Respiratory Syncytial Virus and Premature Infants Born at 32 Weeks’ Gestation or Earlier

Hospitalization and Economic Implications of Prophylaxis

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**Objectives:** To assess the risk of hospitalization associated with respiratory syncytial virus (RSV) and to estimate the economic impact of RSV prophylaxis with either RSV immune globulin (RSV-Ig) or RSV monoclonal antibody (palivizumab) on a cohort of preterm infants born at 32 weeks’ gestation or earlier.

**Design:** Historical cohort study.

**Setting:** A 12-county neonatal network served by the regional center in Rochester, NY.

**Participants:** One thousand twenty-nine infants born at 32 weeks’ gestation or earlier followed up until 1 year of corrected age.

**Main Outcome Measures:** Rate of hospitalization with an RSV-associated illness; cost per hospitalization prevented resulting from either form of RSV prophylaxis.

**Results:** The probability of hospitalization with an RSV-associated illness for infants born at 32 weeks’ gestation or earlier was estimated at 11.2%. The incidence of RSV hospitalization increased with decreasing gestational age (13.9% vs 4.4% for infants born at ≤ 26 weeks’ gestation vs those born at 30-32 weeks’ gestation). Infants requiring respiratory support at 36 weeks of postconceptual age (PCA) or older had a higher hospitalization rate (16.8% vs 6.2%), longer hospital stays, and higher hospital charges than infants requiring respiratory support at less than 36 weeks of PCA. For infants requiring respiratory support at less than 36 weeks of PCA, the incidence of RSV hospitalization still increased with decreasing gestational age (10.2% vs 4.3% for infants ≤ 26 weeks’ gestation vs those 30-32 weeks’ gestation). Analysis indicated that both forms of RSV prophylaxis would increase the net cost of care for all groups. Palivizumab was more cost-effective than RSV-Ig for preventing RSV hospitalization among infants who required respiratory support at less than 36 weeks of PCA, especially those born at 26 weeks’ gestation or earlier. Overall, RSV-Ig was more cost-effective than palivizumab for infants requiring respiratory support at 36 weeks of PCA or older.

**Conclusions:** This analysis suggests that available forms of RSV prophylaxis would increase the net cost of care not only for the entire cohort but for each of the subgroups studied. However, the RSV hospitalization rate and the cost-effectiveness of prophylaxis varied markedly by subgroup.


**Editor’s Note:** This study provides a good model for cost-effective analysis, especially for expensive, effective pharmacological products. In this case, the ultimate decision is where you want to spend the money.

*Editor’s Note: Catherine D. DeAngelis, MD*

Respiratory syncytial virus (RSV) is a major cause of morbidity and mortality after the neonatal period, especially for premature infants and infants with bronchopulmonary dysplasia. Up to 2% of all children and up to 20% of infants with bronchopulmonary dysplasia who acquire RSV will require hospital admission. Recently, 2 drugs that provide passive immunity against RSV have been approved for use in children by the US Food and Drug Administration. Respiratory syncytial virus immune globulin (RSV-Ig) (Respigam; Medimmune Inc, Gaithersburg, Md) deceased the risk of RSV hospitalization by 41% to 63% in high-risk infants. Palivizumab (Synagis; Medimmune Inc) decreased the risk of RSV hospitalization by 55% in high-risk infants. Concerns regarding cost and difficulty in administration have led the American Academy of Pediatrics to issue risk-stratified guidelines for the use of RSV-Ig and palivizumab. The objectives of this study were to assess the risk of RSV hospitalization and to evaluate the economic impact of RSV prophylaxis with either RSV-Ig or palivizumab on a cohort of preterm infants born at 32 weeks’ gestation or earlier.
SUBJECTS, MATERIALS, AND METHODS

DESIGN

A historical cohort of children born at 32 weeks’ gestation or earlier were followed up from birth until 1 year of corrected age (1 year past 40 weeks of postconceptual age [PCA]) to estimate the RSV hospitalization rate and cost-effectiveness of RSV prophylaxis in the first year of life.

STUDY POPULATION

The population consisted of 1029 consecutive premature infants born at 32 weeks’ gestation or earlier surviving to discharge from the regional neonatal intensive care unit at the Children’s Hospital at Strong (CHaS), Rochester, NY, during a 3-year period, which included the RSV seasons of 1992 through 1996. All infants born at 32 weeks’ gestation or earlier within the 12-county region, which has 24,000 live births per year, are born at or transferred to the tertiary care neonatal intensive care unit at CHaS.

OUTCOME ASCERTAINMENT

Outcome (RSV hospitalization) was ascertained directly at university hospitals and estimated for hospitals throughout the region. University hospitals included CHaS, the sole tertiary care hospital in the region, and Rochester General Hospital, a university-affiliated community teaching hospital with services closely integrated with those of CHaS. Regional hospitals included university hospitals and hospitals in the 12 counties served by the Rochester area neonatal network. Children who were hospitalized with RSV infections at university hospitals were identified through a database of all hospitalized children with a positive RSV culture or antigen detection assay. To allow room sharing of RSV-infected patients, all patients with viral respiratory symptoms were tested for RSV. Hospitalization rates for the university hospitals were calculated using the number of RSV hospitalizations in the cohort as the numerator and the entire cohort (N = 1029) as the denominator. Actual hospital charges, hospital length of stay, and number of pediatric intensive care unit (PICU) admissions were obtained for all patients admitted to either CHaS or Rochester General Hospital with an RSV-associated illness.

EXTRAPOLATION TO REGION

To enhance the generalizability of study findings, we extrapolated from data collected at the university hospitals to generate estimates for our entire region. A regional database maintained by New York State showed that 2051 children younger than 1 year were admitted to regional hospitals with a lower respiratory tract infection (LRTI) during the study period. Patients with an LRTI were identified using International Classification of Diseases, Ninth Revision (ICD-9) codes for discharge diagnoses as previously described. Of these 2051 infants, 1390 (67.8%) were admitted to a university hospital. In extrapolating to the region, the fundamental assumption was that the ratio of university hospital to regional admissions for the cohort of premature infants was the same as the ratio of university hospital to regional admissions for infants admitted with any LRTI. Thus, the number of RSV-associated admissions for the region (n = 115) was estimated by dividing the number of university RSV-positive admissions (n = 78) by the ratio of university to total regional LRTI admissions (0.678). Extrapolation should provide valid estimates for the region because (1) a majority of the regional hospitalizations (67.8%) are included in the university (Rochester General Hospital and CHaS) data, (2) no nonuniversity hospital in the region had more than 14% of the infant LRTI admissions for the region, and (3) CHaS has the only PICU in the region and

RESULTS

RSV HOSPITALIZATIONS

During the 5-year period, 1029 infants were born at 32 weeks’ gestation or earlier, and 78 of these were subsequently admitted to one of the university hospitals with RSV (Table 1). For the 12-county region, an estimated 115 infants would be admitted. Thus, the RSV hospitalization rate was estimated as 11.2% (115/1029) (Table 2). The 78 infants admitted to university hospitals had an average length of stay of 5.9 days and generated average charges of $11,083 (Table 1). Twelve infants required PICU admission. There were no deaths due to RSV. Most admissions (94%) occurred between December and March.

ANALYSIS BY GESTATIONAL AGE

Infants born at less than or equal to 26 weeks’ gestation and infants born at 26 to 28 weeks’ gestation were more likely to require hospitalization than infants born at 30 to 32 weeks’ gestation (Table 1). There were no significant differences among the gestational age subgroups in hospital length of stay, need for PICU admission, or average hospital charges.

ANALYSIS BY DURATION OF RESPIRATORY SUPPORT

Infants using respiratory support beyond 36 weeks of PCA were 2.5 times more likely to be admitted with RSV than were infants with respiratory support up to 36 weeks of PCA (16.8% vs 6.2%, P < .001 by χ² test) (Table 1). When infants receiving respiratory support beyond 36 weeks of PCA were excluded from the analysis, infants born at 26 weeks’ gestation or earlier were still significantly more likely to require hospitalization than infants born at 30 to 32 weeks’ gestation (10.2% vs 4.3%, P = .03 by χ² test) (Table 1). This suggests that gestational age as well as duration of respiratory support contributes to the need for hospitalization with an RSV-associated illness.
consequently receives all critically ill children. Consequently, an estimated 115 formerly premature infants would be admitted to regional hospitals with an RSV-related illness. This number served as the numerator for estimating the total RSV hospitalization rate for the entire cohort of 1029 premature infants. Thus, the regional RSV hospitalization rate was 115/1029 = 11.2%. This calculation overestimates the true value if premature infants are underrepresented among LRTI hospitalizations to nonuniversity hospitals, ie, if premature infants are more likely to be referred back to the university hospitals for an RSV-associated hospital admission. Because formerly premature infants are often medically fragile, over-estimation seems likely.

COST ANALYSIS AND ASSUMPTIONS

For calculations of cost-effectiveness, regional estimates of RSV-associated admission rates were used because they should yield the most accurate estimates for the regional economic impact of prophylaxis. Four calculations relating to cost-effectiveness were made.

1. Costs of prophylaxis were estimated as the product of the number of infants in a group at risk and the cost of RSV prophylaxis. The costs of RSV-Ig and palivizumab were estimated at $2841 and $2774, respectively. This estimate assumes that a 3.5-kg patient would receive 5 doses of drug per RSV season at the manufacturer’s recommended dosage (750 mg/kg and 15 mg/kg for RSV-Ig and palivizumab, respectively) and a commercial cost ($216.50/g of RSV-Ig and $1056 per 100-mg vial of palivizumab, respectively). This calculation assumed no drug wastage. For palivizumab, this is a conservative assumption because, once reconstituted, the drug has a shelf life of 6 hours, making some drug wastage nearly inevitable.

2. For the cost of RSV prophylaxis to prevent 1 hospitalization, the number of RSV hospitalizations prevented was estimated by multiplying the number of RSV hospitalizations by the percent reduction in these hospitalizations previously reported.6,7 The estimated reductions for RSV-Ig6 were 41%, 49%, and 20%, for all subjects, those 36 weeks of PCA or older, and those less than 36 weeks of PCA, respectively. The estimated reductions for palivizumab7 were 59%, 39%, and 78% for the same 3 groups.

3. The incremental cost of prophylaxis to prevent 1 hospitalization was calculated as the product of the number of infants requiring prophylaxis to prevent 1 hospitalization and the cost of prophylaxis minus the anticipated savings in hospital charges.

4. The number of infants requiring prophylaxis to prevent 1 hospitalization was calculated as the division of the number of RSV hospitalizations prevented by the incremental cost of prophylaxis to prevent 1 hospitalization.

In this calculation we assumed that all infants born at 32 weeks’ gestation or earlier would receive a full course of RSV prophylaxis.

STATISTICAL ANALYSIS

Cohort members were grouped for analysis by gestational age and duration of respiratory support in the neonatal period, expressed as weeks of PCA. We defined the need for respiratory support beyond 36 weeks of PCA as a need for oxygen, nasal cannula flow, continuous positive airway pressure, or mechanical ventilation. Both bronchopulmonary dysplasia and apnea of prematurity, the 2 most common reasons for ongoing respiratory support, are associated with increased risk of an RSV hospitalization.4,5,13

The t test was used to assess statistical significance in differences between means. The χ2 test and Fisher exact test were used to assess differences between proportions.

COST-EFFECTIVENESS BY SUBGROUP

Because we wished to assess the anticipated economic impact of implementing RSV prophylaxis for the entire region rather than for care in university hospitals alone, cost-effectiveness calculations were performed using regional estimates. For RSV hospitalization rates, the relationship of the university collected data (Table 1) and the regional estimated data (Table 2) is shown in Figure 1. Because the RSV hospitalization rates are higher for the estimated regional data than for the collected university data, cost-effectiveness is greater (eg, lower cost per hospitalization prevented). Because regional estimates assumed a greater number of RSV-associated admissions than observed in the university hospitals, the incremental cost of prophylaxis per hospitalization prevented was estimated to be lower for the region than for the university hospitals. Because the region-based estimates should most closely approximate the true cost-effectiveness of the drug, only the regional estimates of cost-effectiveness are discussed (Table 3). For the entire cohort, the cost of prophylaxis to prevent 1 hospitalization increased substantially with increasing gestational age for both RSV-Ig and palivizumab (Table 3). For example, for palivizumab, it increased from $24 476 for infants born at 26 weeks’ gestation or earlier vs to $78 785 for infants born at 30 to 32 weeks’ gestation. The cost of RSV prophylaxis per hospitalization prevented (Table 3) similarly increased with gestational age. Although RSV prophylaxis is costly, it does decrease the risk of an RSV hospitalization and therefore decreases anticipated hospital charges. The incremental cost of prophylaxis to prevent 1 hospitalization is presented in Table 3 by gestational age and by duration of respiratory support (Table 3 and Figure 2). This index of cost-effectiveness is also presented in Table 3 by gestational age for the subgroup of infants requiring respiratory support at less than 36 weeks of PCA.

The number of infants needing prophylaxis to prevent 1 RSV hospitalization increased with increasing gestational age for all infants and also for infants requiring respiratory support at less than 36 weeks of PCA (Table 3).
3). The number of infants needing prophylaxis to prevent 1 RSV-associated hospitalization was higher for infants requiring respiratory support at 36 weeks of PCA or older than for infants requiring respiratory support at less than 36 weeks of PCA (Table 3).

The probability of hospitalization with RSV at less than 1 year corrected age in a cohort of infants born at less than 32 weeks’ gestation was estimated at 11.2%. This estimate for our region was similar to values reported in the literature. Other key observations of RSV hospitalizations were as follows: (1) The incidence of hospitalization increased with decreasing gestational age. (2) Infants requiring respiratory support at 36 weeks of PCA had a significantly higher incidence of hospitalization, longer hospital stays, and greater hospital charges than infants requiring a shorter period of respiratory support. (3) For infants requiring respiratory support at less than 36 weeks of PCA, the incidence of hospitalization still increased with decreasing gestational age. (4) Although the study did not demonstrate a net cost savings of RSV prophylaxis for the entire cohort of high-
risk infants or for any of the subgroups analyzed, cost-effectiveness of RSV prophylaxis varied by subgroup and by type of prophylactic drug used. It was most cost-effective among infants requiring respiratory support at 36 weeks of PCA or older treated with RSV-Ig, followed by infants requiring respiratory support at less than 36 weeks of PCA who were born at 26 weeks' gestation or earlier treated with palivizumab. Prophylaxis was least cost-effective among infants requiring respiratory support who were younger than 36 weeks of PCA and born at 30 to 32 weeks' gestation. (5) Palivizumab was substantially more cost-effective than RSV-Ig for preventing RSV hospitalization among premature infants requiring respiratory support who were younger than 36 weeks of PCA ($32 792 vs $148 002). This was also true for each gestational age subgroup requiring respiratory support who were younger than 36 weeks of PCA. (6) RSV-Ig was more cost-effective than palivizumab for infants requiring respiratory support at 36 weeks of PCA or older ($11 468 vs $16 851).

Infants in their first year with chronic lung disease are at high risk for RSV, with hospitalization rates ranging from 12.8% to 25.9%.6,7,15 These data compare with our study, in which 24.4% of infants requiring respiratory support at 36 weeks of PCA or younger were hospitalized. When infants requiring respiratory support at 36 weeks of PCA or older were excluded, a significant increase in RSV hospitalization rates was still seen as gestational age decreased. An explanation might be that extremely premature infants who survive the neonatal period have residual lung disease that does not require respiratory support at 36 weeks of PCA, but does make them susceptible to later serious LRTI. Another explanation is the decreased transfer of maternal antibody to the most extremely premature infants.1

Our study was prompted by a desire to evaluate the cost implications of RSV prophylaxis before implementing the service in our region. For this region, annual drug costs alone would be $411 778 for RSV-Ig and $397 990 for palivizumab to provide prophylaxis to all infants born at 32 weeks' gestation or earlier. Although RSV prophylaxis would be cost-additive for all subgroups studied, cost-effectiveness varied greatly by subgroup and type of prophylactic drug used. Because infants requiring respiratory support at 36 weeks of PCA or older were the most likely to require hospitalization and RSV-Ig was more efficacious than palivizumab in preventing hospitalization for this highest-risk subgroup (49% vs 39%), RSV-Ig given to infants requiring respiratory support at 36 weeks of PCA or older was the most cost-effective scenario ($11 468 incremental cost per hospitalization prevented). The next most cost-effective was palivizumab for infants requiring respiratory support at younger than

![Figure 1. Respiratory syncytial virus–associated hospitalization rates for university and regional estimated data by gestational age and duration of respiratory support. PCA indicates postconceptual age.](image-url)
to prevent 1 hospitalization of a 3.3-kg infant.9 Some of that reported by Robbins et al,18 and seems attributable to prevent 1 hospitalization in our study is lower than consequence of prophylaxis. The number needed to treat chance, respectively, of preventing hospitalization as a

infants in these groups have only a 1 in 28 and 1 in 14 respectively, of preventing hospitalization as a consequence of prophylaxis. The number needed to treat to prevent 1 hospitalization in our study is lower than that reported by Robbins et al,19 and seems attributable to differences in study population. We chose the less than or equal to 32 weeks’ gestational age cut-off for our study because it is the age group at high risk for severe RSV illness.15

Although both RSV-Ig and palivizumab have been shown to reduce RSV hospitalizations, neither has been shown to prevent RSV illness in children. No information is available on clinical illness, outpatient costs, physician visits, or lost parental wages for infants with RSV and prior treatment with either RSV-Ig or palivizumab. Further study is needed to characterize the effect of RSV prophylaxis on outpatient direct and indirect medical and social costs.

Several strategies might increase the cost-effectiveness of RSV prophylaxis. The most premature infants and infants requiring prolonged respiratory support, who have both the highest rehospitalization rate and the lowest incremental cost per hospitalization prevented, may be the best candidates for RSV prophylaxis. In our region, where 94% of RSV hospitalizations occur in the 4-month period between December and March, cost-effectiveness could be improved by delivering RSV prophylaxis during a 4-month period rather than the 5 months recommended. Decreasing the period of prophylaxis from 5 months to 4 should decrease prophylaxis costs by 20% while still providing coverage for 94% of hospitalizations. Further study of subgroups of high-risk patients, including those living in high-risk environments (parental smoking, crowding, and so on), may improve the cost-effectiveness of RSV prophylaxis.

Our analysis did not demonstrate a net cost savings of RSV prophylaxis for the entire cohort of high-risk infants or for any of the subgroups analyzed. However, the RSV hospitalization rate and the RSV prophylaxis cost-effectiveness analysis did vary markedly by subgroup and by prophylactic drug. Our analysis supports the general American Academy of Pediatrics Red Book Committee recommendation that RSV prophylaxis should be considered on a risk-stratified basis for both premature infants and infants requiring prolonged respiratory support in the neonatal period.11 Precisely where along the risk continuum the threshold for use of RSV prophylaxis should lie remains a question for families, providers, payers, and society.

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REFERENCES


5. Groothuis JR, Simoes EAF, Levin MJ, et al. Prophylactic administration of respiratory syncytial virus immune globulin to high-risk infants and young chil-