

Respiratory Syncytial Virus Infection and the “Mildly” Preterm Infant

Howard B. Panitch, M.D.

Director, Division of Pulmonary Medicine
Children's Hospital of Philadelphia
Professor of Pediatrics, University of Pennsylvania
Philadelphia, PA 19104
Phone (215) 590 3749
FAX (215) 590 3500

Bronchiolitis resulting from infection with respiratory syncytial virus (RSV) is the most common cause for hospitalization in infants under one year of age¹. In the United States, an estimated 125,000 hospitalizations per year occur for RSV lower respiratory tract infections in infants². Children with underlying conditions like premature birth, chronic lung disease, hemodynamically significant congenital heart disease, neuromuscular disease, and congenital airway anomalies are considered to be at high risk for developing RSV lower respiratory tract infections severe enough to warrant hospitalization³. As such, these are the very groups of infants whom the American Academy of Pediatrics suggests should be considered for immunoprophylaxis against RSV.

Although premature infants comprise only 7.5% of all births in the United States⁴, they represent the largest group of infants with an underlying condition that increases the risk for RSV-related hospitalization. Furthermore, of the approximately 300,000 infants born in the United States at gestational ages (GA) below 36 weeks in 2001, 74% were born between 32 and 35 weeks GA⁴. Immunoprophylaxis against RSV, while effective, is expensive. For this reason, the American Academy of Pediatrics and other expert panels recommend limiting the use of immunoprophylaxis to those children most at risk for severe RSV disease^{3, 5, 6}. Preterm infants \leq 32 weeks GA are considered candidates for prophylaxis based on a combination of gestational age and chronological age at time of onset of the RSV season. Because the “mildly” premature infant group (32 to <36 week GA) is so large, recommendations for immunoprophylaxis in this group are limited to situations in which added risk factors increase the likelihood or severity of RSV illness³. Implicit in these recommendations are the concepts that risk of severe RSV disease correlates with GA among premature infants, and that outcomes after RSV disease are better for the mildly preterm infant than for the moderately or severely preterm infant. Published data, however, do not support these concepts.

Hospitalization rates for RSV

Infants with gestational ages (GA) \leq 36 weeks comprise anywhere from 12 to 28% of those hospitalized with RSV infection⁷⁻¹¹. In a prospective study of 1,516 infants hospitalized for RSV infection across 9 centers in Canada, 21% were born prematurely but without other risk factors⁸; 12.9% of the cohort (or 62% of all premature infants), however, was born between 33 and 36 weeks GA¹². Risk of RSV-related hospitalization does not correlate with GA. Boyce et al retrospectively reviewed all RSV-related

hospitalizations for all children <3 years old covered under the Tennessee Medicaid program over a 4 year period ⁹. The risk of RSV-related hospitalization for any premature child <6 months of age was approximately twice that of same-aged children born at term with no underlying condition, no matter how premature the child was. Specifically, hospitalization risk was no different among those born ≤ 28 weeks GA, 29 to <33 weeks GA, or 33 to <36 weeks GA.

When mildly preterm infants are hospitalized with an RSV illness, their courses have been shown to be no better or perhaps worse than those of infants born at younger gestational ages. In a study that sought to determine whether hospital resource use and illness outcomes were associated with GA, Horn and Smout retrospectively analyzed hospital records of 304 children ≤ 12 months of age from 9 centers, hospitalized with a documented RSV lower respiratory tract infection ¹³. Of those born prematurely (<37 weeks GA), 28 were ≤ 32 weeks GA, 31 were 33 to 35 weeks GA, and 30 were born at 36 weeks GA. Those infants born between 33 and 35 weeks GA had the highest hospital and ICU length of stay and significantly higher intubation rates than any other gestational age group, even when comorbidities, severity of illness measures, and site-specific variations in medical practice were controlled for. The authors concluded that prematurity, whether 33-35 weeks GA or ≤ 32 weeks GA, is associated with a similar level of risk of poor hospital outcomes and greater hospital resource use. Furthermore, there was no evidence of a linear relationship between degree of prematurity and outcomes or resource utilization; all infants born ≤ 35 weeks GA were at a similar increased risk for more severe disease when hospitalized for an RSV infection.

Health care utilization after RSV hospitalization

Former premature infants with a past history of RSV-related hospitalization also subsequently utilize more health care resources after that hospitalization than matched infants never hospitalized for RSV infection. A study from the United Kingdom described greater numbers of subsequent hospital days, outpatient visits, use of inhaled bronchodilators, and more medication use in general from 2 to 4 years of age in 33 children with a history of extreme prematurity (≤ 32 weeks GA) and chronic lung disease (bronchopulmonary dysplasia, BPD) who were hospitalized within the first 2 years of life with an RSV illness compared to a matched cohort of 157 children never hospitalized for RSV disease ¹⁴.

When only mildly preterm infants with no chronic lung disease have been analyzed, however, the results are similar. Using hospital discharge data, Sampalis identified 2,415 Canadian infants with a proven or probable RSV-related hospitalization, born between 32 and 35 weeks gestation ¹⁵. He compared their subsequent health care resource utilization with that of 20,254 infants matched for gender, GA, and province of birth. All infants with identified congenital anomalies or history of BPD were excluded. In the subsequent 1 to 4 year (median 2 year) follow-up period, those former preterm infants with a history of RSV hospitalization required more than twice the number of hospitalizations (2.96 vs. 1.28, $p < 0.001$), longer cumulative hospital stays (14.71 vs. 5.04 days, $p < 0.001$), and more than double the number of outpatient visits (18.4 vs. 7.54, $p < 0.001$). Furthermore, during hospital admissions, the group with prior RSV hospitalizations required much

more in the way of resource utilization: they were admitted to special care units 50% more often, received respiratory therapy services three times more frequently, physician consults 4 times more often, and had 25% more diagnostic and therapeutic procedures than did those former preterms without a past RSV hospitalization. Also of note, the overall mortality rate throughout the follow-up period was 5 times higher in the RSV hospitalized group (8.1% vs. 1.6%), and the RSV hospitalized group also had a significantly higher incidence of sudden or unexplained death compared with the controls (6.1 vs. 0.3%). Together, these findings led the authors to speculate that RSV infection in the 32 to 35 week gestation infant might affect the infant's overall health and have consequences beyond the respiratory system. They also noted that health care costs associated with RSV hospitalizations in mildly premature infants extend well beyond those associated with the initial hospitalization.

Recurrent episodes of wheezing or the development of asthma, which can also increase long term costs and health care utilization, have been associated with RSV infection in infancy¹⁶. A recent international prospective study among former premature infants between 24 and 35 weeks GA without BPD or congenital heart disease sought to determine if palivizumab immunoprophylaxis could reduce the incidence of subsequent recurrent wheezing or asthma¹⁷. The treatment group consisted of 191 former preterm infants who received at least 3 doses of palivizumab in the first 12 months of life. Controls were matched for chronological and gestational ages, and did not receive immunoprophylaxis. The control (untreated) group included 230 infants, 76 of whom had been hospitalized for an RSV illness and 154 who were not. Over the 2 year follow up period, proportionally fewer children in the palivizumab treated group experienced episodes of recurrent wheezing (49% relative reduction) or physician-diagnosed recurrent wheezing (51% relative reduction) ($p \leq 0.01$). When the groups were stratified by gestational age, the relative risk of recurrent wheezing was similar among those <29 weeks GA, 20 to 32 weeks GA, and > 32 weeks GA. The numbers of subjects in each stratum was small, however, limiting statistical power. For all groups, the rate of recurrent wheezing and GA were inversely related. Of note, in a logistic regression model, each week increase in GA was associated with an 11% to 21% reduced risk of recurrent wheezing, independent of palivizumab treatment. Nevertheless, this study introduces an important consideration when costs and benefits of immunoprophylaxis are debated for mildly preterm infants. Clearly, studies evaluating the long-term effects of immunoprophylaxis involving larger numbers of mildly premature infants will be required to determine whether or not substantial long-term morbidity can be prevented in this group.

Risk of severe RSV disease

To determine which infants are most at risk for hospitalization from an RSV infection, two different issues must be considered: 1) which factors increase severity of an RSV illness once infection occurs; and 2) which factors increase the risk to a particular infant of acquiring an RSV infection. The two most often cited reasons for the observed increased severity of RSV disease in otherwise healthy former premature infants are reductions in lung function and a poor immune response. Infants born <36 weeks GA with no lung disease demonstrate lower forced expiratory flows in the first months of life

¹⁸, and the reduction in forced expiratory flows persists at 1 year of age ¹⁹. These findings suggest that the airways of infants born prematurely are narrower than those of term infants, and that airway size or function does not normalize at least over the first year. Of interest, infants whose mothers smoked during pregnancy have been found to have lower lung function over the first year of life when compared with matched infants whose mothers never smoked ^{20, 21}. The combination of premature delivery and prenatal tobacco smoke exposure thus may have especially deleterious effects on postnatal lung function.

We also know from epidemiological studies in healthy term infants that those who are born with low lung function are more likely to demonstrate wheezing illnesses when challenged with viral infections ^{22, 23}. Similarly, among 71 infants with BPD evaluated retrospectively, a value of forced expiratory flows <60% of predicted (approximately -1 z score) was significantly associated with RSV hospitalization (p=0.001), with an odds ratio of 16.8 (2.1, 135.6 CI) ²⁴. Furthermore, when applying a forward stepwise logistic regression, a Z score for forced expiratory flow < -2 was the strongest single factor associated with hospitalization. Reduced lung function in otherwise healthy premature infants, then, can increase the risk for significant airway obstruction in the setting of an RSV infection ²⁵. It is also possible that those mildly premature infants with the greatest reduction of airway function at baseline are also those at greatest risk for severe RSV disease, although this concept has not been studied in the mildly premature population.

Immune function is also altered by premature birth. Transfer of maternal antibodies occurs during the third trimester. Premature birth decreases the opportunity for such transfer, and results in a reduction in antibody levels in even the mildly premature infant; total IgG levels in 32 – 35 week GA infants are approximately half of that found in term infants ²⁶. Cell mediated immunity may also be impaired in those infants who develop severe RSV disease ²⁷. Some other factors that have been associated with more severe RSV disease after infection include low birth weight (independent of GA) ²⁸, young age at the onset of the RSV season ²⁹, and pre- and post-natal tobacco smoke exposure ^{9, 30, 31}.

Some of the factors that have been associated with an increased risk of acquiring an RSV infection in all infants include day care attendance ³², crowded living conditions ^{30, 32}, presence of school-aged siblings in the home ³, and birth near the onset of the RSV season ⁹. Similar factors were noted in a study that confined the population to premature infants <33 weeks GA ³³. More recently, two groups of investigators sought to identify those risk factors for increasing the likelihood of RSV-related hospitalization in infants born with a history of mild prematurity.

Law and coworkers conducted a prospective, multicenter cohort study over two consecutive RSV seasons, capturing infants across Canada of 33 to 35 6/7 weeks GA born between November 1 and April 30 ¹². Infants who received RSV immunoprophylaxis were excluded from the study. Of the 1,860 infants enrolled, 1,784 (97.4%) were discharged from the nursery before or during the local RSV season and 1,832 (97.8%) were followed for at least 1 month. Epidemiological information was collected at enrollment and then monthly. During the follow-up period, 950 infants

experienced at least 1 respiratory illness. Of those, 140 required hospitalization for a lower respiratory tract infection: 66 (3.6% of the entire cohort) had a proven RSV infection, 30 tested negative for RSV, and 44 were not tested for RSV and so were excluded from further analysis. When those infants hospitalized for RSV disease were compared with those never hospitalized (n = 1,692), univariate analysis demonstrated the following factors each to be significantly associated with risk of RSV hospitalization: birth in the first half of the RSV season (November to January); male gender; birth weight <10th percentile for GA; preschool-aged siblings attending day care; crowded living conditions, with >5 people in the household, including the infant; day care attendance of the index case; absence of breastfeeding; and at least 2 smokers in the home. Using these factors, stepwise logistic regression analysis yielded a final model with 5 independent predictors of risk for RSV hospitalization (OR; 95% CI): birth in the first half of the RSV season (4.88; 2.57,9.29); male gender (1.91; 1.10,3.31); small for gestational age (2.19; 1.14,4.22); day care attendance (12.32; 2.56,59.34); preschool aged siblings (2.76; 1.51,5.03); ≥ 2 smokers in the home (1.71; 0.97, 3.00); and >5 individuals in the home (1.69; 0.93,3.10). One limitation of the study was the limited power resulting from the relatively small number of infants hospitalized for an RSV illness, with possible underestimation of this number because of the 44 infants not tested. Additionally, most subjects lived in urban areas, limiting generalizability for more rural populations. Finally, the reported socioeconomic status of study families was higher than average, a fact that could have reduced the risk for RSV illness based on previous studies⁹.

A similar study to detect risk factors for RSV hospitalization in mildly premature infants was conducted in Spain³⁴. Investigators conducted a prospective multicenter case/control study among 33 – 35 6/7 week GA preterm infants over a single RSV season, using ~2 retrospective controls per case. A total of 186 infants were discharged from a participating center and then rehospitalized for a proven RSV illness, and 371 control infants were enrolled after the RSV season, never having been re-hospitalized. Infants with underlying heart or lung disease, as well as those who received RSV immunoprophylaxis, were excluded from the study. There were no perinatal events that affected subsequent risk of RSV hospitalization. Univariate analysis demonstrated significant associations between risk of RSV hospitalization and: age at the start of the RSV season; breast feeding ≤ 2 months; prenatal tobacco smoke exposure; school aged (>3 years old) sibling; crowded living conditions with >4 individuals or habitual visitors in the home; presence of furred pets; family history of wheezing or eczema; and low level of parental education. Only 3 of the case infants and <5% of the total study population had attended day care, so its effect on RSV hospitalization could not be determined. The logistic regression analysis performed using these factors, adjusted for medical center, resulted in a model that showed a significant relationship between RSV hospitalization and (OR; 95%CI): absolute chronological age ≤ 10 weeks at onset of the RSV season (3.95; 2.65,5.90); breast feeding ≤ 2 months (3.26; 1.96,5.42); ≥ 1 school aged sibling (2.85; 1.88,4.33); 4 or more residents/visitors in the home, excluding the infant and school aged siblings (1.91; 1.19,3.07); and family history of wheezing (1.90; 1.19,3.01). The authors calculated that if 2 risk factors were present in a particular infant, the risk of experiencing an RSV-related hospitalization would be increased between 3.62 and 12.87

times. While tobacco smoke exposure was not found to be a significant risk factor in the multivariate analysis, there had been a reduction in exposure to tobacco smoke at home in Spain from 52% to 30% over the course of the study, which may have altered the impact of secondhand tobacco smoke.

Summary

These studies, in general, confirm many of the risk factors that have been identified for RSV hospitalization in other populations of children³⁵ to be important for infants with a history of mild prematurity as well. Taken together, they suggest that young age at the beginning of the RSV season, crowded living conditions, and presence of preschool or school aged siblings all increase the risk for an RSV-related hospitalization in mildly premature infants. What is unique about the 32 – 35 week preterm infant? The mildly premature infant is likely to be discharged at an earlier chronological age from the NICU than more premature infants, and so will be exposed at a younger age to community pathogens like RSV. At the same time, the mildly preterm infant still has reductions in lung function and immune function similar to those of more premature infants. The mildly preterm infant with no underlying conditions is also viewed as healthy, and so may be more likely to be placed in a day care environment than a severely preterm infant who may still be viewed as fragile after discharge from the nursery.

Expert panels recommend limiting the use of palivizumab in mildly preterm infants because of its cost and because 32 – 35 week GA infants represent the largest group of premature babies. Emerging data suggest that mildly preterm infants not only have a risk of RSV-related hospitalization equal to that of more severely premature infants, but that they also have similar or worse hospital courses than more premature infants and also experience long-term morbidity after RSV-related hospitalization. Until the true cost of a severe RSV illness, including subsequent morbidity and associated health care resource utilization can be determined, however, immunoprophylaxis in this group will continue to be limited. Certainly, reminding parents to wash hands, to limit the infant's exposure to sick people and crowded environments during the RSV season, to avoid exposure of the infant to secondhand tobacco smoke, to avoid placement of the infant in day care if possible, and to encourage breastfeeding as long as possible all can do much to reduce the infant's risk of acquiring an RSV infection. Similarly, those mildly premature infants who are > 3 months of age at the onset of the RSV season, who do not have siblings, will not be placed in day care, will not be exposed to secondhand tobacco smoke, and who are being breast fed do not have the greatest risk factors for acquiring an RSV infection, and probably should not be in the group targeted for immunoprophylaxis. There are compelling data, however, to support the use of immunoprophylaxis in those otherwise healthy mildly premature infants who are at increased risk to acquire an RSV lower respiratory tract infection.

References

1. Leader S, Kohlhasse K. Respiratory syncytial virus-coded pediatric hospitalizations, 1997 to 1999 *Pediatr Infect Dis J* 2002;21:629-32.
2. Shay DK, Holman RC, Newman RD, et al. Bronchiolitis-associated hospitalizations among US children, 1980-1996 *JAMA* 1999;282:1440-6.
3. American Academy of Pediatrics. Respiratory syncytial virus. In: Pickering L, editor. Red Book. 27th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2006. p. 560-566.
4. Division of Vital Statistics. National Vital Statistics Report: NCHS; 2002 December. Report No.: 2.
5. Statement on the recommended use of monoclonal anti-RSV antibody (palivizumab) *Can Commun Dis Rep* 2003;29:1-15.
6. Carbonell Estrany X, Quero Jimenez J. Recommendations for the prevention of respiratory syncytial virus infections. Standards Committee of the Spanish Society of Neonatology. Board of Directors of the Spanish Society of Neonatology *An Esp Pediatr* 2000;52:372-4.
7. Meert K, Heidemann S, Abella B, et al. Does prematurity alter the course of respiratory syncytial virus infection? *Crit Care Med* 1990;18:1357-9.
8. Wang EE, Law BJ, Stephens D. Pediatric Investigators Collaborative Network on Infections in Canada (PICNIC) prospective study of risk factors and outcomes in patients hospitalized with respiratory syncytial viral lower respiratory tract infection *J Pediatr* 1995;126:212-9.
9. Boyce TG, Mellen BG, Mitchel EF, Jr., et al. Rates of hospitalization for respiratory syncytial virus infection among children in medicaid *J Pediatr* 2000;137:865-70.
10. Berner R, Schwoerer F, Schumacher RF, et al. Community and nosocomially acquired respiratory syncytial virus infection in a German paediatric hospital from 1988 to 1999 *Eur J Pediatr* 2001;160:541-7.
11. Weigl JA, Puppe W, Schmitt HJ. Incidence of respiratory syncytial virus-positive hospitalizations in Germany *Eur J Clin Microbiol Infect Dis* 2001;20:452-9.
12. Law BJ, Langley JM, Allen U, et al. The Pediatric Investigators Collaborative Network on Infections in Canada study of predictors of hospitalization for respiratory syncytial virus infection for infants born at 33 through 35 completed weeks of gestation *Pediatr Infect Dis J* 2004;23:806-14.
13. Horn SD, Smout RJ. Effect of prematurity on respiratory syncytial virus hospital resource use and outcomes *J Pediatr* 2003;143:S133-41.
14. Greenough A, Alexander J, Burgess S, et al. Health care utilisation of prematurely born, preschool children related to hospitalisation for RSV infection *Arch Dis Child* 2004;89:673-8.
15. Sampalis JS. Morbidity and mortality after RSV-associated hospitalizations among premature Canadian infants *J Pediatr* 2003;143:S150-6.
16. Panitch HB. The relationship between early respiratory viral infections and subsequent wheezing and asthma *Clin Pediatr (Phila)* 2007;46:392-400.

17. Simoes EA, Groothuis JR, Carbonell-Estrany X, et al. Palivizumab prophylaxis, respiratory syncytial virus, and subsequent recurrent wheezing *J Pediatr* 2007;151:34-42, 42 e1.
18. Friedrich L, Stein RT, Pitrez PM, et al. Reduced lung function in healthy preterm infants in the first months of life *Am J Respir Crit Care Med* 2006;173:442-7.
19. Hoo AF, Dezateux C, Henschen M, et al. Development of airway function in infancy after preterm delivery *J Pediatr* 2002;141:652-8.
20. Hanrahan JP, Tager IB, Segal MR, et al. The effect of maternal smoking during pregnancy on early infant lung function *Am Rev Respir Dis* 1992;145:1129-35.
21. Young S, Sherrill DL, Arnott J, et al. Parental factors affecting respiratory function during the first year of life *Pediatr Pulmonol* 2000;29:331-40.
22. Martinez FD, Morgan WJ, Wright AL, et al. Initial airway function is a risk factor for recurrent wheezing respiratory illnesses during the first three years of life. Group Health Medical Associates *Am Rev Respir Dis* 1991;143:312-6.
23. Young S, O'Keefe PT, Arnott J, et al. Lung function, airway responsiveness, and respiratory symptoms before and after bronchiolitis *Arch Dis Child* 1995;72:16-24.
24. Panitch HB. Viral respiratory infections in children with technology dependence and neuromuscular disorders *Pediatr Infect Dis J* 2004;23:S222-7.
25. Broughton S, Bhat R, Roberts A, et al. Diminished lung function, RSV infection, and respiratory morbidity in prematurely born infants *Arch Dis Child* 2006;91:26-30.
26. Yeung CY, Hobbs JR. Serum-gamma-G-globulin levels in normal premature, post-mature, and "small-for-dates" newborn babies *Lancet* 1968;1:1167-70.
27. Bont L, Kimpen JL. Immunological mechanisms of severe respiratory syncytial virus bronchiolitis *Intensive Care Med* 2002;28:616-21.
28. Holman RC, Shay DK, Curns AT, et al. Risk factors for bronchiolitis-associated deaths among infants in the United States *Pediatr Infect Dis J* 2003;22:483-90.
29. Carbonell-Estrany X, Quero J. Hospitalization rates for respiratory syncytial virus infection in premature infants born during two consecutive seasons *Pediatr Infect Dis J* 2001;20:874-9.
30. Groothuis JR, Gutierrez KM, Lauer BA. Respiratory syncytial virus infection in children with bronchopulmonary dysplasia *Pediatrics* 1988;82:199-203.
31. Stensballe LG, Kristensen K, Simoes EA, et al. Atopic disposition, wheezing, and subsequent respiratory syncytial virus hospitalization in Danish children younger than 18 months: a nested case-control study *Pediatrics* 2006;118:e1360-8.
32. Anderson LJ, Parker RA, Strikas RA, et al. Day-care center attendance and hospitalization for lower respiratory tract illness *Pediatrics* 1988;82:300-8.
33. Carbonell-Estrany X, Quero J, Bustos G, et al. Rehospitalization because of respiratory syncytial virus infection in premature infants younger than 33 weeks of gestation: a prospective study. IRIS Study Group *Pediatr Infect Dis J* 2000;19:592-7.
34. Figueras-Aloy J, Carbonell-Estrany X, Quero J. Case-control study of the risk factors linked to respiratory syncytial virus infection requiring hospitalization in premature infants born at a gestational age of 33-35 weeks in Spain *Pediatr Infect Dis J* 2004;23:815-20.
35. Simoes EA. Environmental and demographic risk factors for respiratory syncytial virus lower respiratory tract disease *J Pediatr* 2003;143:S118-26.