

Preventing Respiratory Syncytial Virus in High Risk Populations

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Summary

Respiratory syncytial virus (RSV) continues to be a major cause of infant morbidity, resulting in rising hospital admission rates and costs. Infection with this virus early in life can have long-term consequences such as asthma. Children with certain risk factors are particularly vulnerable to infection with RSV and should receive prophylaxis during the RSV season. Emerging data indicates that appropriate prophylaxis in high-risk children reduces long-term respiratory morbidity.

Key Points

- All patients are not equally at risk for life-threatening or life-changing RSV infections.
- Those at most risk for severe RSV infection include children with premature birth, chronic lung disease, congenital heart disease, neuromuscular disease, and immune deficiency.
- Prevention of severe RSV infections includes prevention of preterm birth, deliberate hand washing, minimizing exposure of the vulnerable patient to the virus, and palivizumab prophylaxis in high-risk children.
- Palivizumab has been shown to reduce hospitalization of high-risk children.
- There is a possible beneficial role of palivizumab prophylaxis in the reduction of long-term respiratory morbidity.

MANY OF THE DRIVERS OF PEDIATRIC CRITICAL care hospitalizations are preventable or partially preventable. One of these is respiratory syncytial virus (RSV). Preventing RSV infection in vulnerable populations is an example of where the United States can do a much better job when it comes to preventative health.

There are approximately 4 million births every year with 12.5 percent being preterm (less than 37 weeks gestation).¹ Of the premature babies born each year, those who survive face the risk of life long health consequences, such as breathing and feeding problems, cerebral palsy, and learning problems. Although the rate of preterm births has been consistent for 25 years, the number of preterm survivors has been increasing because of advances in neonatal care.

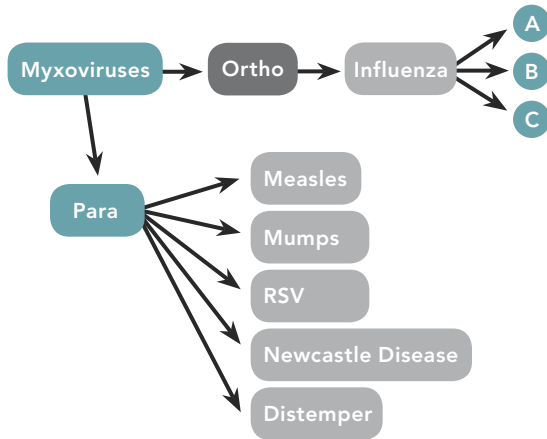
The initial costs of caring for preterm infants are enormous. Approximately \$50 billion a year is spent in the United States on preterm care. From one retrospective review of 84 children, the average hospital cost at discharge for a term infant was about

\$5,000.² In late preterm infants (defined as 33 to 36 weeks in this study), the cost increased to \$10,000. The costs for the shortest gestational age infants were dramatically increased: \$50,000 for 29 to 32 weeks and \$200,000 for 26 to 28 weeks. Overall, preterm infants are disproportionate users of health care resources.

Preterm infants are uniquely vulnerable for morbidity and mortality. Mortality rates for infants born even a few weeks early, or late preterm (between 34 to 36 weeks of gestation) are three times those for full-term infants.³ Late preterm and preterm infants are very much alike anatomically, physiologically, and immunologically. Late preterm infants are within the same stage of lung development as 28 to 32 week gestational age infants.¹ These late preterm infants also have half of the maternally transferred passive immunity against RSV of term infants.⁴ This increases the risk of severe RSV infection.⁵

RSV is a member of a common family of mammalian pathogens (Exhibit 1). Nearly every child

Exhibit 1: RSV Is a Member of a Common Family of Mammalian Pathogens



has been infected with RSV by the age of 2. Unfortunately, humans do not have immune “memory” to RSV so we can be infected over and over, even within the same season.

Like influenza, RSV is a seasonal disease.⁶ For reasons not yet understood, RSV is a year round disease in much of Florida.

RSV is easily transmitted through contact with infectious secretions via hand contamination, self-inoculation via the eyes, nose, or mouth, direct or close physical contact, or contact with a contami-

nated surface. RSV often spreads in crowded households and daycare centers.

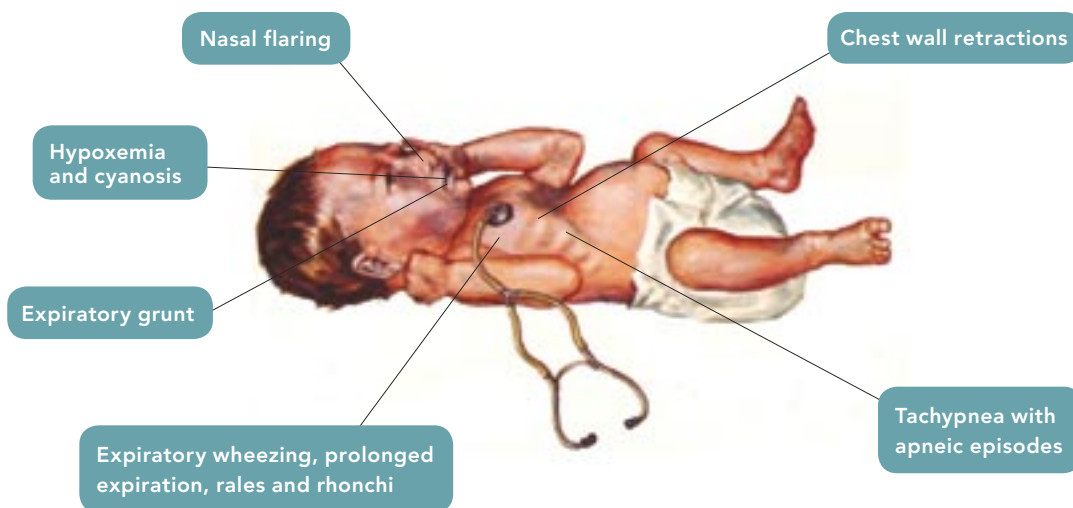
Acute RSV infections can be in the upper or lower respiratory tract. Lower tract infections result in emergency department visits, acute hospitalization, intensive care admission, and mechanical ventilation. In one study of emergency department visits in kids younger than 7, RSV accounted for 37.6 percent of positive virus tests.⁷

Exhibit 2 shows the typical clinical features of RSV infection in infants.⁸ These infected infants can progress to respiratory arrest requiring intubation. Unfortunately there are no specific treatments for RSV; care is primarily supportive.

RSV bronchiolitis is the top cause of infant hospitalization.⁹ RSV infections result in 125,000 hospitalizations among infants each year and more than \$3 million in cost. RSV disease burden exceeds influenza in children aged 1 to 4 years.¹⁰ Of the infants who are hospitalized due to severe RSV disease each year, approximately 20 percent were born preterm.¹¹ When looking at annual mortality, in infants, RSV is the leading cause of viral death, with nearly nine times the mortality of influenza.¹²

Preterm infants have about a twofold increased rate of RSV hospitalization compared to term infants.¹³ Once in the hospital, preterm infants have worse hospital outcomes than full-term infants. They have longer length of stay, higher rates of intubation, and longer intensive care unit stays. Considering all preterm infants, there appears to be a similar rate of hospitalization due to RSV indepen-

Exhibit 2: Clinical Features: Infant with Respiratory Distress



Reference 7

Exhibit 3: Children at Increased Risk of Severe RSV Infection

Conditions	Pathophysiology
Premature birth	Interrupted lung development Absence of maternal antibody
Chronic lung disease	Bronchial hyperresponsiveness Reduced lung reserve
Congenital heart disease	Pulmonary hypertension
Neuromuscular disease	Decreased respiratory muscle strength and endurance
Immune deficiency	Decreased host defense

Reference: 15, 16

dent of gestational age.¹⁴ Previously it was thought that the younger the gestational age, the more likely the infant was to require hospitalization for RSV.

Risk assessment is important when determining preventive strategies for RSV. By identifying those at highest risk for severe RSV disease, the health care system can target interventions to maximize risk reduction and outcomes. Not all children are at risk for severe RSV infection. Those at most risk include children with premature birth, chronic lung disease, congenital heart disease, neuromuscular disease, and immune deficiency (Exhibit 3).^{15,16} A number of large retrospective studies have tried to identify those at most risk for hospitalization because of an RSV infection.^{17,18} The best predictors of hospitalization in

late preterm infants are being born during RSV season and daycare attendance (Exhibit 4).

Although hospitalization rates appear independent of gestational age, mortality is not. The younger the gestational age of the infant, the higher the mortality rate. Infants 32 to 35 weeks gestational age have a fivefold greater risk of bronchiolitis-associated death than full term infants.¹⁹ Infants less than 32 weeks gestational age have a 17-fold greater risk of bronchiolitis-associated death than full term infants.¹⁹

RSV hospitalizations are associated with increasing health care costs. From 1997 to 2002, RSV hospitalization rates among infants <1 year of age increased by 25 percent.²⁰ Mean hospital charges for RSV hospitalizations increased by 39 percent during this same period, totaling more than \$1.1 billion in 2002. These numbers are going to increase as younger and younger gestational age survival rates increase. Exhibit 5 illustrates the differences in health care resource utilization between full term infants, preterm infants, and those with cardiovascular or pulmonary disease when requiring hospitalization for RSV.²¹⁻²⁷

An RSV hospitalization also influences a child's future health care costs. Premature infants born at 32 to 35 weeks GA who had an RSV infection were hospitalized 2.3 times more and had 2.4 times more outpatient visits during the two years following an initial RSV hospitalization.²⁷

Because RSV infection has significant consequences, prevention of infections would be ideal. The American Academy of Pediatrics bronchiolitis guidelines make several recommendations:

Exhibit 4: Risk Factors for RSV Hospitalization 33-35 Weeks GA

Spanish Study	
Risk Factors	OR (P value)
Absolute chronologic age at start of RSV season ≥ 10 wk	3.95 (P<.001)
≥ 1 school-age siblings	2.85 (P<.001)
≥ 4 residents or visitors 1.91	1.91 (P=.0074)
Breast-feeding ≥ 2 months	3.26 (P<.001)
Family history of wheezing	1.90 (P=.0068)
Smoking not a risk factor: During the study, smoking in Spain decreased from 52% to 30% due to a national campaign	

Agreement between studies.

Canadian Study	
Risk Factors	OR (P value)
Born Nov., Dec., or Jan.	4.88 (P<.001)
Preschool-age siblings	2.76 (P=.001)
>5 individuals in home	1.69 (P=.088)
Small for GA	2.19 (P=.019)
Daycare attendance	12.32 (P=.002)
≥ 2 smokers in household	1.71 (P=.064)?

Reference: 17,18

Exhibit 5: Hospitalization and Hospital Resource Utilization for RSV Disease

High-Risk Group	Hospitalizations for RSV	RSV hospitalizations leading to	
		ICU Admission	Ventilation
Term (>36 weeks)	1%-3%	11%	4.6%
Premature (<35 weeks)	10.6%	28%-31%	12%-22%
BPD	12.8%	32%	17%
CHD	9.7%	26%-33%	19%-24%

References: 21-27

- Alcohol-based rubs are preferred for hand decontamination.
- Hand washing with antimicrobial soap is an acceptable alternative.
- Clinicians should educate personnel and families about hand sanitation.
- Breastfeeding to reduce the likelihood of lower respiratory tract infections should be encouraged.
- Infants should not be exposed to passive smoke.²⁸

Another important preventive measure is reduction of the preterm birth rate.

Medications also can be used to prevent severe RSV infections. AAP recommends that palivizumab prophylaxis may be administered to children with chronic lung disease, a history of prematurity (<35 weeks gestation), or with congenital heart disease.²⁸ When given, five doses should be given at 30-day intervals starting in November or December.

In the IMPact-RSV study, significantly lower RSV hospitalization rates were observed among premature infants who received palivizumab than among those who received placebo in each of the subgroups (Exhibit 6).²² This study was a randomized, double-blind, placebo-controlled trial conducted in 139 centers across the United States, the United Kingdom, and Canada during the 1996 to 1997 RSV season. For the primary endpoint of the trial, the intent-to-treat analysis showed a 55 percent reduction in hospitalizations among all children enrolled. Although the study was not powered to demonstrate efficacy in subgroups, there were statis-

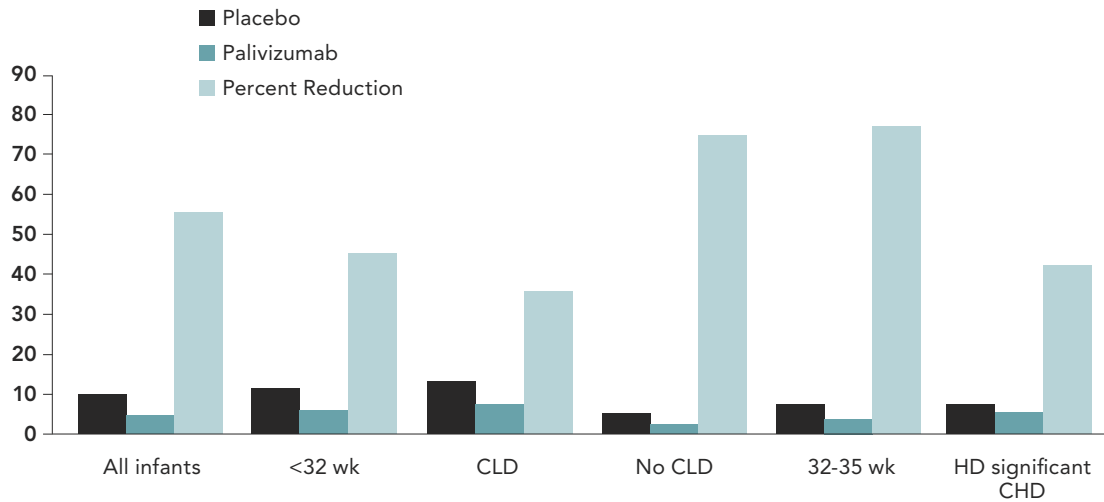
tically significant reductions in RSV hospitalization rates in several subgroups. In infants of gestational age <32 weeks, RSV prophylaxis with palivizumab reduced hospitalizations by 47 percent ($p = 0.003$). The highest reduction in hospitalization rate was seen in infants of gestational age 32 to 35 weeks; RSV prophylaxis with palivizumab reduced hospitalizations by 80 percent ($p = 0.002$).

The Cardiac Synagis Study Group showed that palivizumab prophylaxis reduces hospitalization due to RSV in young children with hemodynamically significant congenital heart disease (also included in Exhibit 5). In the intent-to-treat patient population, incidence of RSV hospitalization was lower for children receiving palivizumab ($n=639$) than for children receiving placebo ($n=648$) (5.3 percent versus 9.7 percent, respectively; $p=0.003$), for a 45 percent reduction in hospitalization rate.²³

Although reduction of RSV hospitalizations is a desirable outcome with palivizumab prophylaxis, data seems to indicate that the disease burden of RSV infection does not end with hospitalization but may include long-term effects such as recurrent wheezing or asthma.

RSV disease in infancy appears to be an important risk factor for asthma/recurrent wheezing up to age 13 (Exhibit 7).^{29,30} Sigurs and colleagues recruited 47 infants hospitalized with RSV bronchiolitis and 93 controls and followed them for 13 years. At 7 years, the cumulative prevalence of asthma was 30 percent in the RSV group compared with 3 percent

Exhibit 6: Palivizumab Reduces RSV-Related Hospitalization Rates in Selected Populations



Reference: 22, 23

in the control group.²⁹ In the 13-year follow-up, current asthma or recurrent wheezing was reported in 43 percent and 8 percent of children in the RSV group and control group, respectively.³⁰

Stein and colleagues followed a subset of children in the Tucson Children’s Respiratory Study born between 1980 and 1984 with a mild lower respiratory tract infection before age 3. This study found significantly increased risk of frequent and infrequent wheeze by age 6 among 207 children with mild outpatient treated RSV during infancy compared with a reference group of children with no RSV infection during the first three years of life ($p < 0.01$).³¹ The risk of frequent wheeze was still significantly increased at age 11 ($p < 0.1$).³¹ By age 13, there were no significant differences between groups. Compared with children with no RSV infection, children with RSV infection before age 3 were 3.2 times more likely to have infrequent wheeze and 4.3 times more likely to have frequent wheeze at age 6. Therefore, even mild infection with RSV before age 3 is associated with significant increase in risk of subsequent wheezing during the first 10 years of life.

In a small retrospective study of high-risk children who had received prophylaxis with RSV immune globulin (Respigam[®]), a possible long-term protective effect was identified. Although no differences were seen in pulmonary function tests, there were fewer colds, asthma attacks, and school days missed in the children who had received prophylaxis earlier in life.³²

A study done in 27 centers across the country pro-

spectively addressed the issue of whether palivizumab prophylaxis confers long-term benefits. At one year after infection, the incidence of physician-diagnosed recurrent wheezing were significantly lower in the 191 palivizumab-treated subjects (8 percent) compared with all 230 untreated subjects (16 percent, $p = .011$).³³

Conclusion

RSV has emerged as a formidable pathogen akin to influenza, parainfluenza, and rhinovirus in causing significant disease. All patients are not equally at risk for life-threatening or life-changing infections. Prevention begins with preventing preterm labor, deliberate hand washing, and minimizing exposure of the uniquely vulnerable patient. Palivizumab prophylaxis has been shown to reduce hospitalization of high-risk children. The recent prospective report of the potentially beneficial role of palivizumab prophylaxis on the reduction of long-term respiratory morbidity is exciting and encouraging. More data delineating the clinical and public-health impact of RSV infection beyond acute bronchiolitis in infants are needed. **JMCM**

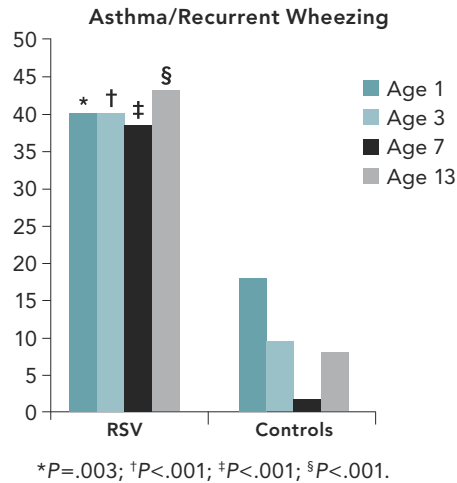
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Exhibit 7: RSV Disease in Infancy Is an Important Risk-Factor for Asthma/Recurrent Wheezing up to 13-Years of Age

- 47 children hospitalized for RSV lower respiratory infection (LRI) in the 1st year of life
- 93 controls with no RSV LRI
- Risk of wheezing was significantly higher at 13 years compared with controls ($P < .001$)?



Reference: 29,30

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