



INLAND EMPIRE HEALTH PLAN

**Clinical Practice Guideline
Prevention of Respiratory Syncytial
Virus (RSV)**

Renewed November 2010

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INTRODUCTION

Respiratory syncytial virus (RSV) is the most common cause of lower respiratory tract infections in infants and children. It generally occurs in the fall, winter and early spring and is seen as a “cold” in infants and children with healthy immune systems. The average incubation period is 3 to 5 days after exposure to the virus. RSV disease generally begins as a simple upper respiratory tract infection, clear nasal secretions, mild cough and low-grade fever. It can progress to more severe cough, wheezing, subcostal and intercostal retraction and tachypnea at rest and serious respiratory infections (eg, pneumonia, bronchiolitis, respiratory failure) in infants and children with inadequate immune systems (eg, premature infants, children with bronchopulmonary dysplasia, congenital heart disease, congenital or acquired immunodeficiency and cystic fibrosis).¹⁻⁷ In the United States, over 90,000 children are hospitalized each year due to RSV disease and 4,500 die.^{1,3,8} The average cost of hospitalization is \$70,000.¹ Historically, the only way to prevent RSV disease was to prevent person-to-person transmission by observing good hand washing techniques and isolation procedures.⁹

Respiratory syncytial virus immune globulin intravenous (RSV-IGIV) is indicated for the prevention of serious lower respiratory tract infection caused by RSV in children under 24 months of age with bronchopulmonary dysplasia or a history of premature birth (\leq 35 weeks gestation). RSV-IGIV has reduced the incidence and duration of RSV hospitalization and the severity of RSV illness in these high-risk infants.¹⁰ The indications for RSV-IGIV recognized by the American Academy of Pediatrics (AAP) are:¹¹

- Infants and children less than 2 years of age who have bronchopulmonary dysplasia and are receiving or have received oxygen therapy in the 6 months before the next RSV season;
- Infants born at \leq 32 weeks gestation who do not have bronchopulmonary dysplasia or do not meet the above criterion;
- Infants with asymptomatic acyanotic congenital heart disease who have any of the above indications for prophylaxis, except infants with cyanotic congenital heart disease;
- Severely immunocompromised infants and children who receive monthly IGIV.

Palivizumab is the newest drug approved for the prevention of serious lower respiratory tract disease caused by RSV in high-risk pediatric patients.^{1,3,7,12} Both drugs are marketed by MedImmune, Inc. and neither agent is approved for the treatment of RSV infection.^{1,3,7,13} The AAP has identified the following as appropriate candidates for prophylaxis:¹⁴

- Infants younger than age 2 years who currently receive or have recently required medical therapy for chronic lung disease (CLD);
- Infants born at \leq 28 weeks' gestation who are \leq 12 months old at the start of the RSV season; and
- Infants born at 29 to 32 weeks who are \leq 6 months old at the start of the RSV season.

CLINICAL PHARMACOLOGY

RSV infection carries a high risk of morbidity and mortality in children less than 2 years of age, especially preterm infants less than 6 months old and young children with underlying pulmonary or cardiac disease or immunodeficiency. Preterm infants born at 28 weeks or less of gestation have lower levels of maternally transferred RSV antibody titers than other infants.^{6,15-19}

Maintenance of serum titers of respiratory syncytial virus-neutralizing antibody between 1:200 and 1:400 may prevent RSV infection in the lower respiratory tract.^{15,16,18,20} High circulating levels of maternally derived antibody protect against infection and severe disease during the first 2 to 4 months of life in term infants, while premature infants with low maternal antibodies have particularly severe RSV infection. This realization led to investigation of passively administered antibody for the prevention of RSV infection.^{16,21} A phase I study was conducted in which infants with moderate-to-severe bronchopulmonary dysplasia or congenital heart disease were treated with intravenous gamma globulin (IGIV) at doses of 500 to 750 mg/kg monthly. The IGIV had an RSV neutralizing antibody titer of 1:1100. Peak RSV titers ranging from 1:90 to 1:136 were achieved following the 750 mg/kg dose. These titers were higher than those achieved with 500 mg/kg and 600 mg/kg doses, but are still too low for prophylaxis against RSV infection.²² Titers necessary to prevent the development of RSV infection following administration of ordinary intravenous immune globulin are achieved only after enormous doses are given at frequent intervals.^{16,18,21}

A microneutralization assay has been used to identify plasma donors with high levels of protective RSV antibodies and to prepare a human RSV-IGIV. This screened immune globulin has a five-fold greater RSV neutralizing activity than standard immune globulin.^{16,19} Lyophilized human RSV-IGIV with titers ranging from 1:2400 to 1:8073 has been evaluated with favorable results.¹⁵ Trough serum titers among children treated with 750 mg/kg doses monthly generally exceeded 1:200, with mean trough serum RSV neutralization titers of 1:297 one month after the first infusion, 1:477 one month after the second infusion, 1:490 one month after the third infusion and 1:429 one month after the fourth infusion. The mean half-life of serum RSV neutralizing antibodies is 22 to 28 days.^{10,15} Commercially available RSV-IGIV (*RespiGam*) is an immunoglobulin G containing neutralizing antibody to RSV. It is obtained from purified pooled adult human plasma selected for high titers of neutralizing antibody against RSV and is treated with a solvent-detergent viral inactivation process to decrease the risk of transmission of bloodborne pathogens.¹⁰

Palivizumab is a humanized monoclonal antibody (IgG1κ) produced by recombinant DNA technology. The monoclonal antibody sequence is 95% human and 5% murine to reduce the risk of antibody formation. It works by binding to the “F” protein in the A antigenic site on the surface of the virus and preventing its ability to infect the cells.^{1,4-7,23-25} Administration of palivizumab results in a reduction in pulmonary RSV titer.^{25,26} Its activity against RSV titers is 50 to 100 times more than RSV-IGIV in *in vitro* models.^{7,26}

COMPARATIVE CLINICAL EFFICACY

Palivizumab

Earlier studies with palivizumab showed it was effective in lowering pulmonary RSV titers.^{5-7,26-}

³¹ The main randomized, double-blind, placebo controlled trial (IMPact-RSV trial) was conducted in the United States, Canada and the United Kingdom and enrolled 1,502 children between November 15 and December 13, 1996. The children were ≤ 24 months of age with bronchopulmonary dysplasia or children with premature birth (≤ 35 weeks gestation) who were ≤ 6 months of age at study entry. Each patient received five monthly intramuscular injections of placebo (n=500) or palivizumab 15 mg/kg (n=1,002). Hospitalization due to RSV disease occurred in 10.6% of those treated with placebo and 4.8% of those treated with palivizumab. This represented a 55% reduction ($p < 0.001$). The hospitalization rate for those with bronchopulmonary dysplasia was 12.8% and 7.9%, respectively, and 8.1% and 1.8% in those patients who were born premature without bronchopulmonary dysplasia. The incidence of admission to the ICU was 3% and 1.3%, respectively, but the duration of the time in the ICU was no different. The incidence and duration of hospitalization for non-RSV respiratory illness or the incidence of otitis media was unaltered.⁷

TABLE 1. Summary of Clinical Efficacy of the Impact-RSV Study Group

Summary of Clinical Efficacy for Palivizumab				
Parameter	Rates		% Reduction	P Value
	Placebo	Palivizumab		
Incidence of RSV hospitalization, %	10.6	4.8	55	<.001
RSV hospitalizations/100 children, day	62.4	36.4	42	<.001
O ₂ requirement/100 children, day	50.6	30.3	40	<.001
Incidence RSV ICU care, %	3.0	1.3	57	.026
ICU/100 children, day	12.7	13.3	—	NS
Mechanical ventilation, %	.2	.7†	—	NS
Mechanical ventilation, total number of days	1.7	8.4	—	.210
All respiratory hospitalizations, %	22	16	27	.008
Respiratory hospitalizations/100 children, day (including RSV)	180	124	31	.004
Otitis media, %	40	42	—	NS
Deaths, %	1	.4	—	

TABLE 2. Subgroup Analyses of the Impact-RSV Study Group

Subgroup Analyses of RSV Hospitalization by Treatment Group*				
Group	Rate, %		% Reduction	P Value
	Placebo	Palivizumab		
All infants	10.6	4.8	55	.00004
Premature infants with CLD	12.8	7.9	39	.038
Premature infants without CLD	8.1	1.8	78	<.001
Neonatal Weight				
>5 kg	10.7	5.2	51	.014
<5 kg	10.5	4.5	57	.001
Neonatal gestational age				
<32 wk	11.0	5.8	47	.0026
32-35 wk†	9.8	2.0	80	<.001

* CLD indicates chronic lung disease.

† Rates for infants ($N=355$ total) born at 32 to 35 weeks of gestation, but without CLD, were 10% and 1.8% for placebo and palivizumab recipients, respectively.

RSV-IGIV

RSV-IGIV was evaluated in a 54-center, randomized, placebo controlled, double-blind study enrolling 510 infants and children with bronchopulmonary dysplasia (< 24 months of age) or premature birth (<35 weeks gestation and less than 6 months of age at study entry). The study was called “the PREVENT trial”. From November through April the infants and children enrolled in this study received either RSV-IGIV 750 mg/kg (15 mL/kg) or 1% albumin 15 mL/kg as a control. Results are summarized in Table 3. Significant reductions in hospitalization due to RSV, hospitalization due to any respiratory illness, RSV hospital days, RSV hospital days with increased supplemental O₂ or RSV hospital days with moderate-to-severe lower respiratory tract infection or illness were observed in the RSV-IGIV treatment group. The greatest reductions in RSV hospitalization occurred in children greater than 6 months of age, all of whom had bronchopulmonary dysplasia.^{10,32}

Table 3. Summary of Results of the PREVENT Trial:^{10,32}

Clinical Endpoint	Control (n = 260)	RSV-IGIV (n = 250)	% Reduction
Hospitalization due to RSV	35 (13.5%)	20 (8%)	41%*
Hospitalization for any respiratory illness	69 (26.5%)	41 (16.4%)	38%*
Total days of hospitalization for respiratory illness/100 children	217	170	46%*
RSV hospital days/100 children	129	60	53%*
RSV hospital days with moderate-to-severe LRI/100 children	106	49	54%*
RSV hospital days with increased supplemental O ₂ /100 children	85	34	60%*
RSV ICU days/100 children	50	28	44%
Days of RSV mechanical ventilation/100 children	20	18	10%

LRI = Lower respiratory tract infection/illness

* p < 0.05

Prophylactic administration of RSV-IGIV was also evaluated in a randomized, single-blind, controlled study enrolling 249 infants and young children (mean age 8 months) who had bronchopulmonary dysplasia due to prematurity, congenital heart disease or prematurity alone (the NIAID trial).¹⁵ Children were monitored and treated through one RSV season (from December through March/April) during which time they were assigned to receive either high-dose RSV-IGIV 750 mg/kg or low-dose RSV-IGIV 150 mg/kg each month or assigned to a control group that received no RSV-IGIV. The low dose was administered intravenously over 1 hour, and the high dose was administered over 2 hours. Intravenous access was a problem at least once in 60% of the children; however, at least 75% of the prescribed dose of RSV-IGIV was infused at 85% of the visits. Compliance with monthly clinic visits was better in the treatment groups, with high-dose patients missing 10 of 319 visits (3.1%), low-dose patients missing 21 of 322 visits (6.5%) and the control patients missing 34 of 376 visits (9%). The overall frequency of lower respiratory tract infection was reduced by 48%, and the frequency of moderate and severe lower respiratory tract infection was reduced by 62%. Recipients of high-dose prophylaxis had a 62% reduction in the incidence of RSV infection of the lower respiratory tract and a 72% reduction in all moderate or severe RSV lower respiratory tract infections. Milder RSV disease was reflected by lower respiratory scores in the high-dose group (1.58) compared to the control group (2.34). Recipients of the low-dose RSV-IGIV did not have significantly lower scores than the controls. Children who received low-dose RSV-IGIV had only a 27% reduction in the overall frequency of RSV lower respiratory infection and a 53% reduction in moderate or severe RSV lower respiratory tract infection compared to controls, which was not a significant difference. The rates of infection are summarized in Table 4.

Table 4. Infection Rates in the NIAID Trial:¹⁵

Infection	High Dose (n = 81)	Low Dose (n = 79)	Control (n = 89)
<i>Acute respiratory disease</i>	84	93	101
RSV	19	16	29
Non-RSV	65	77	72
<i>LRI</i>	21*	35	44
RSV	7*	13	20
Non-RSV	14	22	24
<i>Moderate-to-severe LRI</i>	5*	9	17
RSV	3*	5	12
Non-RSV	2	4	5

* $p \leq 0.05$ compared to control

Children in the high-dose group were hospitalized 63% less frequently than control children and spent fewer total days in the hospital for RSV infections. Fewer admissions to the intensive care unit were observed in both the low-dose and high-dose groups compared with control, and the number of days of ribavirin therapy were reduced in the high-dose group. The number of days in the intensive care unit were reduced 97% to 100% over that of controls. Greatest improvement was among preterm infants and infants with bronchopulmonary dysplasia. Hospitalization data are summarized in Table 5.

Table 5. Hospitalization Rates from the NIAID Trial:¹⁵

Parameters	High Dose (n = 81)	Low Dose (n = 79)	Control (n = 89)
Admissions to ICU	1*	0*	6
Days in hospital **	43*	63	128
Days in ICU	1*	0*	34
Hospitalizations ***	6*	10	18

* $p \leq 0.05$

** = Numbers shown are the total number of days for each child.

*** = Only the first hospitalization for each child is included.

Adverse reactions included fluid overload, mild reduction in oxygen saturation and fever. During a second RSV season, 210 of the 249 children were followed but none received RSV-IGIV. Of these, 18 in the high-dose group, 11 in the low-dose group and 14 in the control group developed RSV illness. Six deaths occurred (three in the high-dose group and three in the low-dose group) between the start of RSV-IGIV therapy and within 4 months of the last infusion. No

basis for attributing these deaths to RSV-IGIV administration was revealed. Since five of the children had heart disease, independent re-analysis of data on RSV-IGIV administration in a cohort of 87 patients with cardiac disorders was performed. Three of the deaths were attributed to complications of cardiac surgery, while the other three were due to medical causes and

occurred 2 weeks, 1 month and 3 months after an infusion. Overall, high-dose RSV-IGIV was well tolerated and effectively reduced the incidence of RSV infection, reduced RSV infection severity and decreased hospitalization.¹⁵ Following publication of this study, 25 children were identified who had been enrolled and randomized to treatment but were not included in the intention-to-treat analysis. When these children are included, the total patient enrollment is increased to 274. Compared to control children, the children randomized to receive high-dose RSV-IGIV had a 57% reduction in the incidence of RSV hospitalization, a 59% reduction in total days of RSV hospitalization, a 97% reduction in RSV ICU days and 100% reduction in mechanical ventilation. The efficacy of the high-dose RSV-IGIV remained significant after inclusion of these children.^{10,33,34} Concerns regarding the randomization procedures in this study, a lack of consistency of treatment effect across sites and an imbalance in treatment assignments among patients that dropped out of the study were raised during the initial FDA review of this product in 1993.³³

In response to the cardiac deaths in the NIAID trial, a trial was performed to further evaluate the efficacy and safety of RSV-IGIV in 429 children with congenital heart disease. The mean age of the children at entry to this study was 9 months (range 0 to 47 months). Trends suggesting efficacy with RSV-IGIV were observed, but the efficacy and safety of RSV-IGIV in this population could not be confirmed. The incidence of side effects was similar in the two groups; however, the RSV-IGIV treated children had more severe or life-threatening adverse reactions.¹⁰

Overall Considerations

As noted earlier, palivizumab decreases risk of severe RSV disease, as does RSV-IGIV. No direct studies were done to compare relative efficacy of the two products. Palivizumab is not a human blood product and, therefore, is not associated with risks of acquisition of blood-borne pathogens, a potential risk with RSV-IGIV. Because of its ease of administration, palivizumab is favored over RSV-IGIV (1 intramuscular injection vs a 4-hour intravenous infusion). Furthermore, the availability of palivizumab is not contingent on the blood donor pool. Currently, palivizumab is only available in an intramuscular formulation; however, an intravenous formulation will likely be available in the near future. The only rationale for such a formulation is to provide the capability of administering this product intravenously if the infant has an intravenous line in place for other reasons.

Escape mutants (ie, resistant viruses) to palivizumab have not been identified after the administration of this product; however, the administration of other monoclonal antibodies has been associated with development of such resistant mutants. Surveillance will be required to identify the risk for such events.

A critical aspect of RSV prevention in high-risk infants is the education of parents and other caregivers about the importance of reducing exposure to and transmission of RSV. Preventive measures include eliminating exposure to cigarette smoke and limiting exposure to contagious settings (eg, child care centers). Emphasis on hand-washing in all settings, including the home, especially during periods when contacts of high-risk children have respiratory infections or are at high risk for exposure to respiratory infections from siblings who are in child care or attend school, is also important.

Clinical Selection of RSV-IGIV Over Palivizumab

Although palivizumab provides effective protection against RSV for eligible infants, and has greater ease of administration and fewer adverse effects than RSV-IGIV, there may be certain considerations that might favor the use of RSV-IGIV. Specifically, in the RSV-IGIV trial, immunoprophylaxis decreased the overall rate of hospitalizations for non-RSV respiratory infections, whereas palivizumab did not. This may be of value in those infants younger than 6 months who are not eligible for influenza vaccination as well as for those infants and children with severe pulmonary disease for whom respiratory infections other than those caused by RSV may be medically important. Similarly, there was a statistically significant reduction in the overall frequency of otitis media, although this latter point alone is unlikely to justify use of RSV-IGIV. Palivizumab has not been tested in the treatment of children with CHD. Neither product is licensed by the FDA for use in children with CHD, and RSV-IGIV should not be administered to children with cyanotic CHD.

DOSING

The recommended dose of palivizumab is 15 mg/kg of body weight. The dose should be administered intramuscularly once a month throughout the RSV season (November through April). The first dose of palivizumab should be administered prior to the start of the RSV season (eg, November). The anterolateral aspect of the thigh is the preferred site of administration. Administration in the gluteal muscle could result in damage to the sciatic nerve.⁷ If the calculated dose is greater than 100 mg, the dose should be given as a divided dose of 1 mL (100 mg/mL) or less at different sites.⁷

The maximum recommended total monthly dosage of RSV-IGIV is 750 mg/kg (15 mL/kg), administered at the following rate:

Time After Start of Infusion	Rate of Infusion
0 - 15 minutes	1.5 mL/kg/hr
15 - 30 minutes	3 mL/kg/hr
30 minutes to end of infusion	6 mL/kg/hr

Vaccination

Palivizumab does not interfere with vaccine administration. Infants and children receiving RSV-IGIV prophylaxis (750-mg/kg dose) immunization with measles-mumps-rubella (MMR) and varicella vaccines should be deferred for 9 months after the last dose. There are no data on the use of RSV-IGIV and the response to hepatitis B vaccine, but there is no reason to anticipate interference because RSV-IGIV does not contain antibodies to hepatitis B surface antigen.

RSV-IGIV use should not alter the primary immunization schedule for diphtheria and tetanus toxoids, whole-cell or acellular pertussis, *Haemophilus influenzae* type b, and poliovirus vaccines (inactivated poliovirus vaccine [IPV] or oral poliovirus vaccine [OPV]). The

manufacturer of RSV-IGIV has suggested that an additional dose of vaccine might be needed to assure an adequate immune response to diphtheria and tetanus toxoids, whole-cell or acellular pertussis, *Haemophilus influenzae* type b, and OPV (refer to the RespiGam package insert), but more information is needed before changes in current immunization recommendations can be made. Currently, the available data do not support the need for supplemental doses of routinely administered vaccines. Parenterally administered immunoglobulin preparations have little, if any, effect on the replication of OPV in the intestinal tract.

Cost-benefit Analyses

Recently, a cost-effectiveness analysis was conducted to compare RSVIG and palivizumab for prophylaxis of RSV disease among infants born prematurely. Decision analysis was used to compare the projected societal cost-effectiveness of three strategies- RSVIG, palivizumab, and no prophylaxis. Probabilities and cost of hospitalization were derived from a cohort of 1721 premature infants discharged from six different NICUs.³⁶

As expected, this study found that the cost-effectiveness of palivizumab and RSVIG varied widely among different subgroups of premature infants based on their risk of hospitalization for RSV. For the highest-risk subgroup –infants born at ≤ 32 weeks, who required ≥ 28 days of oxygen in the NICU, and who were discharged from the NICU within 3 months before the start of RSV season, palivizumab was projected to cost \$12,000 per hospitalization averted. However, among all other subgroups, the cost of preventing a hospitalization was estimated to be $> \$35,000$. The secondary outcomes varied greatly as well, the cost of palivizumab per year of life saved ranged from \$33,000 to \$1,200,000, and the number needed to treat extended from 7.4 to 152.³⁶

The study concludes that the relative cost-ineffectiveness of prophylaxis among most subgroups of infants argues for more restrictive recommendations for the use of both RSVIG and palivizumab than are currently in place. RSV prophylaxis should be most appropriately reserved for infants with active CLD and for premature infants without CLD who have multiple risk factors for RSV hospitalization.³⁶

Factors other than CLD influence the decision about use of prophylaxis, particularly in children with a gestational age of 32 to 35 weeks, including 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, exposure to tobacco smoke in the home, anticipated cardiac surgery, and distance to and availability of hospital care for severe respiratory illness. For many infants qualifying for the approved indications, risk of rehospitalization for serious respiratory illness will be low, and the cost and logistical difficulties associated with prophylaxis may outweigh the potential benefits.

RECOMMENDATIONS

1. Palivizumab or RSV-IGIV Prophylaxis should be considered for infants and children younger than 2 years of age with CLD who have required medical therapy for their CLD within 6 months before the anticipated RSV season. Palivizumab is preferred for most high-risk children because of its ease of administration, safety, and effectiveness. Patients with more severe CLD may benefit from prophylaxis for two RSV seasons, especially those who require medical therapy. Decisions regarding individual patients may need additional consultation from neonatologists, intensivists, or pulmonologists. There are limited data on the efficacy of palivizumab during the second year of age; risk of severe RSV disease exists for children with CLD who require medical therapy. Although those with less severe underlying disease may receive some benefit for the second season, immunoprophylaxis may not be necessary.
2. Infants born at 32 weeks of gestation or earlier without CLD or who do not meet the criteria in recommendation 1 also may benefit from RSV prophylaxis. In these Infants, major risk factors to consider are gestational age and chronologic age at the start of the RSV season. Infants born at 28 weeks of gestation or earlier may benefit from prophylaxis up to 12 months of age. Infants born at 29 to 32 weeks of gestation may benefit most from prophylaxis up to 6 months of age. Decisions regarding duration of prophylaxis should be individualized, according to the duration of the RSV season. Practitioners may wish to use RSV rehospitalization data from their own region to assist in the decision-making process.
3. Given the large number of patients born between 32 to 35 weeks and the cost of the drug, the use of palivizumab in this population should be reserved for those infants with additional risk factors (see "Cost-Benefit Analyses" section) until more data are available.
4. Palivizumab and RSV-IGIV are not licensed by the FDA for patients with CHD. Available data indicate that RSV-IGIV is contraindicated in patients with cyanotic CHD. However, patients with CLD, who are premature, or both, who meet the criteria in recommendations 1 and 2 and who also have asymptomatic acyanotic CHD (eg, patent ductus arteriosus or ventricular septal defect) may benefit from prophylaxis.
5. 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 immune globulin intravenous (IGIV) monthly, physicians may consider substituting RSV-IGIV during the RSV season.
6. RSV prophylaxis should be initiated at the onset of the RSV season and terminated at the end of the RSV season. In most areas of the United States, the usual time for the beginning of RSV outbreaks is October to December, and termination is March to May, but regional differences occur. The onset of RSV infection occurs earlier in southern states than in northern states. Practitioners should contact their health departments and/or diagnostic virology laboratories in their geographic areas to determine the optimal time to begin administration.
7. 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 cohort 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. The need for and efficacy of prophylaxis in these situations has not been evaluated.

8. The guidelines for modification of immunizations after RSV-IGIV have not changed. Palivizumab does not interfere with the response to vaccines.

REFERENCES:

1. Anonymous. MedImmune's *Synagis* (palivizumab) approved for marketing by FDA - First monoclonal antibody for infectious disease. MedImmune, Inc. 19 June 1998.
(<http://www.medimmune.com/press>)
2. Anonymous. RSV infection: Part I. Issues on prevention and nosocomial pneumonia 1994. *Center for Disease Control* 1994
(http://www.cdc.gov/ncidod/diseases/hip/pneumonia/1_rsv.htm)
3. Anonymous. FDA licenses biotech product to prevent serious RSV disease. *FDA Talk Paper* 1998;T98-3:1-2.
4. Ottolini MG, Hemming VG. Prevention and treatment recommendations for respiratory syncytial virus infection: Background and clinical experience 40 years after discovery. *Drugs* 1997;54:867-84.
5. Johnson S, et al. Development of a humanized monoclonal antibody (MEDI-493) with potent *in vitro* and *in vivo* activity against respiratory syncytial virus. *J Infect Dis* 1997;176:1215-24.
6. Welliver RC. Respiratory syncytial virus immunoglobulin and monoclonal antibodies in the prevention and treatment of respiratory syncytial virus infection. *Semin Perinatol* 1998;22:87-95.
7. MedImmune, Inc. Package literature for *Synagis*. June 1998.
8. Anonymous. Update: Respiratory syncytial virus activity -- U.S., 1997-98 season. *Morbidity Mortality Weekly Reports* 1997;46(49):2.
(<http://www.cdc.gov/epo/mmwr/preview/mm4649.html>)
9. Anonymous. Respiratory syncytial virus infection: Recommendations for prevention of nosocomial RSV infections. Center for Disease Control 1994
(http://www.cdc.gov/ncidod/diseases/hip/pneumonia/2_rsv.htm)
10. MedImmune, Inc. Package literature for *RespiGam*. January 1996.
11. American Academy of Pediatrics. Respiratory syncytial virus immune globulin intravenous: Indications for use. *Pediatrics* 1997;99:645-50.
12. Siegel JP. FDA Approval Letter. Food and Drug Administration 19 June 1998.
13. Rodriguez WJ, et al. Respiratory syncytial virus (RSV) immune globulin intravenous therapy for RSV lower respiratory tract infection in infants and young children at high risk for severe RSV infections: Respiratory Syncytial Virus Immune Study Group. *Pediatrics* 1997;99(3):454-61.

14. Committee on Infectious Diseases and Committee on Fetus and Newborn. Prevention of respiratory syncytial virus infections: indications for the use of palivizumab and update on the use of RSV-IVIG. *Pediatrics* 1998;102:1211-16.
15. Groothuis JR, et al. Prophylactic administration of respiratory syncytial virus immune globulin to high-risk infants and young children. *N Engl J Med* 1993;329:1524-30.
16. Siber GR, et al. Protective activity of a human respiratory syncytial virus immune globulin prepared from donors screened by microneutralization assay. *J Infect Dis* 1992;165:456-63.
17. de Sierra TM, et al. Respiratory syncytial virus-specific immunoglobulins in preterm infants. *J Pediatr* 1993;122:787-91.
18. Meissner HC, et al. Mechanisms of immunoglobulin action: Observations on Kawasaki syndrome and RSV prophylaxis. *Immunol Rev* 1994;139:109-23.
19. Hemming VG, et al. Hyperimmune globulins in prevention and treatment of respiratory syncytial virus infections. *Clin Microbiol Rev* 1995;8:22-33.
20. Groothuis JR. Role of antibody and the use of respiratory syncytial virus immunoglobulin in the prevention of respiratory syncytial virus disease in preterm infants with and without bronchopulmonary dysplasia. *Pediatr Infect Dis J* 1994;13:454-8.
21. McIntosh K. Respiratory syncytial virus--successful immunoprophylaxis at last [editorial]. *N Engl J Med* 1993;329:1572-4.
22. Groothuis JR, et al. Use of intravenous gamma globulin to passively immunize high-risk children against respiratory syncytial virus: Safety and pharmacokinetics. *Antimicrob Agents Chemother* 1991;35:1469-73.
23. Crowe JE, et al. Recombinant human respiratory syncytial virus (RSV) monoclonal antibody Fab is effective therapeutically when introduced directly into lungs of RSV-infected mice. *Proc Natl Acad Sci* 1994;91:1386-90.
24. Crowe JE, et al. Isolation of a second recombinant human respiratory syncytial virus monoclonal antibody fragment (Fab RSVF2-5) that exhibits therapeutic efficacy *in vivo*. *J Infect Dis* 1998;177:1073-6.
25. Weltzin R, et al. Intranasal monoclonal IgA antibody to respiratory syncytial virus protects Rhesus monkeys against upper and lower respiratory tract infection. *J Infect Dis* 1996;174:256-61.
26. Subramanian KNS, et al. Safety, tolerance and pharmacokinetics of a humanized monoclonal antibody to respiratory syncytial virus in premature infants and infants with bronchopulmonary dysplasia. *Pediatr Infect Dis J* 1998;17:110-15.
27. Anonymous. MedImmune reports first MEDI-493 clinical trial results. MedImmune, Inc. 10 March 1997. (<http://www.medimmune.com/press/trial493.htm>)

28. Anonymous. MedImmune reports results from double-blind, placebo-controlled, phase I/II clinical trial of MEDI-493. MedImmune, Inc. 20 March 1997. (<http://www.medimmune.com/press/493phas2.htm>)
29. Anonymous. MedImmune reports third set of clinical results evaluating MEDI-493. MedImmune, Inc. 8 April 1997. (<http://www.medimmune.com/press/3rd493.htm>)
30. Anonymous. MedImmune reports fourth set of clinical results evaluating MEDI-493. MedImmune, Inc. 6 May 1997. (<http://www.medimmune.com/press/493cp012.htm>)
31. Saez-Llorens X, et al. Phase I/II, open-label, multi-dose escalation trial of a humanized respiratory syncytial virus (RSV) monoclonal antibody (MEDI-493) administered intramuscularly (IM) in high risk children [abstract]. 37th Interscience Conference Antimicrob Agents Chemother (ICAAC). Toronto; September 28 - October 1, 1997.
32. The PREVENT Study Group. Reduction of respiratory syncytial virus hospitalization among premature infants and infants with bronchopulmonary dysplasia using respiratory syncytial virus immune globulin prophylaxis. *Pediatrics* 1997;99(1):93-9.
33. Ellenberg SS, et al. A trial of RSV immune globulin in infants and young children: The FDA's view [letter]. *N Engl J Med* 1994;331:203-4.
34. Groothuis JR, et al. A trial of RSV immune globulin in infants and young children: The FDA's view [letter]. *N Engl J Med* 1994;331:204-5.
35. Grabenstein JD. ImmunoFacts: Vaccines and immunologic drugs. St. Louis, Missouri: Facts & Comparisons, Inc., 1998.
36. Joffe S, Ray GT, Escobar GJ, Black SB, Lieu TA. Cost-effectiveness of Respiratory Syncytial Virus prophylaxis among preterm infants. *Pediatrics* 1999;104:419-27.