaxis has yet to be evaluated. Concern about the development of viral resistance was raised because anti-palivizumab binding was noted; however, binding was not associated with a pattern of specific adverse events or alteration in palivizumab concentrations.17,18 Consequently, advocating palivizumab for second-season prophylaxis and interchangeability of agents from the first season to the next must be addressed.

Once reconstituted, the product must be administered within six hours.12 If single vials are to be used for multiple patients at an institution, careful coordination of dose times is required.

Palivizumab is available only as a single-dose vial from the manufacturer; thus, multiple entries into the vial are not recommended.12 However, many institutions, in an effort to consolidate administration and decrease waste, have established a practice whereby multiple patients who are due for a dose are given palivizumab during one of a few predetermined sessions (typically scheduled weekly or biweekly). The issue of reimbursement for such action must be addressed, and the amount charged to the payer should be carefully evaluated to avoid overcharging.

Mild to moderate elevations in aspartate transaminase have been noted with palivizumab therapy.16 These increases were not considered to be substantial by the blinded investigator and did not require the patients to discontinue therapy.

Palivizumab use does not offer protection against infection due to respiratory pathogens other than RSV.16 The frequency of hospitalization due to non-RSV-related infections and of AOM has not decreased with palivizumab use.13,23 This difference between RSV-IGIV and palivizumab is most likely attributable to the fact that palivizumab contains antibodies to RSV only.16

Should prophylaxis be used? The decision to provide prophylaxis to a patient is dependent on numerous factors. Current AAP guidelines serve as a basis for determining patients at risk.17 Therapy should be individualized to the patient, and institution-specific variables, such as length and initiation of the RSV season, should be considered. In most patient populations at risk of severe RSV infection (e.g., premature infants5 and patients with BPD8), palivizumab would provide adequate and accessible prophylaxis. In patients already receiving IGIV, the initiation of RSV-IGIV may provide greater coverage against RSV and other respiratory pathogens without increasing demands on the family.19,20 Trials comparing palivizumab and RSV-IGIV are required to determine their specific role in RSV prophylaxis.

The cost of therapy—and strategies for reducing waste—are bound to influence decisions about these agents. The average wholesale price of RSV-IGIV (monthly dose, 750 mg/kg) is $428 for a 1000-mg vial and $717.57 for a 2500-mg vial.24 Palivizumab (monthly dose, 15 mg/kg) has an average wholesale price of $1216.58 for a 100-mg vial. Thus, the doses themselves are expensive and so is discarding unused portions of the single-dose vials.

Conclusion

Prophylactic therapy with RSV-IGIV or palivizumab may reduce the likelihood of RSV infection in high-risk patients.

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