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Pro-Con Debate

# Should respiratory care in preterm infants include prophylaxis against respiratory syncytial virus infection? The case in favour

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SUMMARY

Respiratory syncytial virus (RSV) is the most significant cause of acute respiratory tract infections (RTI) in infants and young children throughout the world. Preterm infants are at increased risk for severe RSV lower respiratory tract infection due to small lung volumes, a reduced lung surface area, small airways and an increased air space wall thickness. Additionally, the airways of preterm infants have been ventilated mechanically and suctioned and potentially damaged by many microtraumas with disruption of endothelial surfaces enabling pathogens to invade more easily. The immune system of preterm infants is immature resulting in low antibody titers (incomplete transplacental transfer of maternal antibodies) and a reduced cellular immunity with reduced viral clearance. Rehospitalization rates of preterm compared to term infants due to RSV infection are increased as are total morbidity and mortality associated with RSV disease. Palivizumab effectively reduces RSV related rehospitalisation in this high-risk population.



## INTRODUCTION

Respiratory syncytial virus (RSV) is the most significant cause of acute respiratory tract infections (RTI) in infants and young children throughout the world.[1] The World Health Organization (WHO) estimates that one third of the 12.2 million annual deaths in children below 5 years are the result of acute infections of the respiratory tract, with RSV, Streptococcus pneumoniae, and Haemophilus influenzae as the predominant pathogens.[2] The severity of RSV outbreaks varies from year to year,[3] perhaps in part because of a variation in circulating strains. RSV has two major antigenic groups, A and B, with additional antigenic variability occurring within each group. The most extensive antigenic and genetic diversity occurs on the G protein on the surface of the virus, which is the attachment glycoprotein.[4] Data collected over a 15-year period in Rochester, NY, show a pattern of 1-to 2-year cycles where group A strains predominate, followed by a year in which at least half of the strains are group B. Group A strains predominate in 9 of the 15 years studied, while group B strains predominated in only 2 years a decade apart.[3] Thus, the antigenic differences occurring among these viruses may contribute to RSV's ability to establish reinfections throughout life.[5]

Mortality associated with primary RSV infection in otherwise healthy children is estimated to be 0.005% to 0.02%,[6] and is approximately 1% to 3%[7] among hospitalized children. Repeated RSV infections are common in all age groups. RSV usually spreads by close contact with infected people or their infectious secretions, which tend to be profuse, especially in young children. RSV in nasal secretions of acutely infected infants remains infectious on countertops for more than 6 hours and on cloth and paper tissue for 30 minutes.[8] Risk factors for acquisition of RSV bronchiolitis in infants and young children include birth during RSV seasonal peaks, day-care attendance, lack of breast-feeding, residence in crowded homes, multiple births, and presence of siblings.[9,10] Risk factors associated with increased severity of RSV infection in healthy infants and children include male gender, low socio-economic status, crowded living conditions, indoor smoke pollution, malnutrition, a family history of asthma or atopy, and lower cord serum RSV antibody titers.[11]

Children born with certain medical conditions including prematurity, bronchopulmonary dysplasia [BPD], congenital heart disease (CHD), neuromuscular impairment, cystic fibrosis, and immune deficiency syndromes have consistently been found to be at increased risk for severe RSV disease compared with children without these conditions and have been the primary risk groups considered for RSV prophylaxis with palivizumab.[12,13] Palivizumab (MedImmune, Gaithersburg, MD) is a humanized monoclonal antibody that recognizes a highly conserved neutralizing epitope on the fusion protein of RSV[14] and is recommended for RSV prophylaxis of at-risk children.[15] Monthly prophylaxis with palivizumab reduced RSV hospitalizations by ~50% compared with placebo in premature infants with and without BPD.[16]

Another phenomenon following early RSV lower respiratory tract infection includes recurrent episodes of wheezing mimicking

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early childhood asthma during childhood. The prevalence of respiratory symptoms appears to diminish over the first years of life, but recent studies observed either reactive airway disease or lung function abnormality until adolescence.[17–19]

This paper reviews the available data on the increased risk of preterm infants with and without BPD for severe RSV infection and the need for RSV prophylaxis with palivizumab at least during the first RSV season.

## RSV AND BPD

BPD is a condition of immature lung development and lung injury, resulting in the need for oxygen supplementation or other medical therapies. The length, timing, and type of therapy that defines BPD vary, but studies have shown consistently that children with BPD have an increased vulnerability to severe RSV disease. This may be due to underdeveloped pulmonary vascular beds, injured epithelium, and damaged clearance mechanisms that lead to increased risk for pulmonary oedema und hypoxia with RSV infection.[20]

Ventilated preterm infants, especially those below 1000 g birth weight, are at high risk for developing BPD. In these infants ventilation-induced volutrauma and oxygen toxicity as well as pre-and postnatal infections can initiate and sustain a pulmonary inflammatory response leading to a possible impaired development of the lung.[21] Groothuis et al[22] first reported on the increased risk of preterm infants with bronchopulmonary dysplasia (BPD) for RSV related prolonged hospitalizations, high rates of admission to the ICU and the need for mechanical ventilation. In their prospective study including 30 infants below 2 years of age with diagnosis of BPD receiving home oxygen therapy after discharge from the hospital, 11 of 15 hospitalizations were due to an RSV infection. Thirty-six percent of the infants were admitted to the ICU and 18% of them required mechanical ventilation.

Early data from the PICNIC study group, including twelve paediatric tertiary care centers during the 1989 to 1990 season, observed 12.6% of hospitalized infants with RSV infection having chronic lung disease and 23.9% being born prematurely.[23] Another data set from the PICNIC study group found underlying illnesses including chronic lung disease like bronchopulmonary dysplasia significantly associated with prolonged hospital stay which was attributable to RSV compared with those who were premature or younger than 6 weeks of age on admission.[24] The proportion of infants with underlying illness was 22.6% in a study population of 689 patients. Sixteen percent were admitted to ICU and 9.1% needed mechanical ventilation. The mortality rates varied across all groups, and the rate was 0.9% in the total study population.

In the PREVENT Study (1997),[25] a randomized placebo controlled trial on the use of intravenous immunoglobulin prophylaxis (RSV-IGIV) in preterm infants with and without BPD, 17.4% infants with BPD (26/149) were rehospitalized due to proven RSV infection. The IMpact-study (1998),[26] a randomized, double-blind, placebo controlled trial conducted in the United States, Canada and the United Kingdom, determining the safety and efficiency of palivizumab, revealed an RSV rehospitalisation rate of 12.8% in infants with BPD, which was reduced to 7.9% (39% reduction) in the group having received palivizumab prophylaxis. Thereafter several other studies revealed RSV hospitalization rates ranging up to 24.4%.[27–30]

Stevens et al (2000)[31] reported on 24.4% rehospitalizations due to RSV infection in a cohort of 131 infants requiring respiratory support beyond 36 weeks postconceptional age. These patients were also more likely to be admitted with RSV than infants with respiratory support only up to 36 weeks postconceptional age. In the study of Carbonell-Estrany (2000)[28] the RSV rehospitalization rate was 15% in infants with chronic lung disease. In the multivariate logistic regression model the higher risk for hospital admission in infants with chronic lung disease was a significant prognostic variable ($p < 0{,}016$).

A 19% readmission rate due to a proven RSV infection was reported by Greenough et al (2001)[30] in a cohort of 235 neonates prematurely born neonates $<$ 32 weeks' gestation and requiring oxygen beyond 28 days after birth. 19% were readmitted to the hospital. A more recent study from The Munich RSV Study Group (2003)[32] reported on a rehospitalisation rate of 15.4% in preterm infants $\leq$ 35 GA with BPD. In the multivariate logistic regression model BPD as well as male sex and day care-attendance of siblings yielded statistical significance as an independent predictor for RSV rehospitalisation. Another prospective German multicentre study from the RSV Paed Study Group[33] found RSV hospitalization rates of 12.3% (50/356) in preterm infants with BPD. The authors also reported on a significantly higher proportion of nosocomially acquired RSV infections in the BPD group (30.8% vs. 9.8%, $p<0.001$).

In the univariate analysis the criterion premature infant having BPD and requiring treatment over the last months was significantly associated with a complicated clinical course and was significantly and independently associated with the combined outcome "complicated course of disease" in the multivariate analysis. A summary of the studies is shown in Table 1.

Of 151 children under 1 year of age admitted to the paediatric intensive care unit (PICU) of the Trousseau Hospital in Paris from 1 January 1996 to 31 December 2003 for management of bronchiolitis caused by proven RSV infection and requiring mechanical ventilation 14 infants, (9.1%) needed extracorporeal membrane oxygenation (ECMO) support.[34] The frequency of BPD was significantly higher amongst children who required ECMO support as compared with those from the group without ECMO support (p=0.001, OR =8.9; 95%CI=2.4–33.1).

## RSV AND PREMATURITY WITHOUT BPD

The risk for RSV related hospitalization is significantly increased in preterm infants. In East Denmark the incidence of RSV infection requiring hospitalization among infants <6 months was estimated to be 34/1000/season, and was 32/1000/season among term infants and 66/1000/season among preterm infants ($p<0.001$).[35] In Southern Austria we observed an incidence of RSV infection

**Table 1**
Bronchopulmonary dysplasia (BPD) and RSV- related rehospitalization rates.

| Study years | Reference No. | Country | Hospitalization rates in % | Study population | Mortality rate in % |
|---|---|---|---|---|---|
| 1985–1986 | 20 | USA | 59 | 30 | 0 |
| 1994 | 21 | USA | 17,4 | 149 | 1,3 |
| 1996 | 22 | USA, Canada, UK | 12,8 | 266 | 1,0 |
| 1992–1996 | 11 | USA | 7,6 | 1029 | 0 |
| 1998–1999 | 14 | Spain | 15 | 53 | 1,8 |
| 1994–1997 | 24 | UK | 19 | 235 | 0 |
| 1998–1999 | 25 | Germany | 15,4 | 53 | 0 |
| 1999–2005 | 26 | Germany | 12,3 | 356 | 8,0 |