

PICNIC (Pediatric Investigators Collaborative Network on Infections in Canada) Study of the Role of Age and Respiratory Syncytial Virus Neutralizing Antibody on Respiratory Syncytial Virus Illness in Patients With Underlying Heart or Lung Disease

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ABSTRACT. *Objective.* To determine the effects of age and respiratory syncytial virus (RSV) antibody status on frequency and severity of RSV infections in children with underlying heart or lung disease.

Design. Cohort study conducted during two consecutive RSV seasons.

Setting. Ambulatory patients at eight Canadian pediatric tertiary care centers.

Methods. Subjects under 3 years old with underlying heart disease who were digoxin-dependent or had not received corrective cardiac surgery or with underlying lung disease were enrolled. Demographic information and an acute sera for RSV neutralizing antibody was obtained on enrollment. Weekly telephone follow-up consisting of a respiratory illness questionnaire was followed with a home visit to obtain a nasopharyngeal aspirate when there was new onset of respiratory symptoms. The specimen was used to detect RSV antigen. RSV illnesses were grouped as upper or lower respiratory tract infection (LRI) based on clinical and radiographic findings. RSV hospitalizations were considered to be those RSV infections that resulted in hospitalization.

Results. Of 427 enrolled subjects, 160 had underlying lung disease only, 253 had underlying heart disease only, and 14 had both. Eleven percent and 12% of lung and heart disease groups, respectively, had an RSV LRI. Three percent and 6% of lung and heart disease groups, respectively, were hospitalized with RSV infection. A significant decrease in frequency of RSV LRI and RSV hospitalization occurred with increasing age, with a major drop in those older than 1 year vs those younger than 1 year. Acute sera were available from 422 subjects. Geo-

metric mean RSV antibody titers demonstrated a U-shaped distribution with increasing age. The trend to lower antibody concentrations in premature infants did not reach statistical significance. The frequency of RSV infection and RSV LRI was lower in patients with antibody at a titer more than 100, although the difference for RSV hospitalization was not statistically significant. These differences remained significant after age adjustment.

Conclusion. Both age and RSV antibody status impact on RSV illness and LRI. Reduction in illness frequency with increasing age may lead to more informed targeting of those children most likely to benefit from RSV immune globulin prophylaxis. *Pediatrics* 1997;99(3). URL: <http://www.pediatrics.org/cgi/content/full/99/3/e9>; *respiratory syncytial virus, cohort study, passive prophylaxis, neutralizing antibody.*

ABBREVIATIONS. RSV, respiratory syncytial virus; LRI, lower respiratory tract infection.

Compared with its course in otherwise healthy children, respiratory syncytial virus (RSV) infections lead to higher mortality and morbidity measured by hospital duration, transfer to intensive care, and ventilation in children with underlying heart or lung disease.^{1,2} Recently, a polyclonal RSV immune globulin preparation, containing high titers of RSV neutralizing antibodies, was approved in the United States for use as a prophylactic agent against severe RSV infections. Licensure followed the demonstration of efficacy in terms of reduced frequency and duration of hospitalizations for RSV lower respiratory tract infection (LRI) among children with underlying lung disease and premature infants.³⁻⁵ Such prophylaxis, however, is expensive and requires monthly intravenous infusions during the RSV season. Given the expense, time commitment, and difficulty gaining intravenous access in premature infants, RSV immune globulin may be more appropriately reserved for those children with the highest risk for complicated disease.

Studies in otherwise healthy children have shown that the frequency of primary and recurrent RSV infection is inversely correlated with the titer of RSV neutralizing antibodies measured before the onset of the RSV season.⁶⁻⁸ Information on illness or hospi-

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talization frequency obtained in this population, however, is likely to underestimate disease in patients with underlying cardiac or pulmonary conditions.

This study was conducted to determine whether pre-season RSV neutralizing antibody titers reduced the frequency of RSV infection in children with underlying heart or lung disease. In addition, current information was obtained regarding hospitalization risk in this population. Such data may be helpful in determining the population who would be most likely to benefit from receipt of prophylactic RSV immune globulin.

PATIENTS AND METHODS

Children followed at eight pediatric hospitals were eligible for enrollment if they had underlying complex congenital heart disease or chronic lung disease diagnosed before the 1993 to 1994 or 1994 to 1995 RSV season. They also had to be 3 years old or younger on September 1 before RSV season. Complex congenital heart disease was defined as a congenital heart abnormality with the need for cardiac surgery or dependence on cardiac medications. Chronic lung disease included bronchopulmonary dysplasia, cystic fibrosis, pulmonary malformation, and recurrent gastroesophageal reflux. Bronchopulmonary dysplasia is defined as beginning with acute lung injury and diagnosed at 28 days of age or later with clinical symptoms of tachypnea and retractions, radiologic findings of hyperinflation or obvious cystic areas with fibrotic strands, and blood gas abnormalities if in ambient air.⁹ Outpatients were enrolled from September 1 until the beginning of the RSV season, defined at each center as the first week in which three or more children were hospitalized with proven RSV infection. The only exceptions to this were hospitalized premature infants who could be enrolled up to December 1 provided they had been discharged home. Prior RSV infection was not a cause for exclusion unless it occurred during a given center's defined enrollment period. The protocol was accepted by the Research Ethics Boards of all participating hospitals and patients were enrolled only after informed consent was obtained. Consent was sought by the study nurse at each center, who also was responsible for follow-up.

After enrollment, demographic data including details about the underlying illness and gestational age, and a serum sample were obtained. Weekly telephone follow-up inquired about respiratory illnesses using a previously described questionnaire.¹⁰ Subjects with a new respiratory illness identified by new respiratory symptoms on the questionnaire were seen by the study nurse to collect nasopharyngeal secretions by aspiration with a syringe and infant feeding catheter. Because of financial constraints, such home visits to collect nasopharyngeal aspirates were made only after the onset of RSV season at each center. Each new illness was classified as an upper or lower respiratory infection with the latter distinguished by radiographic evidence of pneumonia or the new onset of wheezing or exacerbation of preexisting wheezing. Any hospitalizations were noted. Patients continued to have weekly follow-up until an RSV infection was identified or the RSV season ended, defined as the month of May at all sites. Once a nasopharyngeal aspirate had been positive for RSV for a particular patient, no further specimens were obtained in that season.

Nasopharyngeal aspirates were processed in the virology laboratory at each site using immunofluorescence microscopy or enzyme immunoassay as previously described.² Sera were stored at -70°C until sent on dry ice to the study central laboratory in Winnipeg, Manitoba. RSV neutralizing antibody was performed using previously described methods.¹¹ Briefly, sera were heat-inactivated and tested in duplicate without exogenous complement. A 60% plaque reduction assay was performed on microtiter plates lined with HEP2 cells. The RSV test strains A2 (RSV subgroup A) and 18537 (RSV subgroup B), immunoreagents and control sera were provided by Lederle Praxis Biologicals Inc (Rochester, NY). A RSV neutralizing antibody was considered high if the assay was positive at a dilution of 1:100. This approximated the titer of 128 used as a cut-off for high antibody in a study of RSV antibody in healthy children.⁶

A Fisher's exact test was used to compare the proportion of patients with RSV LRI or RSV-associated hospitalization in different age groups. Analysis of covariance was used to determine the effect of age and prematurity on antibody concentrations. Prematurity was defined as a gestational age of less than 33 weeks in this analysis, because one would predict less maternal transfer of RSV antibody in more premature neonates. χ^2 analyses were used to compare RSV neutralizing antibody concentrations with frequency of RSV infection, RSV LRI, RSV hospitalization, and all hospitalizations. A stratified analysis was used to assess the effect of antibody after controlling for the effect due to age.

RESULTS

Four hundred twenty-seven patients were enrolled. Their demographic characteristics are summarized in Table 1. Fourteen patients had both underlying heart and lung disease. Eighty-four patients were followed in both RSV seasons. The most common cardiac lesions included ventriculoseptal defect (59), pulmonary stenosis (39), patent ductus arteriosus (29), atrial septal defect (37), aortic coarctation (27), tetralogy of Fallot (20), atrial ventricular canal defect (17), aortic stenosis (16), and transposition of great vessels (11). Patients with patent ductus arteriosus or atrial septal defect had these anomalies in conjunction with other cardiac defects. Of patients with underlying lung disease, 72 never received home oxygen supplementation, 85 had received it in the past, and 17 were receiving it at the time of study enrollment. Patients were followed for an average of 23.6 weeks. A total of 558 nasopharyngeal aspirates were obtained over the two seasons for an average of 1.3 specimens/patient.

Eleven percent and 12% of lung and heart disease groups, respectively, experienced an RSV LRI. Six percent and 3% of lung and heart groups were hospitalized with RSV infection. There was a reduction in frequency of RSV LRI and RSV hospitalization with increasing age in both heart and lung disease subgroups (Table 2). The subgroup of 114 patients with bronchopulmonary dysplasia was examined

TABLE 1. Demographic Characteristics of Enrolled Patients

	Underlying Lung Disease*	Congenital Heart Disease*
Number of patients	174	267
Number male (%)	102 (59)	136 (51)
Age <1 year (%)	55 (32)	99 (37)
1-2 years (%)	60 (34)	90 (34)
2-3 years (%)	49 (28)	75 (28)
>3 years (%)	10 (6)	3 (1)
Number less than 37 weeks gestational age (%)	133 (76)	44 (16)
Number less than 33 weeks gestational age (%)	114 (66)	17 (6)
Lung disorder-bronchopulmonary dysplasia (%)	115 (66)	NA†
Cystic fibrosis (%)	25 (14)	
Pulmonary malformation (%)	14 (8)	
Recurrent aspiration (%)	14 (8)	
Home oxygen any time (%)	102 (59)	NA
At enrollment (%)	17 (10)	
Number with left-to-right shunt (%)	NA	138 (52)
Number with pulmonary hypertension (%)		27 (10)

* Includes 14 with both lung and heart disease.

† NA = not asked or not applicable.

TABLE 2. Frequency of Respiratory Syncytial Virus (RSV) Lower Respiratory Infection and RSV Hospitalization by Age

Age, (mo)	RSV LRI		RSV Hospitalization	
	Underlying Lung Disease	Congenital Heart Disease	Underlying Lung Disease	Congenital Heart Disease
0-3	0/3 (0)*	6/14 (43)	1/3 (33)	5/14 (36)
3-6	3/13 (23)	6/31 (19)	3/13 (23)	2/31 (6)
6-9	4/15 (27)	1/26 (4)	1/15 (7)	0/26 (0)
9-12	4/24 (17)	7/27 (26)	3/24 (13)	0/27 (0)
12-24	6/59 (10)	6/88 (7)	1/59 (2)	1/88 (1)
24-36	2/50 (4)	5/77 (6)	1/50 (2)	1/77 (1)
>36 mo	1/10 (10)	0/4 (0)	0/4 (0)	0/4 (0)
Overall	20/174 (11)	31/267 (12)	10/174 (6)	9/267 (3)
P value	.07	<.001	.006	<.001

* Number with outcome divided by number total percent. Statistical significance determined by Fisher's exact test.

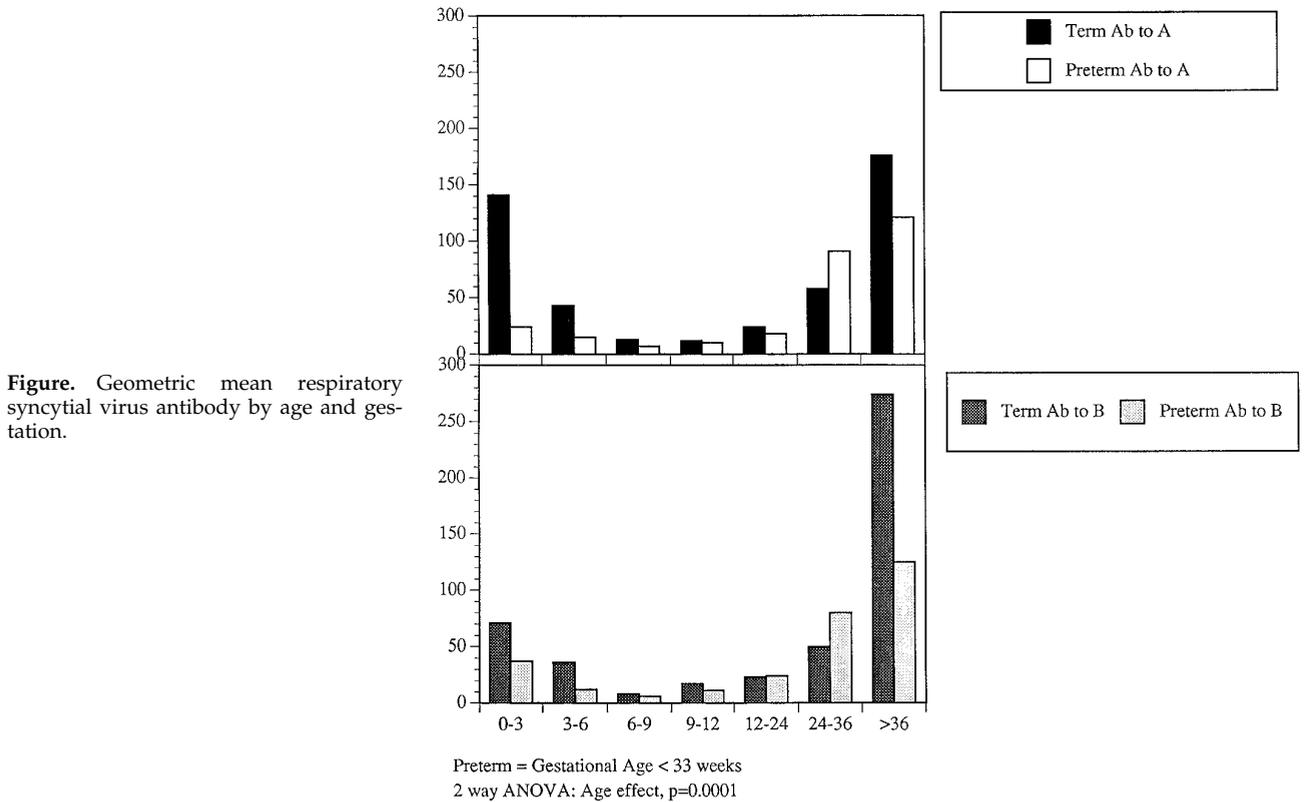


Figure. Geometric mean respiratory syncytial virus antibody by age and gestation.

separately because their premature birth may lead to their having narrower airways and lower RSV neutralizing antibodies predisposing them to more severe disease. Their RSV LRI and RSV-associated hospitalization rates were 11% and 6%, respectively, with similar age specific rates to those observed in the overall group of children with chronic lung disease of any kind. In the entire group, RSV LRI rates were approximately threefold higher and RSV-associated hospitalizations were over fivefold higher in those in the first year of life compared with those rates in older children.

Preseason sera was obtained from 422 patients. Antibody titers varied by age ($P = .0001$) with trends to lower titers in premature versus term infants that did not reach statistical significance (Figure). There was a U-shaped distribution with an initial fall to a nadir at 6 to 9 months followed by a rise in antibody titers. The trends to lower

antibody titers in subgroup B patients in the younger age group as compared with subgroup A did not reach statistical significance. In this analysis, prematurity was defined as gestational age less than 33 weeks. When this analysis was performed again using gestational age less than 37 weeks as the definition of prematurity, the above observations remained the same.

When baseline antibody concentrations were at least 100, a significant reduction was observed in the frequency of RSV infections and LRIs. The reduction in frequency of RSV hospitalizations did not reach statistical significance (Table 3). The significant differences were maintained after age stratification. That the effect was specific for RSV infection was confirmed by the lack of difference in overall LRIs and hospitalizations when children with high and low antibody titers were compared.

TABLE 3. Antibody Status and Frequency of Respiratory Syncytial Virus (RSV) Infection and Hospitalization

Neutralizing RSV Antibody Titer	n	RSV Infection	RSV LRI*	RSV Hospitalization	Any LRI	Any Hospitalization
to A <100	298	75	44	15	93	66
≥100	118	10	5	3	29	22
<i>P</i> value		<.001	.003	>.1	>.1	>.1
to B <100	295	72	40	15	88	69
≥100	121	13	9	3	34	18
<i>P</i> value		.006	.03	>.1	>.1	>.1

* LRI indicates lower respiratory tract infection.

DISCUSSION

The reduction in incidence of RSV LRI and hospitalization with increasing age observed in this patient population is similar to that previously reported in healthy children.^{6,12,13} Because of their compromised cardiopulmonary status, these subjects have a higher RSV-associated hospitalization rate than that observed in otherwise healthy children.⁶ The high rates of LRI and hospitalization in young infants underscore the limited effectiveness of active immunization against RSV if a series of three doses is required. Thus, passive prophylaxis with RSV antibody-enriched immunoglobulin has emerged as an option for prevention of RSV. The overall hospitalization rates of 3% to 6% observed in this study were much lower than the 20% found in controls participating in a randomized controlled trial of RSV hyperimmune globulin.^{3,4} This difference may be attributable to at least four reasons. First, there was a conscious effort to enroll more infants, who are likelier to be hospitalized, into the randomized trial.³ The mean age of children enrolled in the trial approximated 8 months, whereas it was 18 months in our cohort study. Second, given the complexity of the intervention, it is likely that sicker children were enrolled in that trial. Third, the trial only enrolled patients with bronchopulmonary dysplasia, whereas this cohort included term infants with other pulmonary diseases as well. However, the hospitalization rate in our patients with bronchopulmonary dysplasia was the same as the rate for the group with underlying lung disease. Finally, it is possible that there was less complete follow-up in this cohort study compared with that in the trial. This would be supported by the relatively low frequency of procurement of nasopharyngeal aspirates. The limited funds for the study prevented more exhaustive specimen collection: specimens for RSV diagnosis were obtained when patients had respiratory symptoms only after the season had started and further specimens were not obtained in children after their first RSV infection of the season. Such a bias toward underdiagnosis may lead to less detection of LRIs than RSV-associated hospitalizations, because RSV diagnostic testing is routinely performed on all patients admitted to the study hospitals with respiratory illness. In fact, the age-specific LRI rates observed in this study are comparable to those reported in otherwise healthy children⁶ and in the randomized trial of prophylaxis with RSV hyperimmune globulin.^{3,4} Thus, the lower hospitalization rates observed in this cohort are probably related to the first

two factors. The hospitalization rate of 13.4% in the control group in another randomized trial of RSV immune globulin⁵ falling in-between that observed in this cohort study and that of the initial trial³ further supports the variability in this outcome measure even between those participating in randomized trials.

The rates of RSV LRI rates were 18.2% and 20.4% in infants with underlying lung or heart disease. Corresponding hospitalization rates in these groups were 14.5% and 6.9%, respectively. One can use the 'number needed to treat' to help in making a decision on the children who should receive prophylaxis. The number needed to treat to prevent one hospitalization can be calculated using the risk reduction of 67% observed with RSV immune globulin in the randomized trial^{3,4} and an estimate of baseline event rate.¹⁴ Using a baseline event rate of 20% observed in the trial, approximately eight subjects would need to receive prophylaxis to prevent one hospitalization. Using a baseline event rate of 15% as observed in infants with lung disease in this study, 10% in all infants in this study, or 1.4% in 1- to 3-year-old children in this study, then 10, 15, or 100 subjects, respectively, would require prophylaxis to achieve the same benefit. From these calculations, children older than 12 months are less likely to benefit from RSV immune globulin and a cost-benefit analysis may not support its use in this population. Other factors such as prematurity in addition to cardiac or pulmonary compromise should be considered in selecting infants who could most benefit from prophylaxis if the main purpose is the avoidance of hospitalization. Other important benefits of this product are avoidance of the need for intensive care or ventilation. However, these are much rarer events.

Why was there a higher hospitalization rate in patients with underlying pulmonary vs cardiac disease? The bulk of the former group are made up of premature infants. The nadir of endogenous, presumably maternally derived, antibody occurred in both preterm and term infants at about 6 to 9 months. Although the difference did not reach statistical significance, the antibody concentrations in preterm infants are lower throughout the first year of life in the preterm infants. Premature infants have two features contributing to more severe illness: the abnormal lung structure with reduced surface area for gas exchange and the relative lack of maternally derived RSV antibody. As their lung function normalizes, their antibody levels decline during their first year. One would, therefore, predict that the maximum

benefit from exogenous immune globulin in preventing RSV infection would occur early in the first year of life in this group when the airways have not had a chance to grow and there is little RSV neutralizing antibody.

Randomized trials provide the highest quality of evidence about the efficacy of interventions.¹⁵ However, the generalizability of findings from such trials may be limited by differences in trial participants and compliance with the regimen compared with that in the usual clinical setting. This observational study provides additional data to estimate the effectiveness of interventions in the usual setting. The expected reductions in effects compared with those observed in a trial are particularly relevant to decisions regarding implementation of costly interventions.

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