# Palivizumab: a review of its use in the protection of high risk infants against respiratory syncytial virus (RSV)

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**Abstract:** Respiratory syncytial virus (RSV) is a leading cause of hospitalization in children less than 1 year of age and causes substantial morbidity. Although there is not currently a vaccine available to prevent RSV infection, prophylaxis with the humanized monoclonal antibody palivizumab has been shown to reduce the rate of RSV hospitalization in premature infants and those infants with chronic lung disease or congenital heart disease. Because palivizumab has not been shown to have a beneficial clinical effect on established RSV disease such as reducing the rate of mechanical ventilation and mortality in children afflicted with RSV, there has been considerable debate as to the cost-benefit ratio of administering palivizumab according to international guidelines. Palivizumab has demonstrated a favorable side-effect profile in clinical trials without the development of anti-palivizumab antibodies. Future studies are needed to determine whether palivizumab, or other more potent monoclonal antibodies which are currently undergoing clinical trials, will reduce the long-term sequelae of RSV infection such as the development of wheezing and asthma.

**Keywords:** monoclonal antibodies, palivizumab, respiratory syncytial virus, immunoprophylaxis, pediatrics

## Introduction

Despite recent recognition that rhinoviruses (Kusel et al 2006) and human metapneumovirus (Wolf et al 2006) are important lower respiratory pathogens in children, respiratory syncytial virus (RSV) remains the leading cause of hospitalization for respiratory tract illness in infants <1 year of age with 2%–3% of affected infants requiring hospitalization (Hall 2001; Leader and Kohlhase 2003; Holman et al 2004). In the United States, RSV is the most common viral cause of death in children younger than 5 years of age, particularly in children younger than 1 year of age (Thompson et al 2003). Children with a history of premature birth, congenital heart disease (CHD), neurological disorders (Purcell and Fergie 2004), bronchopumonary dysplasia (BPD) (Boyce et al 2000), other pre-existing lung disorders (Arnold et al 1999), immunosuppression (Hall et al 1986), and genetic syndromes (Fjaerli et al 2004) are at increased risk of developing severe RSV infection. While hospitalized with RSV, children are at risk for experiencing complications and injuries resulting from an error in medical management which can lead to a prolonged length of stay and higher costs (Willson et al 2003; McBride et al 2005). In addition, the effects of RSV may not end after hospitalization since there is considerable debate as to whether RSV bronchiolitis in infancy contributes to the development of asthma later in childhood. Some investigators have noted an increased prevalence of asthma later in life in children who acquired RSV at an early age (Sigurs et al 2000, 2005; Henderson et al 2005) while others have not seen an

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increased prevalence of wheezing and asthma up to 20 years after RSV infection (Stein et al 1999; Korppi et al 2004).

RSV is an enveloped paramyxovirus with a single-stranded, negative sense RNA genome that encodes several proteins including the F (fusion) protein which promotes viral entry and syncytia formation, and the G (attachment) protein which promotes viral attachment to the cell. Two subgroups, A and B, either individually or together, are responsible for yearly outbreaks of RSV (Hall et al 1990). Disease severity is similar between subgroups (DeVincenzo 2004). Although various therapeutic modalities have been tried for RSV infection, treatment remains supportive with the aim of maintaining adequate oxygen saturation levels and hydration status (Subcommittee on Diagnosis and Management of Bronchiolitis 2006). The prevention of nosocomial infection by wearing gowns and gloves and establishing cohorts of patients and nursing staff remains an important cost-effective intervention in limiting the burden of RSV infection (Leclair et al 1987; Madge et al 1992; Macartney et al 2000).

The development of a vaccine to prevent RSV infection remains a worldwide priority although previous attempts at vaccine development have been unsuccessful. In the 1960s, recipients of a formalin-inactivated vaccine suffered increased morbidity and mortality upon subsequent exposure to RSV (Chin et al 1969; Fulginiti et al 1969). Since this time, subunit vaccines that target the F and G proteins of RSV, the delivery of vaccine antigens by live viral vectors, and live-attenuated vaccines have undergone testing in clinical trials and may hold promise as future vaccine candidates against RSV (Little-van den Hurk et al 2007). Passive immunization with RSV-IGIV, a purified immunoglobulin G pooled from human plasma selected for high titers of neutralizing antibody against RSV, and palivizumab, a humanized monoclonal antibody that binds RSV F protein, have been shown to reduce RSV-associated hospitalization (Groothuis et al 1993; The PREVENT Study Group 1997; The Impact-RSV Study Group 1998). Palivizumab has since become the preferred choice of RSV immunoprophylaxis because of its lack of concern with fluid overload, particularly in children with pre-existing cardiac or pulmonary disease (Simoes et al 1998). Ease of administration, lack of interference with immunization schedules, and decrease in parental work time loss and emotional costs are also reasons leading to the preference for palivizumab (Robbins et al 2002). Parental partiality for palivizumab, particularly if administered in the home setting, has been shown to improve compliance and lead to a significant reduction in RSV-related hospitalization compared with treatment provided in a physician's office (Golombek et al 2004).

## Palivizumab safety, tolerance, pharmacokinetics, resistance

In preclinical trials, palivizumab was able to neutralize both subtype A and B strains of RSV and was 50- to 100-fold more potent than RSV IVIG. Early animal trials demonstrated a >99% reduction of lung RSV titers in cotton rats at mean serum concentrations of 25–30 μg/mL. All of the animals that achieved a serum concentration of at least 40 μg/mL had at least a 99% reduction in pulmonary RSV titer (Johnson et al 1997). In a phase I/II clinical trial of intravenously administered palivizumab, mean trough concentrations 30 days after infusion were 60.6 μg/mL in patients who received 15 mg/kg palivizumab. These concentrations increased to 70.7 μg/mL 30 days after the second dose. Overall, 71% of patients had concentrations >40 μg/mL after the first dose while 86% of patients achieved this concentration after the second dose (Subramanian 1998). In a phase I/II trial of intramuscular administration of 15 mg/kg palivizumab, the mean serum concentration of palivizumab at 30 days was 49 μg/mL and 69.4 μg/mL 30 days after the second dose (Sáez-Llorens et al 1998). However, optimal dosing in premature infants may differ as trough levels ≥40 μg/mL in palivizumab recipients ≤30 weeks gestation with a mean weight of 1293 ± 236 g were achieved in only 23% of infants before the second dose, with mean trough levels of 32.2 ± 10.5 μg/mL in these subjects (Wu et al 2004).

RNA viruses, such as RSV, are susceptible to high rates of mutation which can occur during replication by virus-encoded RNA-dependent RNA polymerase (Castro et al 2005). Incorporation of these mutations into the viral genome during replication could allow the emergence of viruses with a selective advantage. Although RSV escape mutants have been created in vitro by passing RSV in cell culture in the presence of palivizumab and tested in vivo in cotton rats leading to variable susceptibility of these escape mutants to palivizumab (Zhao et al 2004), surveillance of RSV isolates from hospitalized children demonstrated that none of the 371 RSV strains evaluated failed to bind palivizumab (DeVincenzo et al 2004). Palivizumab was safe and well-tolerated in phase I/II studies. There were no significant changes in urinalysis, hematological values, blood urea nitrogen, creatinine, and transaminase levels (Sáez-Llorens et al 1998; Subramanian et al 1998). Additional safety data were collected in 565 patients in a phase

III and IV multicenter, single arm, open label study. Eleven patients (1.9%) discontinued the study because of an adverse event, 3 of which were deemed possibly or probably related to palivizumab (Groothuis 2001). Adverse events such as injection site reactions (2.3%), fever (1.5%), diarrhea (<1%), and nervousness/irritability (<1%) were comparable with the adverse events in the Impact-RSV trial, which did not demonstrate any significant differences between children who received placebo and those who received palivizumab.

In a review of adverse drug events in children younger than 2 years of age, Moore et al (2002) reported that palivizumab accounted for 28% of reported serious or fatal adverse events to the US Food and Drug Administration's (FDA) Adverse Events Reporting System. However, in a review of the 133 deaths reported to the FDA after palivizumab use, only 2% of children were full-term and born without congenital anomalies. This suggests that children who died after palivizumab treatment were at increased risk of death (Mohan 2004) and therefore no causal link has been established. Palivizumab has also been shown to be safe and well tolerated if used for a second season as no development of specific anti-palivizumab antibody response has been recorded (Lacaze-Masmonteil et al 2003; Null et al 2005).

## Palivizumab efficacy

IMpact-RSV was a multi-center, randomized, double-blinded, placebo-controlled trial that enrolled 1502 children (500 placebo and 1002 palivizumab recipients). Eligible participants were ≤35 week's gestational age and ≤6 months of age or ≤24 months old with a diagnosis of BPD requiring ongoing medical treatment. Groups were well-matched demographically and for the presence of RSV risk factors, and more than 90% of both groups received all 5 monthly injections (The Impact-RSV study group 1998). Monthly prophylaxis resulted in a 55% relative reduction in RSV hospitalization (10.6% placebo, 4.8% palivizumab) with significant relative reductions in children with BPD (39%) and premature children without BPD (78%). Significant decreases in hospitalizations were seen in children greater than 5 kg (51%), less than or equal to 5 kg (57%), and in infants born before 32 weeks gestation (47%). Palivizumab recipients also had significantly reduced hospital days, days with supplemental oxygen requirement, moderate/severe lower respiratory tract infections, and intensive care unit (ICU) admissions. There was no difference between the groups in incidence of mechanical ventilation and mortality rate. The number of adverse events between both groups was similar. The results of this study led to the licensure of palivizumab by the FDA for the prevention of RSV infection. Subsequently, guidelines from the American Academy of Pediatrics (AAP) and other professional organizations were developed (Table 1). Risk factors for RSV hospitalization in these countries can be found in Table 2.

Palivizumab has been shown to reduce the amount of RSV concentration in respiratory secretions obtained from mechanically ventilated children (Malley et al 1998) along with reducing nasal viral replication in premature hospitalized children who have received palivizumab prophylaxis, suggesting that the benefits of reduced hospitalization may come from a reduction in RSV load (DeVincenzo et al 2003).

## Palivizumab prophylaxis in BPD and prematurity

There are considerable disparities in reported RSV hospitalization rates for children born prematurely who have not received RSV immunoprophylaxis, ranging from 3% (Joffe et al 1999) to 43.9% (Singleton et al 2003). Hospitalization rates vary by infant subgroups with rates of hospitalization increasing with decreasing gestational age and increasing in infants requiring oxygen therapy at 36 weeks post-gestational age (PGA) compared with infants not requiring oxygen therapy (Boyce et al 2000; Stevens et al 2000). For example, Stevens et al (2000) estimated an RSV hospitalization rate of 13.9% for infants born at ≤26 weeks gestation compared with 4.4% for those born

**Table 1** Comparison of recommendations for palivizumab prophylaxis by country

| | CLD | ≤28 weeks | | 29–32 weeks | 33–35 weeks | Congenital heart disease |
|---|---|---|---|---|---|---|
| | ≤2 years | ≤12 mo | ≤6 mo | ≤6 months | + risk factors | |
| USA | + | + | | + | + | + |
| UK | + | | | | | + |
| Canada | + | | + | + | + | + |
| Spain | + | | + | + | + | + |
| New Zealand | + | + | | + if BW ≤ 1000 g | | |

(Adapted from Vogel et al 2002)
**Abbreviations:** CLD, chronic lung disease; BW, birth weight.

**Table 2** Risk factors for hospitalization for RSV by different countries[a]

| Author Year (Country) | Risk factors for hospitalization |
|---|---|
| Carbonell-Estrany 2000 (Spain) | Chronic lung disease |
| | Living with school age siblings |
| Cilla 2005 (Spain) | Birth weight <2500 g |
| | Maternal age at delivery <25 years |
| | Birth in the second half of the year |
| | Prematurity |
| | Suburban residence |
| | Congenital heart disease |
| Vogel 2002 (New Zealand) | Home oxygen |
| | <28 weeks gestation |
| Joffe 1999 (USA) | ≤32 weeks gestation |
| | ≥28 days of oxygen usage |
| | NICU discharge between September/November |
| Boyce 2000 (USA) | Congenital heart disease |
| | ≥1 sibling |
| | White race |
| | Maternal smoking |
| | Maternal education <12 years |
| | Rural residence |
| Iwane 2004 (USA) | <12 months age |
| | African-American/Hispanic |
| | Male gender |
| | Underlying chronic illness |
| Deshpande 2004 (UK) | Need for assisted ventilation during neonatal period |
| | Discharge home on oxygen therapy |
| Broughton 2005 (UK) | Number of siblings |
| | Maternal smoking in pregnancy |
| Wang 1995 (Canada) | Aboriginal race |
| | Age <6 weeks |
| | Underlying pulmonary disease |
| | Prematurity |
| | Congenital heart disease |
| | Immunosuppression |

[a]Risk factors for hospitalization are reported only once per country.
**Abbreviations:** RSV, respiratory syncytial virus; NICU, neonatal intensive care unit.

at 30–32 weeks gestation and a 16.8% hospitalization rate for infants requiring oxygen therapy at 36 weeks. Boyce et al (2000) reported RSV hospitalization rates of 7.0% in infants ≤28 weeks gestation compared with 5.7% in infants 33–36 weeks gestation and a 38.8% hospitalization rate in the first year of life of infants with BPD. A comparison of RSV hospitalization rates in the US and other countries can be found in Table 3. International findings were similar to those in the United States with the exception of Cilla et al (2005) who did not report an increasing hospitalization rate with decreasing gestational age. Although no explanation was offered for this finding, by combining gestational age with birth weight there was an increased hospitalization rate with decreasing gestational age. For example, the incidence of RSV hospitalization was 8.1% in infants ≤35 weeks gestation and weighing <2500 g compared with 4.9% in infants 36–37 weeks gestation and weighing <2500 g.

Since the Impact-RSV trial, multiple studies have reported on the hospitalization rates of children at high risk for RSV infection who have received palivizumab (Table 4). All of the studies reported hospitalization rates lower than Impact-RSV's 4.8% except Lacaze-Masmonteil et al (2002), whose 7.6% rate may have reflected the French Pediatric Society's more stringent guidelines for palivizumab administration. The BPD rate was 81% in this study cohort compared with 53% in the Impact-RSV trial. However, these studies did not have a control group to compare palivizumab prophylaxis versus no prophylaxis in the rates of RSV hospitalization, nor was the rate of RSV testing reported in most of the studies.

Multiple studies since the IMpact-RSV trial have compared RSV-related hospitalizations between palivizumab and non-palivizumab recipients (Table 5). Six studies have demonstrated significant improvement in RSV-related hospitalization rates with palivizumab prophylaxis (Pedraz et al 2003; Singleton et al 2003; Grimaldi et al 2004, 2007; Kusuda et al 2006; Mitchell et al 2006) while 2 additional studies have demonstrated a trend toward significance (Shireman 2002; Resch 2006). Only three studies have not demonstrated an improvement in RSV-related hospitalization rates with palivizumab administration (Lacaze-Masmonteil et al 2004; Henckel et al 2004; Navér et al 2004). An explanation for these discordant results may be related to the variable timing and severity of RSV infection from year-to-year (Duppenthaler et al 2003; Terletskaia-Ladwig et al 2005), or differences related to the study populations with regard to known risk factors for RSV hospitalization. For example, if the rate of RSV infection peaks early in the season when infants have not reached a therapeutic trough level of palivizumab the rate of RSV-related hospitalizations may be increased compared with a season characterized by a later peak in RSV activity. Also, if the RSV season was mild when palivizumab was administered compared with a previous year when the RSV season was more severe, the rates of RSV hospitalization in the palivizumab group may demonstrate a more significant improvement in the rates of hospitalization.

Consistent with the Impact-RSV trial, none of these studies reported a significant difference between groups in the rate of mechanical ventilation and mortality. In a study that specifically looked at the ICU admission rate before and after palivizumab availability there was no significant difference

**Table 3** RSV hospitalization rates in premature infants without palivizumab immunoprophylaxis since 2000

| Author Year (Country) | RSV hospitalization rate (gestational age) | RSV hospitalization rate (BPD) |
|---|---|---|
| Boyce 2000 (USA) | 7.0% (≤28 wks); 6.6% (29–<33 wks); 5.7% (33–<36 wks) | 38.8% |
| Stevens 2000 (USA) | 11.2% (<32 wks) | 16.8%[a] |
| Weigl 2001(Germany) | 2.0% (<32 wks);1.2% (32–37 wks) | |
| Liese 2003 (Germany) | 5.2% (≤35 wks) | 15% |
| Carbonell-Estrany 2000 (Spain) | 13.4% (≤32 wks) | |
| Carbonell-Estrany 2001 (Spain) | 13.1% (≤32 wks) | |
| Greenough 2001 (UK) | | 19% |
| McCormick 2002 (UK) | 7.3% (≤32 wks), 6.4% (≤35 wks) | |
| Cilla 2006 (Spain) | 4.4% (<33 wks), 7.8% (33–35 wks) | |

[a]Result reported as respiratory support beyond 36 weeks post-conceptual age.
**Abbreviations:** RSV, respiratory syncytial virus; BPD, bronchopulmonary dysplasia.

in the rate of mechanical ventilation or mortality (Prais et al 2005). One of the reasons that palivizumab may not have an effect on these outcomes is that most ICU admissions did not meet AAP guidelines for the use of palivizumab (Numa 2000; Cilla et al 2006; Prais et al 2005).

## Palivizumab prophylaxis in 33–35 weeks gestation age

Despite most developed countries utilizing palivizumab in infants born less than 33 weeks gestational age (Table 1), controversy exists on administering palivizumab to infants born between 33 and 35 weeks gestation. During the first year of life, the RSV hospitalization rate for children born at 33–35 weeks gestation in the United States is comparable to those born between 29–32 weeks gestation (Boyce et al 2000). In 2001, 5.5% of live births in the US were born at 32–35 weeks gestation (National Center for Health Statistics 2001), and although the Impact-RSV trial (The Impact-RSV Study Group 1998) demonstrated an 80% reduction in RSV hospitalization in palivizumab recipients compared with placebo for this gestational age group (9.8% vs 2.0%), the potential cost of administering palivizumab to such a large group of infants was recognized by the AAP and factored into their recommendations (Committee on Infectious Diseases and Committee on Fetus and Newborn 2003). They suggested that practitioners consider palivizumab prophylaxis if two or more of the following risk factors were present: child care attendance, school-aged siblings, exposure to environmental air pollutants, congenital airway anomalies, or severe neuromuscular disease. Risk factors for RSV hospitalization in this age group were studied prospectively in Spain (Figueras-Aloy et al 2004) and Canada (Law et al 2004). In Spain, age ≤10 weeks at start of RSV season, breast-feeding ≤2 months, at least 1 school age sibling, at least 4 people living in the household (excluding the infant and school-age siblings), and a family history of wheezing were significantly associated with an increased risk of RSV hospitalization (Figueras-Aloy et al 2004). In Canada, significant risk factors for RSV hospitalization in this age group included day-care attendance, November through January birth, preschool siblings, birth weight less than the 10th percentile, male gender, at least 2 smokers in the home and more than 5 people in the home, including the infant (Law et al 2004). Further study is necessary in this age group before definitive, evidence-based recommendations can be made.

**Table 4** RSV-related hospitalization rate after introduction of palivizumab

| Author Year (Country) | RSV hospitalization rate |
|---|---|
| Sorrentino 2000 (US) | 2.3% |
| Cohen 2000 (US) | 2.4% (3.9% CLD) |
| Winchester 2002 (Puerto Rico) | 3.0% |
| Oh 2002 (Canada) | 2.4% (6.0% BPD, 1.6% prematurity) |
| Lacaze-Masmonteil 2002 (France) | 7.6% (9.0% BPD) |
| Palivizumab Outcomes Registry 2003 (US) | 2.9% (5.8% CLD, 2.1% prematurity) |
| Romero 2003 (US) | 1.5% |

**Abbreviations:** RSV, respiratory syncytial virus; CLD, chronic lung disease; BPD, bronchopulmonary dysplasia.

## Palivizumab prophylaxis in congenital heart disease

A total of 1287 children less than or equal to 2 years of age with hemodynamically significant CHD that was uncorrected or palliated were randomized in a double-blind, placebo-controlled trial conducted in Canada, France, Germany, Sweden, United Kingdom, and the United States. Recipients were given either 15 mg/kg of palivizumab or placebo

**Table 5** RSV hospitalization rates in premature infants with and without palivizumab prophylaxis

| Author | Location | Design | Enrolled | RSV hospitalization rate | |
|---|---|---|---|---|---|
| | | | | No Prophylaxis | Prophylaxis |
| Shireman 2002 | US | Retrospective cohort | Medicaid administration claims | 11.7% | 5.8% |
| Singleton 2003 | US | Retrospective cohort | AAP recommendations + ≤32 wks instead of 32 wks and 36 wks with significant respiratory distress during newborn hospitalization | 43.9% | 15.0%[a] |
| Lacaze-Masmonteil 2004 | France | Multicenter prospective longitudinal cohort | <33 wks | 7.2% | 6.1% |
| Resch 2006 | Austria | Observational | 29–32 wks | 8.1% | 3.3%b |
| Henckel 2004 | Sweden | Retrospective cohort | ≤32 wks | 3.9% | 2.7%[c] |
| | | | CLD with therapy | 6.8% | 7.3%[d] |
| Kusuda 2006 | Japan | Non-randomized questionnaire | 29–35 wks | 5.7% | 4.0%a |
| | | | CLD | 8.0% | 10.3% |
| | | | ≤28 wks | 4.6% | 5.2% |
| Grimaldi 2004 | France | Prospective observational cohort | ≤32 wks + BPD | 46.2% | 11.8%, 3.8%[a,e] |
| Pedraz 2003 | Spain | Prospective cohort | ≤32 weeks + ≤6 mo | 13.25% | 3.95%[a] |
| Navér 2004 | Sweden | Prospective cohort | <36 wks | 3.8% | 4.1%f |
| Mitchell 2006 | Canada | Population-based observational | BPD + oxygen ≤32 wks + ≤6 mo | 7.3% | 3.0%[a] |
| Grimaldi 2007 | France | Prospective observational | ≤30 wks – BPD | 13.5% | 1.1%[a] |

[a]denotes statistical significance ($p < 0.05$).
[b]Studied adequate prophylaxis versus inadequate prophylaxis.
[c]Seven ICU admissions not included in hospitalization rate for the no prophylaxis group = 5.1% (29/567)
[d]Two ICU admissions not included in hospitalization rate for CLD with therapy in prophylaxis group = 8.6% (13/151) and 1 ICU admission not included in hospitalization rate for CLD with therapy in no prophylaxis group = 9.1% (4/44).
[e]No prophylaxis group encompassed 1999–2000 while 11.8% and 3.8% refer to 2000–01 and 2001–02, respectively.
[f]Hospitalization rate calculated at <36 weeks, however, palivizumab administered 76% of time according to Swedish recommendations (children < 2years with CLD requiring continuous therapy during last 6 months and children < 26 weeks and <6 months age at start of RSV season).
**Abbreviations:** RSV, respiratory syncytial virus; AAP, American Academy of Pediatrics; CLD, chronic lung disease; BPD, bronchopulmonary dysplasia; ICU, intensive care unit.

via i.m. injection every 30 days for a total of 5 doses. There were no significant differences between the groups in demographic characteristics, RSV risk factors, and characteristics of CHD at study entry. Palivizumab prophylaxis was significantly associated with a 45% relative reduction in hospitalization rates. RSV hospitalization rates were 9.7% in the placebo group and 5.3% in the palivizumab group. Although the study was not powered for subgroup analysis, reductions in RSV hospitalization were significantly greater in the non-cyanotic group (29% relative reduction in the cyanotic group, 58% relative reduction in the non-cyanotic group). Length of hospitalization stay and hospital days with increased oxygen requirement were also significantly reduced in the palivizumab recipients. An expected, but extremely important finding was that mean serum palivizumab concentrations were reduced by 58% after cardiopulmonary bypass leading to a recommendation from the AAP that palivizumab be administered postoperatively once medically stable (American Academy of Pediatrics 2003).

The low mortality rate in the study cohort resulted in an inability to determine the impact of palivizumab on death reduction from RSV among palivizumab recipients (2 palivizumab recipients died from RSV infection compared with 4 placebo recipients). Adverse events were similar in both groups (Feltes et al 2003). A similar rate of hospitalization (4.6%) was found in 108 Japanese infants with CHD who received palivizumab with no children requiring mechanical ventilation and no mortality (Saji et al 2005). Other investigators have found similar or lower incidences of RSV hospitalizations in patients with hemodynamically significant CHD than the 9.7% rate reported in the placebo arm of Feltes et al (2003) who were not given palivizumab prophylaxis (Duppenthaler et al 2004; Meberg and Bruu 2006). RSV hospitalization rates in patients with severe CHD

in Norway were 9.2% (Meberg and Bruu 2006) and only 2.4% in Switzerland (Duppenthaler et al 2004).

## Palivizumab in bone marrow transplant recipients

Palivizumab has been shown to reduce pulmonary RSV titers in immunosuppressed cotton rats. However, multiple doses of palivizumab at 4-day intervals were needed to reduce rebound viral replication (Ottolini et al 2002). Hematopoietic stem cell transplant (HSCT) recipients were administered 15 mg/kg of palivizumab intravenously in two phase 1 studies. The first study enrolled 6 HSCT patients who didn't have active RSV infection whereas the second study enrolled 15 patients who had active RSV infection (12 lower respiratory tract, 3 upper respiratory tract). Aerosolized ribavarin was administered in all of study two's 15 patients. The mean serum half-life of palivizumab was 22.4 days in study one and 10.7 days in study two, while serum concentrations >40 μg/mL were maintained for 21 days in 83% of study one patients and 73% of study two patients. RSV was detected by culture on day 21 in 16.7% of patients. Palivizumab appeared to be safe and well tolerated in HSCT recipients with 10 (83%) of 12 patients who had lower respiratory tract RSV infection surviving (Boeckh et al 2001). A decision analysis model recently concluded that there would be a 10% absolute increase in survival from RSV-related lung disease in pediatric bone marrow transplant (BMT) patients if they received palivizumab prophylaxis with the number needed to treat of 12 to prevent 1 death (Thomas et al 2007). Clinical guidelines from the American Society of Transplantation recommend using either palivizumab or RSV immune globulin intravenous in combination with ribavarin if patients have RSV lower respiratory tract disease. The use of palivizumab in children less than 1 year of age who receive their transplant during RSV season can be considered (Community-acquired respiratory viruses 2004).

## Palivizumab in cystic fibrosis

In a study of 22 infants with cystic fibrosis (CF) less than 2 years of age compared with 27 age-matched controls, CF children infected with RSV were 4 times more likely to develop lower respiratory tract infection, had a greater risk of hospitalization, and developed a decrease in lung function that lasted for several months (Hiatt 1999). A national questionnaire survey of CF centers in the UK found that 16/143 (11.2%) of CF infants were hospitalized with RSV without ICU admissions or deaths. Palivizumab was administered to 14/143 infants (9.8%) with 1 infant (7.1%) requiring hospitalization after receiving prophylaxis. Two of the three centers that used palivizumab had a negotiated funding agreement and offered RSV prophylaxis to children less than 1 year of age. Survey respondents were more likely to prescribe palivizumab if funding were not an issue (McCormick and Southern 2007). In a phase IV study examining the safety of palivizumab in 186 children with CF, 92 children were randomized to palivizumab and 94 children were randomized to placebo. The overall adverse events were similar in both groups and no serious adverse events were related to palivizumab. The hospitalization rate was 1.1% in both groups (Cohen et al 2005).

## Palivizumab usage in hospitalized infants and children

Fifty-nine previously healthy children less than or equal to 2 years of age hospitalized with acute RSV infection were given IV palivizumab or placebo in a phase I/II, multicenter, randomized, double-blind, placebo-controlled, escalating-dose clinical trial (Sáez-Llorens et al 2004). After at least 12 children received 5 mg/kg dose of palivizumab and were followed for at least 5 days without experiencing dose-limiting toxicity or a serious adverse event, dose-escalation to 15 mg/kg palivizumab occurred. There were no significant differences in adverse events between the groups. Mean serum concentrations of palivizumab 60 minutes after administration was 61.2 and 303.4 μg/mL in the 5- and 15-mg/kg groups, respectively. At 30 days mean serum concentrations of palivizumab were 11.2 and 38.4 μg/mL in the 5- and 15-mg/kg groups, respectively. The small number of patients randomized in this study was not sufficiently powered to show efficacy of adopting this strategy in the management of children hospitalized with acute RSV infection; however, there were no significant differences in clinical outcomes between groups. Additionally, a randomized, double-blind, placebo-controlled trial of 35 mechanically ventilated children <2 years of age with RSV infection demonstrated no differences in measures of disease severity between groups (Malley et al 1998), suggesting the lack of therapeutic benefit to palivizumab administration during active RSV infection.

Palivizumab has been used to control outbreaks of nosocomial RSV infection in premature infants (Cox et al 2001; Abadesso et al 2004). The implementation of standard infection control measures that were adopted in addition to the administration of palivizumab makes it difficult to assess whether palivizumab was solely, or even partially,

responsible for halting further outbreak of RSV infections (Cox et al 2001). However, the use of palivizumab may be effective in halting further cases of RSV if infection control measures fail (Abadesso et al 2004).

## Pharmacoeconomic considerations of palivizumab usage

One of the most contentious issues surrounding palivizumab use is its cost-benefit ratio, which was noted by the American Academy of Pediatrics in their revised recommendations for RSV immunoprophylaxis (Meissner and Long 2003). It is difficult to evaluate and interpret pharmacoeconomic analyses. For example, 67% of submissions by pharmaceutical companies to the Department of Health and Aged Care in Australia for the purpose of getting the cost of drugs reimbursed had significant problems. Uncertainty in the estimates of comparative clinical efficacy, modeling issues such as clinical assumptions and cost estimates, calculation errors, and disagreement in choice of comparator were all noted (Hill et al 2000).

A systematic review of 12 studies that performed a pharmacoeconomic analysis of immunoprophylaxis agents against RSV found conflicting results as to whether palivizumab or RSV-IGIV was cost-effective in different infant subgroups. The authors suggested that neither agent was considered cost-effective if administered according to AAP guidelines (Kamal-Bahl et al 2002). Differences in study methods and assumptions regarding the cost of RSV-related hospitalization, number of doses administered, weight of infants receiving immunoprophylaxis, and whether the study had financial support from the manufacturer of the two agents contributed to the disparate findings. A recent cost-effectiveness analysis was conducted from a societal perspective in a hypothetical cohort of infants born between 26 and 32 weeks gestation without chronic lung disease. Factors measured included parental lost wages for an infant RSV-related emergency department (ED) visit and hospitalization, costs for asthma-related care, palivizumab acquisition, injection administration, ED services, and RSV hospitalization. Palivizumab was not found to be cost-effective, irrespective of gestational age, if there was no causal relationship between RSV and asthma. Palivizumab was considered cost-effective in infants born at 26 and 29 weeks gestation who had a reduced quality of life due to asthma and if palivizumab costs were reduced to 25% of their current value for these infants (Elhassan et al 2006). A more restrictive guideline that offered palivizumab to infants born at 26 or 27 weeks gestation was suggested, which is similar to Swedish guidelines recommending the use of palivizumab in infants less than 6 months of age who were born before 26 weeks gestation (Swedish Consensus Group 2001) and guidelines in New Zealand which recommend palivizumab be offered to infants born at less than or equal to 28 weeks gestation, although best estimates did not find a positive cost benefit in any group (Vogel et al 2002). A systematic review in the United Kingdom suggested that palivizumab is cost-effective if the probability of RSV hospitalization is at least 31% (Simpson and Burls 2001), leading to a recommendation from Embleton et al (2005) that pre-term infants without other risk factors such as chronic lung disease or hemodynamically significant cardiac disease should not be offered palivizumab.

Similar concerns of cost-effectiveness of palivizumab administration in CHD have also been raised. A decision analysis model by Yount and Mahle (2004) found the cost of providing palivizumab was 3 times more expensive than 1 day in the hospital and was cost-effective only if one assumed that palivizumab reduced in-hospital mortality from RSV infection in children with CHD. Another review found no evidence that palivizumab administration given prior to hospital discharge leads to reduced hospitalization in premature infants compared with administration after hospital discharge. The practice of requiring palivizumab after discharge represents significant potential cost avoidance to hospitals since many third-party payers do not separately reimburse hospitals for in-hospital immunizations (Geskey et al 2004) and less than 1% of infants who received palivizumab in the home setting were subsequently hospitalized with RSV infection (Golombek et al 2004).

## Future directions

Future studies are required to determine whether prophylaxis with palivizumab decreases the prevalence of asthma in children with known risk factors. This area of research is crucial as palivizumab has been shown in vitro to block airway permeability in human bronchial epithelial cell cultures (Kilani et al 2004) and also lung inflammation, airway obstruction, and airway hyper-responsiveness in mice (Mejías et al 2004). The recent development and study of MEDI-524, which has more potent anti-RSV neutralizing activity than palivizumab, demonstrated reduced lung RSV loads and significantly less inflammation than palivizumab when given 24 hours prior to inoculation with RSV in a mouse model. However, when given after infection, neither monoclonal antibody was able to reverse the lung injury that had already occurred after RSV infection (Mejías et al 2005). This demonstrates the continued need for a

vaccine to reduce the substantial morbidity that occurs with RSV infection and highlights that the engineering of even more potent monoclonal antibodies that have the potential to reduce not only the RSV hospitalization rate but also the long-term pulmonary abnormalities that may occur from RSV infection.

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