AMERICAN ACADEMY OF PEDIATRICS

TECHNICAL REPORT

H. Cody Meissner, MD; Sarah S. Long, MD; and the 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 respiratory syncytial virus (RSV) infections in high-risk infants, children younger than 24 months with chronic lung disease (formerly called bronchopulmonary dysplasia), and certain preterm infants. This report summarizes the clinical trial information on which the guidance in the accompanying policy statement for administering RSV prophylaxis to certain children with a history of preterm birth, chronic lung disease, or congenital heart disease is based. On the basis of results of a recently completed clinical trial, 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.

ABBREVIATIONS. RSV, respiratory syncytial virus; RSV-IGIV, Respiratory Syncytial Virus Immune Globulin Intravenous; CLD, chronic lung disease; CHD, congenital heart disease; BPD, bronchopulmonary dysplasia; ICU, intensive care unit.

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 BPD]) 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, immunoprophylaxis should be reserved for use in infants and children at greatest risk of severe RSV infection because of the high cost of this intervention.

The guidance in this report does not indicate an exclusive course of treatment or serve as a standard of medical care. Variations, taking into account individual circumstances, may be appropriate.

BACKGROUND

RSV-IGIV (RespiGam, Massachusetts Public Health Biological Laboratories and MedImmune Inc, Gaithersburg, MD) was licensed by the Food and Drug Administration in January 1996 for prevention of severe RSV lower respiratory tract disease in infants and children younger than 24 months with CLD or a history of preterm birth (≤35 weeks' gestation). Two randomized, controlled clinical trials demonstrated that monthly RSV-IGIV infusions in high-risk infants resulted in a 41% to 63% decrease in the rate of hospitalization attributable to RSV infection of the lower respiratory tract.[1,2] Although this was the first agent with demonstrated efficacy for prophylaxis against RSV infections of the lower respiratory tract, several disadvantages are associated with this product. RSV-IGIV is contraindicated for use in children with hemodynamically significant heart disease, particularly cyanotic heart disease, because of safety concerns detailed later in this report. Further, RSV-IGIV prophylaxis requires intravenous access with a 4-hour infusion each month during the RSV season and infrequently presents problems with volume overload. Immune Globulin Intravenous is known to interfere with the immune response to some live-virus vaccines. Although no issues of contamination with adventitious agents have been encountered, this is a theoretic concern. Finally, shortages of RSV-IGIV occurred during 2 RSV seasons.

In June 1998, the Food and Drug Administration

licensed palivizumab (Synagis, MedImmune, Gaithersburg, MD) for administration as a monthly intramuscular injection for the prevention of serious respiratory disease caused by RSV in infants and children with a history of preterm birth (≤35 weeks' gestation) or CLD. Approval was based on results of a randomized, placebo-controlled trial (IMpact-RSV trial) that demonstrated a 55% decrease in the rate of hospitalization among children with a history of preterm birth and/or CLD.[3] A second trial with palivizumab has been completed in infants and children with hemodynamically significant CHD that demonstrated safety and a 45% decrease in the rate of RSV-associated hospitalization compared with placebo recipients.[4] Because palivizumab is not derived from Human Immune Globulin, it is free of potential contamination by infectious agents. It can be produced readily in batch lots, and therefore shortages are not anticipated. Palivizumab will not interfere with the immune response to any vaccine in the immunization schedule. Thus, palivizumab has become the agent of choice for monthly prophylaxis in most high-risk infants. Recommendations for the use of both products have been summarized by the American Academy of Pediatrics.[5,6] The purpose of this report is to update clinicians on the appropriate use of RSV-IGIV and palivizumab on the basis of data from 5 clinical trials.

CLINICAL STUDIES WITH RSV-IGIV

Results of the first multicenter randomized controlled trial with prophylactic RSV-IGIV in infants younger than 48 months at enrollment with underlying BPD, CHD, or a history of preterm birth (≤35 weeks' gestation) are shown in Table 1.[1] Eighty-one infants received RSV-IGIV at a dosage of 750 mg/kg per infusion, 79 infants received 150 mg/kg, and 89 infants received no infusions. Participants in the intervention arms received monthly RSV-IGIV infusions from mid-November through March or April; at least 75% of the dose was infused at 85% of the visits. Infants receiving RSV-IGIV at a dosage of 750 mg/kg had significantly decreased RSV-associated lower respiratory tract disease severity, frequency of hospital admissions, and number of days in the hospital or intensive care unit (ICU). Monthly RSV-IGIV infusions were well tolerated. Serum RSV-neutralizing antibody titers in infants receiving RSV-IGIV at a dosage of 750 mg/kg usually exceeded 1:200, a titer close to the threshold required for protection in animals. Adverse reactions occurred in 3% of 580 infusions and consisted of mild decreases in oxygen saturation, fever, and mild fluid overload. Six deaths occurred (3 in the high-dose group and 3 in the low-dose group); none of the deaths were considered related to infusion of RSV-IGIV or to RSV infection, and 3 of the deaths were related to complications of cardiac surgery. Monthly RSV-IGIV infusions during the respiratory season resulted in a 63% and 82% decrease in the rate of RSV-associated hospitalization and disease severity, respectively. Patients benefiting most were preterm infants and infants with BPD.

Results from a second multicenter randomized albumin placebo-controlled trial (PREVENT study[2]) in 510 infants younger than 24 months with BPD and/or history of preterm birth are shown in Table 2. Monthly RSV-IGIV infusions decreased the RSV-associated illness frequency and severity by 41% to 60%. The decrease in the rate of RSV-associated hospitalization was greater for infants and children with BPD than for those with history of preterm birth only (49% vs 20%, respectively; Table 2). Moderate to severe adverse events consisting of fever, increased respiratory distress, and rash were no more frequent in patients receiving RSV-IGIV than in control patients. These adverse events were easily managed medically and did not occur with subsequent infusions. Of additional interest, children receiving RSV-IGIV had a 50% decrease in the rate of hospitalization for respiratory illness of any cause. In addition, recipients of high-dose RSV-IGIV experienced significantly fewer episodes of acute otitis media than did children in the control group.[7]

RSV-IGIV USE IN PATIENTS WITH CHD

Two trials with RSV-IGIV included infants and children with CHD.[1,8] As part of the initial National Institutes of Health-sponsored RSV-IGIV trial, 87 infants with CHD were enrolled among 249 high-risk subjects. Results of this trial demonstrated an overall 63% decrease in the rate of RSV-associated hospitalization compared with the control group, but the trial was not powered for subgroup analysis, and thus the results for children with cardiac disease were not analyzed separately.[1] A second trial conducted in 1994–1995 evaluated 416 children younger than 48 months with CHD who were assigned to a group receiving monthly RSV-IGIV or a control

TABLE 1. RSV-IGIV Prophylaxis in High-Risk Infants*

Measurement	Control	High-Dose RSV-IGIV†	Reduction (%)	*P* Value
No. of children	89	81	—	—
RSV lower respiratory tract illness				
Any	22%	9%	62	.01
Moderate to severe	13%	4%	73	.03
Respiratory disease score	2.3	1.6	32	.01
Hospitalization	20%	7%	63	.02
Total hospital days per 100 children	144	53	63	.02
ICU admission	7%	1%	82	.12
Total ICU days per 100 children	38	1.2	97	.05

* Modified from Groothius et al.[1]
† 750 mg/kg infusion; low-dose (150 mg/kg) data in 79 patients are not shown.

TABLE 2. RSV-IGIV Prophylaxis Trial: The PREVENT Study*

Measurement	Placebo	RSV-IGIV	Reduction (%)	*P* Value
No. of children	260	250	—	—
RSV hospitalization (all children)	13.5%	8.0%	41	.047
Infants with BPD	17.4%	8.9%	49	†
Preterm infants without BPD	8.1%	6.5%	20	†
RSV hospital days per 100 patients	129	60	53	.045
RSV hospital days receiving oxygen per 100 children	85	34	60	.007
RSV hospital days with moderate or severe lower respiratory tract infection per 100 children	106	49	54	.049
Hospitalization for any respiratory illness	27%	16%	41	.005
Any respiratory illness hospital days per 100 children	317	170	46	.005
Moderate or severe adverse event	1.2%	2.4%	—	NS

NS indicates not significant.
* From the PREVENT Study Group. The data on RSV hospitalization rates in patients with BPD were used with permission (E. Connor, MD, written communication, November 1996).
† The study was not powered for subgroup analysis.

group.[8] Results showed a trend in RSV disease prevention that did not reach statistical significance. Interpretation of results in the second study was confounded by an unexplained difference in randomization between treatment and control groups, resulting in a significantly higher proportion of children with cyanotic CHD in the treatment group than in the control group. In both trials, an unexpected increase in surgically related adverse events, including mortality, in RSV-IGIV recipients occurred. Although the precise explanation for the increase in mortality in infants with cyanotic heart disease is unclear, it may have been caused by an alteration in blood viscosity after administration of RSV-IGIV to patients with an elevated hematocrit concentration. As a consequence of the concerns raised by these studies, RSV-IGIV is contraindicated for use in infants with severe CHD.

CLINICAL STUDIES OF EFFICACY OF PALIVIZUMAB

Primary Analysis

Two randomized, placebo-controlled trials with palivizumab have demonstrated safety and efficacy in high-risk infants and children.[3,4] In the IMpact-RSV trial, 1502 infants were enrolled in a multicenter, double-blind, randomized clinical trial of palivizumab (2:1 randomization, treated versus placebo group).[3] Beginning at the onset of the RSV season, 5 intramuscular injections (15 mg/kg) of palivizumab or placebo were administered at 30-day intervals. This dose was selected to maintain serum concentrations of palivizumab ≥30 μg/mL, a concentration that decreases pulmonary RSV replication in the cotton rat model by >100-fold.[9] Children eligible for participation in the clinical trial were younger than 24 months with CLD who required continuing medical therapy (supplemental oxygen, bronchodilator, diuretic, or corticosteroid therapy within the past 6 months) and children born at 35 weeks' gestation or less who were younger than 6 months at the start of the RSV season. The primary endpoint was efficacy of prophylaxis in decreasing the incidence of hospitalization for RSV infections. Secondary endpoints included the total number of hospital days attributable to RSV and other respiratory viruses, days of moderate to severe lower respiratory tract infection, days of ICU management, days of mechanical ventilation, and incidence of otitis media.

One hundred thirty-nine sites in the United States, Canada, and the United Kingdom participated in the IMpact-RSV trial. Placebo and prophylaxis groups were matched at study entry for demographics and RSV infection risk factors (ie, preterm birth or CLD). Prophylaxis resulted in a 55% overall decrease in the rate of RSV-related hospitalization (10.6%–4.8% in placebo versus palivizumab recipients, respectively [$P < .001$]; Table 3). Differences in rates of hospitalization between placebo and prophylaxis groups were similar in different geographic regions. These rates were 10.3% for prophylaxis compared with 4.6% for placebo groups in the United States, 14.7% for prophylaxis compared with 8.8% for placebo groups in Canada, and 10.3% for prophylaxis compared with 3.6% for placebo groups in the United Kingdom.

The number of days of hospitalization for RSV infection per 100 children was decreased from 62.6 for patients receiving placebo to 36.4 for those receiving palivizumab ($P < .001$). Clinical benefit was demonstrated for additional secondary endpoints including decreased requirement for supplemental oxygen, a decrease in the number of days of moderate or severe (illness severity score) lower respiratory tract illness per 100 children, and a decrease in the requirement for hospitalization in an ICU (Table 3). No significant differences were identified for the requirement of mechanical ventilation or in the incidence of otitis media. The mortality rate was low in both groups. Among placebo recipients, 5 children died (1.0%), compared with 4 children who received palivizumab (0.4%).

Differences in injection-related adverse events were not significant. Overall, the development of erythema, pain, and induration at the site of intramuscular injection occurred in 1.8% of placebo recipients and in 2.7% of infants receiving palivizumab. There were no significant differences in adverse event rates or in the appearance of antibodies to the monoclonal antibody.[10]

TABLE 3. RSV Prophylaxis With Palivizumab: Summary of IMpact-RSV Trial[3]

Measurement	Rates		Reduction (%)	*P* Value
	Placebo	Palivizumab		
RSV hospitalization	10.6%	4.8%	55	<.001
RSV hospitalization days per 100 children	62.6	36.4	42	<.001
RSV hospital days receiving oxygen per 100 children	50.6	30.3	40	<.001
Incidence of RSV ICU admissions	3.0%	1.3%	57	.026
ICU days per 100 children	12.7	13.3	—	NS
Mechanical ventilation	0.2%	0.7*	—	NS
Mechanical ventilation, total number of days	1.7	8.4	—	NS
All respiratory hospitalizations, %	22%	16%	27	.008
Respiratory hospital days per 100 children (includes RSV)	180	124	31	.004
Otitis media	40%	42%	—	NS
Deaths	1.0%	0.4%	—	NS

NS indicates not significant.
* Includes 3 infants who required prolonged ventilatory support.

Subgroup Analysis

Palivizumab decreased the severity of clinical illness in all subgroups evaluated (Table 4). Preterm infants without CLD had an overall 78% decrease in rate of hospitalization (8.1% in the placebo group vs 2.0% in the palivizumab group [$P < .001$]). Preterm infants with CLD had a 39% decrease in rate of hospitalization (12.8% in the placebo group vs 7.9% in the palivizumab group [$P = .038$]). In a retrospective subgroup analysis, a decrease in the rate of RSV-associated hospitalization from 10.0% in the placebo group to 1.8% in the palivizumab group was noted for children born between 32 and 35 weeks' gestation who did not have CLD (82% decrease [$P = .001$]).

CARDIAC TRIAL

A randomized, double-blind, placebo-controlled trial with palivizumab was conducted between 1998 and 2002 involving 1287 infants and children with hemodynamically significant CHD.[4] Subjects were randomized 1:1 to receive 5 monthly intramuscular injections of palivizumab (15 mg/kg) or placebo and stratified at entry by cardiac lesion to a cyanotic or noncyanotic group. Palivizumab recipients had a 45% decrease in the rate of RSV-related hospitalization (9.7% in the placebo group vs 5.3% in the palivizumab group [$P = .003$]). There was a 56% decrease in total days of RSV-associated hospitalization per 100 children ($P = .003$) and a 73% decrease in total RSV-associated hospital days with supplemental oxygen per 100 children ($P = .014$). Serious adverse events occurred in 63.1% of placebo recipients and 55.4% of palivizumab recipients ($P < .005$). No serious adverse events were related to palivizumab. There was not a significant difference in deaths between groups (3.7% in placebo recipients vs 3.3% in palivizumab recipients). No deaths were attributed to the study drug. After cardiac bypass surgery, the mean serum palivizumab concentration was decreased by 58%. The results of this study demonstrated safety and efficacy of monthly palivizumab immunoprophylaxis in infants and children with hemodynamically significant CHD.

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

TABLE 4. RSV Prophylaxis With Palivizumab: Summary of Subgroup Analysis of IMpact-RSV Study Trial[3]

Measurement	Placebo (%)	Palivizumab (%)	Reduction (%)	*P* Value
All respiratory hospitalizations	21.8	16.1	26	.008
RSV hospitalizations	10.6	4.8	55	<.001
Non-RSV hospitalizations	14.4	13.0		NS
All preterm infants				
With CLD ($n = 762$)	12.8	7.9	39	.038
Without CLD ($n = 740$)	8.1	1.8	78	<.001
Infants 32–35 weeks' gestation				
All ($n = 373$)	9.8	2.0	80	.002
Without CLD ($n = 335$)	10.0	1.8	82	.001
Infants <32 weeks' gestation ($n = 1111$)	11.0	5.8	47	.008
Infants >5 kg ($n = 617$)	10.7	5.2	51	.014
Infants ≤5 kg ($n = 885$)	10.5	4.5	57	.001

NS indicates not significant.

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 generally is favored over RSV-IGIV (an intramuscular injection vs a 4-hour intravenous infusion).

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.[11] In addition, limited experience from postmarketing data suggest 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.[11]

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.[12,13] 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.[11]

Palivizumab attaches to a well-conserved epitope in the A-antigenic site of the F protein of RSV.[9] 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.

COST-BENEFIT ANALYSES

Several economic analyses of RSV immunoprophylaxis have been published[14–20] and reviewed.[21] 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.

INDICATIONS FOR RSV PROPHYLAXIS

Detailed recommendations for RSV prophylaxis are available in the accompanying policy statement.[22]

Tonse Raju, MD, DCH
National Institutes of Health
Laura E. Riley, MD
American College of Obstetricians and Gynecologists
Kay M. Tomashek, MD
Centers for Disease Control and Prevention
Carol Wallman, MSN, RNC, NNP
National Association of Neonatal Nurses

STAFF
Jim Couto, MA

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