Impact of Respiratory Syncytial Virus Immune Globulin in 1996-1997
A Local Controlled Comparison

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Background: Immune globulin containing high titers of neutralizing antibodies specific for respiratory syncytial virus (RSV) is clinically used to prevent hospitalizations for RSV-related respiratory infections among high-risk infants. However, recommendations regarding which patient populations should receive RSV immune globulin are inconsistent.

Objective: To compare hospitalization rates for prematurely born infants with and without chronic lung disease who received RSV immune globulin with similar infants whose parents refused such treatment during the 1996-1997 winter season.

Design: Inception cohort study.

Participants: Infants born at less than 35 weeks’ gestation and less than 6 months old without lung disease and children who had been born prematurely, had chronic respiratory disease, and were less than 2 years old at the onset of the RSV season.

Main Outcome Measure: Hospitalization for an RSV-related respiratory illness.

Results: Seventy-six infants (66 [87%] with chronic lung disease and 10 [13%] born prematurely without lung disease) received RSV immune globulin; 65 infants (18 [28%] with chronic lung disease and 47 [72%] born prematurely without lung disease) did not. Three (4%) of the treated group and 2 (3%) of the untreated group were hospitalized for RSV infections. Of those with chronic lung disease, 5% (3/66) of those treated with RSV immune globulin were hospitalized, compared with 11% (2/18) of those untreated. Of those born prematurely without lung disease, no infant in the treated (0/10) or untreated (0/47) group was hospitalized.

Conclusions: The risk of hospitalization of infants born prematurely who are younger than 6 months without lung disease is low. Current recommendations for preventing RSV illness in this group by using RSV immune globulin may require inclusion of more specific clinical characteristics rather than gestational age alone.

SUBJECTS AND METHODS

Before the RSV season’s onset in 1996, a priority system was established in Seattle by consensus to determine who should receive RSV immune globulin. The categories in the priority system are given in Table 1. Categories 1 and 2 included infants with BPD; categories 3 through 5 included infants born prematurely at various gestational ages who had no lung disease and did not require ongoing respiratory care. Bronchopulmonary dysplasia was defined as a condition of persistent respiratory signs, an abnormal chest radiograph consistent with the diagnosis, and need for supplemental oxygen at 28 days of life after an acute respiratory illness during the first week of life. Seventy-six infants were enrolled to receive RSV immune globulin at CHRMC as a result of referrals from community physicians, pulmonologists, and neonatologists on the basis of these priorities.

During the same period of enrollment (October to mid-December 1996), additional premature infants with and without BPD who qualified for RSV immune globulin were identified by reviewing the discharge records of the 3 neonatal intensive care units (NICUs) in Seattle during the 6-month period before the anticipated onset of the RSV season (December 1). Forty-five of the 110 infants identified by chart review were already enrolled in the RSV immune globulin program. Families of 65 of 67 infants who refused RSV immune globulin agreed to be contacted after conclusion of the RSV season. These 65 high-risk infants constituted an untreated concurrent control group during the 1996-1997 RSV season. In all cases, allocation to a specific group was the choice of both the parents and the primary health care provider. Both the infants who received RSV immune globulin and the control group were categorized according to the same priority system.

The RSV immune globulin–treated group was monitored throughout the RSV season by communication with parents and primary care providers via monthly clinic visits and telephone calls. Both the control group families and their primary care providers were interviewed only at the end of the RSV season. The protocol was approved by the institutional review board at CHRMC.

The medical charts of all hospitalized children in both groups were reviewed for diagnosis on discharge, duration of hospital stay, days of mechanical ventilation, and number of hospitalizations in the 1996-1997 RSV season, defined as lasting from December 1, 1996, through May 1, 1997. Hospitalization because of RSV was documented by fluorescent antibody tests of nasopharyngeal secretions, ordered by inpatient attending physicians. All hospitalizations of the infants in both groups occurred at CHRMC, which is the only tertiary inpatient facility in Seattle for high-risk infants who might require intensive care because of acute lower respiratory tract infections.

Continuous characteristics between the groups were statistically compared by means of an unpaired 2-tailed t test. Proportions of children in each group for dichotomous data were compared with χ² methods. A P value of less than .05 was considered statistically significant. Hospitalization for an RSV-related respiratory illness was the primary outcome variable.

The RSV epidemic of 1996-1997 was the first season during which RSV immune globulin was used clinically. During that season, Children’s Hospital and Regional Medical Center (CHRMC) in Seattle, Wash, developed a referral clinic specifically for high-risk infants to receive RSV immune globulin as outpatients. Concurrently, additional families with equally high-risk infants (born prematurely with and without BPD) refused the option to receive RSV immune globulin. We prospectively followed up the infants of these families as a control group to compare the rates of hospitalization between a group of untreated age-matched high-risk infants with those who received RSV immune globulin during the same RSV season.

Immune Inc, Gaithersburg, Md) significantly reduces hospitalizations resulting from RSV when administered intravenously on a monthly basis during winter as a preventive strategy. In January 1996, the Food and Drug Administration approved use of RSV immune globulin in children less than 24 months of age with BPD and premature infants who were born at less than 35 weeks’ gestation and who are less than 6 months of age. In contrast, the American Academy of Pediatrics recommended RSV immune globulin use for premature infants without BPD born at 32 weeks’ gestation or earlier and who are younger than 6 months and for infants born at 28 weeks’ gestation or earlier and who are 12 months of age or younger.

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Table 1. RSV Immune Globulin Priority Score for the 1996-1997 RSV Season*

<table>
<thead>
<tr>
<th>Priority Score</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>Infants with chronic lung disease (BPD) receiving treatment (oral corticosteroids, oxygen-assisted ventilation, or CPAP via tracheostomy) who are &lt;24 mo old</td>
</tr>
<tr>
<td>2</td>
<td>Infants with chronic lung disease (BPD) not receiving therapy within last 6 mo who are &lt;24 mo old</td>
</tr>
<tr>
<td>3</td>
<td>Infants born at &lt;30 wk gestation and &lt;6 mo old</td>
</tr>
<tr>
<td>4</td>
<td>Infants born at &lt;32 wk gestation and &lt;4 mo old</td>
</tr>
<tr>
<td>5</td>
<td>Infants born at &lt;35 wk gestation and &lt;4 mo old with additional risk factors†</td>
</tr>
</tbody>
</table>

* A consensus of the pulmonary and neonatology groups of Seattle, Wash. RSV indicates respiratory syncytial virus; BPD, bronchopulmonary dysplasia; and CPAP, continuous positive airway pressure.
† Additional risk factors exist when an infant is in a high-risk environment such as day care, home with siblings, exposure to tobacco smoke, or one of multiple births. If additional risk factors exist, the infant moves up 1 level in priority.

Seventy-six infants received RSV immune globulin and 65 infants received no preventive therapy. The demographic profiles of each group are listed in Table 2. Sixty-six infants (87%) among those receiving RSV immune globulin were categorized as having BPD (priority 1 or 2); only...
10 infants (13%) in the treated group were premature infants without BPD. Conversely, 47 (72%) of 65 infants in the control group were prematurely born with no evidence of ongoing lung disease (priority 3-5), while 18 (28%) of 65 had BPD. Gestational age for the 2 groups differed significantly (Table 2). Gestational ages of infants with chronic lung disease were not significantly different between the groups (28.8 ± 4.2 vs 30.1 ± 5.5 weeks in the RSV immune globulin vs control groups; P = .36). However, gestational ages at birth among the premature infants without BPD in the RSV immune globulin group were significantly less than those of premature infants in the control group (28.9 ± 4.0 vs 32.6 ± 1.3 weeks; P < .001). Seventeen (36%) of the 47 infants without lung disease in the control group were born at less than 32 weeks’ gestation and were less than 6 months old at the onset of the RSV season, and all were less than 35 weeks’ gestation in accordance with the priority score. There was no difference between the groups regarding postnatal age, the proportions in each group exposed to household smoke, or households with siblings, twin births, or triplets.

The RSV immune globulin was administered from November 20, 1996, to April 24, 1997. Forty-six (60%) of the 76 participants received their first dose in the NICU before discharge and their follow-up doses at CHRMHC as outpatients. The number of doses received per recipient varied from 1 to 5 depending on the month of enrollment during the RSV season. Eighty percent (53/66) of the infants with BPD (priority 1 and 2) received 3 or more doses of RSV immune globulin. Thirty percent (20/66) of these infants received 5 doses. Eight (80%) of the 10 premature infants in categories 3 through 5 enrolled in the RSV immune globulin program also received 3 or more doses.

None (0/47) of the premature infants without lung disease in the control group were hospitalized for RSV-related illnesses.

Table 2. Demographic Features of Treated and Control Groups*

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>RSV Immune Globulin (n = 76)</th>
<th>Control (n = 65)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic lung disease, No. (%)</td>
<td>66 (87)</td>
<td>18 (28)</td>
<td></td>
</tr>
<tr>
<td>Premature, No. (%)</td>
<td>10 (13)</td>
<td>47 (72)</td>
<td></td>
</tr>
<tr>
<td>Sex, No. M.F (%)</td>
<td>40:36 (53)</td>
<td>42:23 (65)</td>
<td></td>
</tr>
<tr>
<td>Gestational age, mean ± SD, wk</td>
<td>29 ± 4</td>
<td>32 ± 3.3</td>
<td>.001</td>
</tr>
<tr>
<td>Postnatal age, mean ± SD, mo†</td>
<td>4.5 ± 3.6</td>
<td>5.0 ± 3.7</td>
<td>.44</td>
</tr>
<tr>
<td>Household smoke exposure, No. (%)</td>
<td>19/76 (25)</td>
<td>12/65 (18)</td>
<td>.40</td>
</tr>
<tr>
<td>Participants with siblings, No. (%)</td>
<td>53/76 (70)</td>
<td>41/65 (63)</td>
<td>.55</td>
</tr>
<tr>
<td>Families with twins or triplets‡</td>
<td>12/69 (17)</td>
<td>14/51 (27)</td>
<td>.28</td>
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*RSV indicates respiratory syncytial virus; ellipses, not applicable.
†Denotes chronological age at initiation of RSV immune globulin therapy in treated group and chronological age when RSV immune globulin therapy was declined in control group.
‡Seventy-six RSV immune globulin participants occurred in 69 families; 65 control participants occurred in 51 families.

This study compared the hospitalization rate within a local region among high-risk infants receiving RSV immune globulin and a similar group of high-risk infants who received no immunoprophylaxis to prevent RSV-related respiratory infections during the winter of 1996-1997. Both groups contained infants born prematurely with and without BPD at the onset of the RSV season. However, the composition of the groups was unbalanced. The majority of infants in the RSV immune globulin-treated group had BPD, while the majority of infants in the control group were born prematurely but had no chronic lung disease. In addition, the mean gestational age of the prematurely born infants without BPD was younger for the treated group than for the control group. Thirty-eight percent of infants in the control group were born at less than 32 weeks’ gestation, while 62% were born at 32 to 35 weeks’ gestation. The infants born at less than 32 weeks’ gestation would have qualified for RSV immune globulin immunoprophylaxis in accordance with the American Academy of Pediatrics guidelines, yet all of the control infants would have qualified for RSV immune globulin on the basis of Food and Drug Administration approved indications.

None (0/47) of the premature infants without lung disease in the control group were hospitalized for RSV-related illnesses.

The most common problem associated with RSV immune globulin administration was difficult intravenous access. Increased respiratory work and/or decreased oxyhemoglobin saturation (>4%) were noted during 16 (8.5%) of the 189 monthly visits, 2 or more attempts by experienced nurses were required to start intravenous infusions. Increased respiratory work and/or decreased oxyhemoglobin saturation (>4%) were noted during 16 (8.5%) of the 189 infusions. Interventions, including intravenous furosemide, additional supplemental oxygen, and slowing of the infusion rate, were required during 10 (5.3%) of the 198 administrations of the drug. No infant experienced anaphylaxis.

Of the 76 children who received RSV immune globulin therapy, 3 (4%) were hospitalized for RSV bronchiolitis or pneumonia. All 3 children had BPD and were assigned to priority group 1 or 2 at the onset of the RSV season. The hospitalization rate was 5% (3/66) among infants with BPD and 0% (0/10) for premature infants without underlying lung disease who received RSV immune globulin. All 3 infants acquired RSV within the 4-week interval between RSV immune globulin doses and had received at least 1 dose before the onset of the illness. The durations of hospitalization for these 3 infants were 4, 5, and 8 days.

Two (3%) of the 65 infants in the control group were hospitalized for RSV-related respiratory infections. Both children had chronic lung disease. The hospitalization rate attributable to RSV for children in priority 1 and 2 who did not receive RSV immune globulin was therefore 11% (2/18). None (0/47) of the premature infants without lung disease in the control group were hospitalized for RSV-related illnesses. The length of hospital stay for the 2 control children was 8 and 12 days. No infant in either group required mechanical ventilation, nor were any infants hospitalized more than once in 1996-1997 for an RSV-related illness.
Any impact of RSV immune globulin is obscured in this study because no premature infant without BPD from either group was hospitalized. This low rate of RSV-related hospitalizations among the 47 premature infants without chronic lung disease in the control group is the most important finding of the study. In contrast, the hospitalization rates for infants born prematurely with ongoing chronic lung disease were 11% for infants in the control group and 3% for infants with BPD in the treated group. This difference in proportions hospitalized was not statistically significant because of the small numbers of infants followed up in this study. However, these values are similar to those reported in the PREVENT study, the phase III clinical trial of RSV immune globulin conducted during the RSV season of 1995-1996.10

Given that RSV seasons vary in severity from year to year,13 one weakness of this study is that it reflects only 1 year’s experience. To put this information in perspective, the RSV epidemics for the 2 preceding years were compared with the year of this study with hospital census records for bronchiolitis and RSV pneumonia at CHRMC used as surrogate descriptors for the severity of the RSV epidemics in Seattle. This information is summarized in Table 3. The RSV epidemic in 1996-1997 led to a similar number of admissions as 1994-1995 but fewer hospitalizations than in 1995-1996. The number of intensive care days was also less in 1996-1997 than in either of the preceding 2 years. The RSV epidemic of 1996-1997 produced less severe disease and shorter durations of hospitalization but similar numbers of admissions compared with the 2 preceding winter seasons. These characteristics might account for shorter hospital stays but do not explain the reduced rate of hospitalization of premature infants without lung disease in the control group in 1996-1997.

There are other potential weaknesses in this study. The study, unlike the PREVENT trial, was unblinded to the investigators. Infants in the RSV immune globulin group were seen monthly in a clinic and could have received more aggressive outpatient care. This concern is obviated somewhat by the fact that the control infants were not under the care of the investigators. The low hospital admission rate among the control infants resulted from the counseling and care provided by multiple individual primary care providers and the parents rather than the team that provided RSV immune globulin in Seattle. Another limitation is that the study does not necessarily pertain to other geographic regions. The 1997 Red Book from the American Academy of Pediatrics states that “regional data on hospitalization rates for RSV infection may assist in the decision-making process” regarding which premature infants without underlying lung disease should receive RSV immune globulin.14

There has been a trend during the last decade of less hospitalization of both premature infants and those with BPD for RSV-related illness. A follow-up study of prematurely born infants in 1985-1986 reported that rehospitalization rates because of respiratory illnesses for infants discharged from an NICU with and without BPD were 45% and 25%, respectively.1 In 1988, Groothuis et al12 reported a hospitalization rate for RSV respiratory infections among infants with BPD receiving home oxygen therapy to be 36% (11/30). In 1993, the RSV-related hospitalization rate for a control group of 89 infants who had BPD, congenital heart disease, or prematurity during a 1-year multicenter study was 29%.13 In contrast, the PREVENT study group found the hospitalization rate among a control group of 260 infants with prematurity and BPD to be 13.5% in 1994-1995.6 The hospitalization rate for the subgroup of infants who were less than 6 months old (and therefore predominantly infants who were premature without persistent lung disease) in this study was 9%, which was lower than in older infants with BPD.9 In 1995-1996, 11.8% of the control group of infants born prematurely with and without BPD participating in a phase 3 clinical trial of a monoclonal anti-RSV antibody were hospitalized for RSV-related infections (Daniel Burch, MD, SmithKline Beecham Inc, Collegeville, PA, written communication, January 10, 1997). In addition, a review of rehospitalization rates within 1 year after birth for RSV-related illnesses among infants with low birth weight (1500-2500 g) and very low birth weight (<1500 g) graduating from NICUs in Stony Brook, NY, from 1993 through 1995 were 2.8% and 6.4%, respectively.10 Our data reflect hospitalization rates for both premature infants and infants with BPD within the control group that are lower than previously reported. The data were collected prospectively during 1 RSV season. This decline in hospitalization rates may reflect in part an increasing trend toward structured education and counseling about RSV within NICUs for families whose infants are approaching discharge to home during fall and winter.

Although these results encompass only 1 RSV season in 1 locale that was less severe than in some previous years, they raise the question as to whether infants born at either 32 or 35 weeks’ gestation without persistent lung disease continue to be at substantially greater risk of hospitalization for RSV-related respiratory disease than normal full-term infants and whether immunoprophylaxis with polyclonal antibodies is warranted for all members of this patient population. Nachman et al10 reported specific attributes of very-low-birth-weight premature infants that correlated with earlier rehospitalization for RSV-related respiratory disease. These included ventilator use in the NICU, bacteremia, and

<table>
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<th>Table 3. RSV-Related Inpatient Data at CHRMC*</th>
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<tr>
<td>Year</td>
</tr>
<tr>
<td>1994-1995</td>
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<td>1995-1996</td>
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<td>1996-1997</td>
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* RSV indicates respiratory syncytial virus; CHRMC, Children’s Hospital and Regional Medical Center, Seattle, Wash; IICU, infant intensive care unit; PICU, pediatric intensive care unit; and LOS, length of stay.

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intraventricular hemorrhage. Whether such criteria would more clearly identify prematurely born infants without BPD at greatest risk to be hospitalized for RSV-related disease will require further study. As educational programs emphasizing hand washing at home and avoidance of crowds increase among NICUs, the need for RSV immune globulin to prevent RSV-related hospitalizations among healthy premature infants may further diminish in many communities. Multicenter prospective evaluations of infants within this patient population will help to refine the current guidelines for RSV immune globulin. Local reviews of data describing hospitalization frequencies for prematurely born infants of various gestational ages may also assist clinicians in deciding who merits RSV immunoprophylaxis.

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REFERENCES