

AMERICAN ACADEMY OF PEDIATRICS' RSV PROPHYLAXIS GUIDELINES*

Briana Buckley, PharmD[†]ABSTRACT

Respiratory syncytial virus is a common disease in young children, affecting approximately 2 out of 3 children aged younger than 1 year and responsible for between 75 000 and 100 000 hospitalizations in each age group. With no safe, effective treatment, the goal is to prevent the disease in high-risk infants with the humanized monoclonal antibody palivizumab. A 3- to 5-injection course of immunoprophylaxis with palivizumab is expensive, which restricts its use to those most likely to be hospitalized. A recent policy statement from the American Academy of Pediatrics modified the recommendations for 3 or fewer doses of prophylaxis in infants born between 32 weeks and 34 weeks, 6 days. The criteria have been simplified to include infants with at least 1 of 2 risk factors: childcare attendance and/or a sibling aged younger than 5 years.

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Although respiratory syncytial virus (RSV) is a common disease in young children, affecting approximately 2 out of 3 children aged younger than 1 year and responsible for between 75 000 and 100 000 hospitalizations in that age group each year, there is no standard treatment protocol.¹

Most children recover without incident within 8 to 15 days.² However, children with chronic lung disease (CLD), congenital heart disease (CHD), or premature birth have a high risk of serious complications or even death.¹

Palivizumab is a humanized monoclonal antibody licensed in June 1998 for the prevention of serious lower respiratory tract disease caused by RSV in pediatric patients at high risk of the disease.³ Patients indicated for palivizumab are those born at or before 35 weeks of gestational age, with or without CLD or CHD.³

The efficacy of palivizumab was based on 2 pivotal multicenter, placebo-controlled, randomized clinical trials. The primary end point for each was the reduction of RSV-related hospitalization.^{4,5}

The IMPact-RSV trial showed that 5 doses of prophylaxis resulted in a 55% reduction in hospitalization rates in all infants, with statistically significant reductions in subpopulations of infants (Table 1).⁴ The study involved 1502 children with prematurity (≤ 35 weeks) or bronchopulmonary dysplasia (BPD; now called CLD) in the United States, United Kingdom, and Canada who were followed during the 1996 to 1997 RSV season. Patients were randomized to either an injection of palivizumab (15 mg/kg) or placebo once every 30 days for 5 months and followed for 30 days after the last injection. Most (99%) of the children in both groups completed the protocol and 93% received all 5 injections. Table 1 depicts the results. Children with prematurity but without BPD had a 78% reduction in RSV hospitalization (8.1% vs 1.8%); children with BPD had a 39% reduction (12.8% vs 7.9%).

The second study also included 5 monthly injections, but involved 1287 children with CHD and a mean age at entry of 6.8 months (palivizumab) and 6.5 months (placebo). This trial demonstrated a 45% relative reduction in RSV hospitalizations ($P = .003$),

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Table 1. IMpact-RSV Trial

	Placebo (n = 500)	Palivizumab (n = 1002)	Reduction
All infants, <6 mo (n = 1502)	10.6%	4.8%	55%
Infants with BPD, <24 mo (n = 762)	12.8%	7.9%	39%
Infants, <32 wk (n = 1111)	11%	5.8%	47%
Infants without BPD, <6 mo (n = 740)	8.1%	1.8%	78%
Preterm infants born at 32–35 wk (n = 373)	9.8%	2%	80%
Preterm infants without BPD born at 32–35 wk (n = 335)	10%	1.8%	82%

BPD = bronchopulmonary dysplasia; RSV = respiratory syncytial virus.
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a 56% reduction in total days of RSV hospitalization per 100 children ($P = .003$), and a 73% reduction in total RSV hospital days with increased supplemental oxygen per 100 children ($P = .014$) with similar rates of adverse events. None of the serious adverse events were related to palivizumab, nor were any of the deaths (21 in palivizumab group [3.3%] and 27 [4.2%] in the placebo group).⁵

No prospective, randomized clinical trial has demonstrated a significant decrease in the rate of mortality attributed to RSV or in the rate of recurrent wheezing among infants who receive prophylaxis.⁶

While effective, palivizumab is expensive. The wholesale acquisition cost in 2009 was \$955 per 50-mg (0.5-mL) vial and \$1802 per 100-mg (1-mL) vial, for a cost between \$4775 and \$9010 per season in infants receiving all 5 doses.⁷ Economic analyses vary widely depending on the country, cost of the drug, and population studied. One analysis found that the cost per avoided hospitalization associated with palivizumab immunoprophylaxis ranged from \$12 000 in the highest-risk infants to \$420 000 in lower-risk infants (1995 US dollars).⁸

The American Academy of Pediatrics (AAP) published a policy statement on the use of palivizumab in high-risk infants in November 1998.⁹ The statement was revised in December 2003¹⁰ and, most recently, in December 2009.¹¹

The most recent update was designed to ensure an optimal balance of benefit and cost from palivizumab. The group noted that optimal cost benefit is achieved during peak outbreak months, with initiation in November continuing for 5 monthly doses shown to provide protection through April in most parts of the United States.¹¹ It is important to note that trough serum concentrations of palivizumab continue well above the protective concentration more than 30 days after the fifth dose. Given that the typical RSV season lasts for 17 weeks, this provides up to 20 weeks of protection.¹¹

Most of the high-risk groups for which the AAP recommends prophylaxis have not changed since the 2003 recommendations¹¹:

- Infants and children aged younger than 24 months with CLD who received medical therapy for CLD within 6 months before the start of the RSV season
- Infants born 31 weeks, 6 days gestation or earlier even without CLD up to 6 months of age, and up to 12 months for those born 28 weeks gestation or earlier (although once begun, prophylaxis should continue throughout the RSV season regardless of infant age)
- Infants or children (age not specified) receiving medication for CHD, with moderate-to-severe pulmonary hypertension, or with cyanotic heart disease. A postoperative dose of palivizumab should be administered after surgical procedures using cardiopulmonary bypass for children who continue to require prophylaxis as soon as the patient is medically stable.
- Infants or young children (≤ 1 year) with congenital abnormalities of the airways or neuromuscular diseases that could compromise their ability to manage respiratory secretions. Clinicians are advised to confer with specialists to determine whether prophylaxis is required for children with cystic fibrosis.

New in the 2009 statement is a recommendation for prophylaxis in infants born between 32 weeks and 34 weeks, 6 days, with at least 1 identified risk factor. The recommendations are intended to reduce the risk of RSV hospitalization during the period of greatest risk (the first 3 months of life) in infants in this age group who either attend childcare and/or have a sibling who is younger than 5 years of age. Note that just 3 or fewer prophylactic doses are recommended for

Table 2. Maximum Number of Palivizumab Doses*

Month of Birth	28 wk, 6 d of Gestation and <12 mo of Age at Start of Season	29 wk, 0 d Through 31 wk, 6 d of Gestation and <6 mo of Age at Start of Season	32 wk, 0 d Through 34 wk, 6 d of Gestation and with Risk Factor
November 1– March 31 of previous RSV season	5	0	0
April	5	0	0
May	5	5	0
June	5	5	0
July	5	5	0
August	5	5	1
September	5	5	2
October	5	5	3
November	5	5	3
December	4	4	3
January	3	3	3
February	2	2	2
March	1	1	1

*Table based on an RSV season that starts November 1, which is representative of most of the United States but which may differ based on geographical locations.
RSV = respiratory syncytial virus.
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this group.¹¹ Table 2 depicts the maximum number of palivizumab doses based on the child's birth date, gestational age, and presence of risk factors.¹¹

The major difference between the new guidelines and the palivizumab labeling occurs in the recommendation for no more than 3 doses in infants born between 32 weeks and 34 weeks, 6 days. Given that palivizumab was evaluated based on 5 doses throughout the RSV season, the issue of age at the start of the season was not evaluated. Nor were risk factors such as childcare or sibling age considered. The new guidelines also do not consider the risk in infants born between 35 weeks and 35 weeks, 6 days gestation, although palivizumab was studied in infants born up to age 36 weeks.¹¹

The recommendations also note the importance of compliance with monthly administration. Such compliance can be improved with the use of home-based programs, as well as reduced exposure of high-risk children to infection.¹²

CONCLUSIONS

Although most children with RSV recover without incident, the disease is the leading cause of hospitalization among young children. The humanized monoclonal antibody palivizumab may be used as immunoprophylaxis to prevent RSV in high-risk infants. However, the high cost of the drug makes its widespread use unrealistic. To that end, the AAP provides guidelines for the appropriate use of palivizumab. The AAP updated these recommendations in late 2009. Changes include the recommendation for prophylaxis in infants born between 32 weeks and 34 weeks, 6 days with at least 1 identified risk factor. Risk factors include attendance at childcare and/or a sibling in the home who is younger than 5 years of age. It is important that pharmacists are familiar with the new guidelines so they can work with parents and clinicians to ensure that the most appropriate children receive prophylaxis.

DISCUSSION

Dr Rich: At what age is cystic fibrosis diagnosed? I do not think you will know it at birth. But is it something that shows up soon after birth?

Dr Buckley: We do see children who are younger than 2 years of age diagnosed with cystic fibrosis, so they are young.

Dr Rich: So you are saying that if they are diagnosed with cystic fibrosis within that age range, and typically it is younger than 6 months through the time they are maybe 2 years old, they should receive RSV prophylaxis? But in some cases, it may be pushed up to 2 or 3 years old for prophylaxis, depending on diagnosis?

Dr Buckley: Yes. Definitely up to 2 years old. Most of the data with prophylaxis are in children aged younger than 24 months. So that is kind of the imaginary line for the age break. But definitely, you start to see more in children who are aged 2 or 3 years when they have severe diseases.

Dr Rich: Briana, the AAP did not make any comment as far as the European data?

Dr Buckley: Nope. The only thing brought up was the Canadian data and it was just one sentence saying we looked at it and we did not think it was enough to use their validated tool.

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