Rehospitalization With Respiratory Syncytial Virus After Neonatal Intensive Care Unit Discharge: A 3-Year Follow-up

Sharon A. Nachman, MD; Maryam Navaie-Waliser, MPH; and Muhammad Z. Qureshi, MD

ABSTRACT. *Objectives.* **This study sought to determine 1) the incidence of rehospitalization with respiratory syncytial virus (RSV) infection within a 3-year follow-up among infants discharged from the neonatal intensive care unit (NICU), and 2) to examine associations between age at readmission and medical and sociodemographic characteristics among infants rehospitalized with RSV.**

Methods. **A 3-year retrospective review of NICU discharges at a tertiary care center identified 2506 infants. Using medical record numbers linked with International Classification of Diseases, 9th ed, diagnostic codes for RSV infection, bronchiolitis, or respiratory distress, 67 NICU graduates were identified as having been readmitted from November to April (RSV season). Bivariate analyses and logistic regression modeling were applied to determine the association between a series of predictor variables and age at readmission with RSV by 90 days, 125 days, and 180 days after discharge from the NICU.**

Results. **The 3-year incidence of readmission with RSV infection after NICU discharge was 2.7%. During the 3-year follow-up, 6.4% of very low birth weight infants, 2.8% of low birth weight infants, and 1.7% of normal weight infants were readmitted with RSV. Crude results revealed that the presence of bacteremia, intraventricular hemorrhage, and necrotizing enterocolitis, as well as ventilation use, were associated with younger age at readmission with RSV. Simultaneous consideration of the effects of all of these medical predictors and birth weight on age at readmission revealed that normal birth weight was the only significant factor associated with younger age at readmission with RSV.**

Conclusions. **This study found significantly lower rates of RSV readmission among NICU graduates than those reported previously in the literature. Based on these data, prophylactic treatment of all preterm infants may not be warranted.** *Pediatrics* **1997;100(6). URL: http://www.pediatrics.org/cgi/content/full/100/6/e8;** ***respiratory syncytial virus, NICU graduates.***

ABBREVIATIONS. RSV, respiratory syncytial virus; IVIG, intravenous immune globulin; BPD, bronchopulmonary dysplasia; NICU, neonatal intensive care unit; VLBW, very low birth weight; LBW, low birth weight; NBW, normal birth weight; ICD-9, International Classification of Diseases, 9th ed; NEC, necrotizing enterocolitis; IVH, intraventricular hemorrhage.

From the Department of Pediatrics, School of Medicine, State University of New York at Stony Brook, Stony Brook, New York.

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Reprint requests to (S.A.N.) Department of Pediatrics, School of Medicine, Health Sciences Center, 11th Floor, State University of New York, Stony Brook, NY 11794-8111.

For >4 decades, respiratory syncytial virus (RSV) has been recognized as the most important cause of serious lower respiratory tract infection in children.[1] The virus produces annual epidemics (usually during the winter and early spring) of bronchiolitis and pneumonia in infants and young children throughout the world and causes numerous hospital admissions, substantial morbidity, and mortality predominately in children <2 years of age.[2–5] The highly contagious nature of RSV[6] has led to its effective spread among all age groups. The virus infects essentially all children by 2 to 3 years of age,[6] with at least half of all children becoming infected during their first exposure and the remaining during their second exposure.[7]

Several investigations have identified individual characteristics and environmental conditions that seem to predispose children to serious morbidity and mortality. These include children living in crowded quarters who frequently are from low-income families,[8,9] infants born during the 6 months just before the RSV season,[8,10] children with certain medical conditions such as underlying pulmonary[11–13] and cardiac diseases,[14] and immunocompromised children.[15–17]

A rapidly expanding group at risk for serious RSV illness is low birth weight (LBW) infants born prematurely.[8,18] According to natality statistics, there are an estimated 450 000 premature infants (<35 weeks) born annually in the United States, of whom 80 000 are <32 weeks of age,[19] resulting in an increased pool of highly susceptible children. These infants are up to five times more likely to be hospitalized than term infants.[20,21] Premature infants are also at increased risk for rehospitalization after nursery discharge, and respiratory illness is the most common reason for their readmission.[20,21] In fact, >40% of premature infants will require rehospitalization during the first year of life because of illness associated with acute viral respiratory tract infection.[11,22]

A recent multicenter clinical trial investigated the safety and efficacy of prophylactic administration of an intravenous immune globulin (IVIG) therapy specific to RSV (RSV–IVIG) in high-risk preterm infants and young children.[23] The study reported that administration of high doses of RSVIG was a safe and effective method of preventing lower respiratory tract infection. Subsequent to these findings and supportive documentation from additional clinical trials, the Food and Drug Administration licensed Respigam, an RSV–IVIG product marketed by

MedImmune, Inc, (Gaithersburg, MD) for RSV therapy among infants born at <35 weeks' gestation and infants with bronchopulmonary dysplasia (BPD). Since this licensure, guidelines have been published by the American Academy of Pediatrics for universal administration of RSVIG as prophylaxis for RSV to infants with BPD who have received oxygen therapy and to infants who are born at <32 weeks' gestation.[24]

Since the Food and Drug Administration's approval of RSVIG use for a selected population of infants and young children, no published studies have assessed the number and characteristics of children who could benefit most from RSVIG therapy. This is relevant information to maximize the potential benefits of RSVIG. The objectives of this study were to 1) determine the incidence of rehospitalization with RSV within a 3-year follow-up among infants discharged from the neonatal intensive care unit (NICU), and 2) to examine associations between age at readmission and medical and sociodemographic characteristics among infants rehospitalized with RSV after NICU discharge to identify those most likely to have benefited from administration of RSVIG.

METHODS

Sample Selection

A retrospective review of hospital birth records was conducted to identify all infants who were discharged from the NICU at the University Medical Center of the State University of New York at Stony Brook from January 1, 1993, through December 31, 1995 (before the availability of RSV–IVIG). A total of 2506 infants were identified. Of these, 816 (32%) were born in 1993, 918 (37%) in 1994, and 772 (31%) in 1995. We chose to describe our population based on birth weight rather than on clinical gestational age assessments because of the more objective nature of birth weight measurements. For the purposes of this study, infants were stratified into three categories: very low birth weight (VLBW) if they weighed <1500 g, LBW if they weighed between 1500 and 2499 g, and normal birth weight (NBW) if they weighed ≥2500 g. The percentages of VLBW infants were 12%, 12%, and 15% in 1993, 1994, and 1995, respectively, with a mean of 13% for the 3 years. Similarly, the percentages of LBW infants were 26%, 29%, and 30% in 1993, 1994, and 1995, respectively, with a mean of 28% for the 3-year period. The remaining 59% of children in the study sample (for the 3-year period) were NBW.

Using International Classification of Diseases, 9th ed (ICD-9), diagnostic codes associated with proven or presumed RSV infection including acute bronchiolitis (code 466.1), pneumonia resulting from RSV (480.1), respiratory distress (codes 769, 770.8, and 786.09), and viral infections (code 079.99), a sample of 67 infants was identified from the 2506 infants described above by linkage of birth discharge files with admission files for the year after each infant's birth through matching of medical record numbers. These broad ICD-9 codes were used to minimize the inadvertent exclusion of infants with possible false-negative results for RSV and, thus, all infants with these ICD-9 codes were considered RSV-positive for the purpose of this paper. RSV infection was established by nasal swab testing (Abbott Laboratories [Abbott Park, IL] test pack 2027-16) with confirmation obtained from viral isolation.

Data Collection

Information on birth weight, gestational age, sex, race, age at readmission, illness severity, ventilator use, oxygen use, medical diagnoses, medical procedures during all hospitalization, and insurance carrier was obtained from in-depth medical chart reviews and entered into a computerized database.

Statistical Analysis

Infants were compared for rate of hospital readmission with RSV infection by birth weight (stratified as VLBW, LBW, and NBW). Analysis of continuous measures were performed using the two-tailed Student's t test. Comparisons of proportions for categorical measures were analyzed using the χ^2 test. Fisher's exact test was used when outcome was binary, and the expected number of occurrences in a group was less than five. Means and SD units for selected variables were compared between LBW and NBW infants. For multivariate analyses, factors with an individual association with the response variable (age at readmission with RSV) that were statistically significant were included in a stepwise logistic regression model to assess the relationship between the response variable and the potential predictor variables. Bivariate analyses yielded odds ratios (ORs) and 95% confidence intervals (CIs). Analyses were conducted using three different cutoff points for the response variable: 90 days, 125 days, and 180 days. These cutoff points were selected because they were associated with waning maternal immunity (90 days), the mean age at readmission with RSV infection for the study sample (125 days), and the time before the RSV season when infants were at risk for poor health outcomes associated with RSV-related illness (180 days). A P value of <.05 was considered significant. All analyses were performed with the aid of the SAS computer software.[26]

RESULTS

Incidence of RSV Readmission

The proportion of infants readmitted with RSV after having been discharged from the NICU was approximately the same during each year of the study, and all readmissions occurred during the RSV season. Of the 816 infants admitted to the NICU at birth in 1993, 2% (n = 17) were readmitted with RSV-related illness within 1 year after discharge (12 of 17 had confirmed RSV infection). In 1994 and 1995, this proportion rose to 3% (27 of 918, and 23 of 772 NICU admissions, respectively). Of the readmissions in 1994 and 1995, respectively, 21 and 20 infants had confirmed RSV infection. Overall, for the 3-year period, 2.7% of infants (n = 67) admitted to the NICU at birth were readmitted within 1 year after birth with RSV-related illness; none were readmitted in the second year. Stratification by birth weight revealed that 6.4% of VLBW infants, 2.8% of LBW infants, and 1.7% of NBW infants were readmitted with RSV. The mean age at readmission with RSV was 125 days after NICU discharge (SD ± 89.4).

Sociodemographic Characteristics of Infants Rehospitalized With RSV

All of the 67 NICU infants were readmitted with RSV within 1 year after being discharged. Of these, 17 were readmitted in 1993, 27 in 1994, and 23 in 1995. The racial distribution of the group was 54% white, 19% Latino, 18% African-American, and 9% other ethnic origins. Fifty-five percent of the children were boys; 45% were girls. Approximately 30% of the infants were on Medicaid, 39% had third-party insurance, and 31% were uninsured. Thirty-one percent (n = 21) of the children were born with VLBW, 30% (n = 20) LBW, and 39% (n = 26) NBW. The mean birth weight was 2142 g (SD ± 956), ranging from 697 g to 4500 g. Fifty-five percent (n = 37) were born at <35 weeks' gestation. These sociodemographic characteristics of RSV hospitalized infants were not significantly different from other infants discharged from the NICU at our institution.

Medical Characteristics of Infants Rehospitalized With RSV

The following medical characteristics of the study sample were examined: ventilator use, oxygen use, duration of hospitalization, gestational age, presumed or confirmed bacteremia, diagnosis of necrotizing enterocolitis (NEC), BPD, and intraventricular hemorrhage (IVH). Of the 67 infants who were readmitted with RSV, 24 (36%) had been on a ventilator, 24 (36%) had been on oxygen, 46 (69%) had been presumed to have bacteremia, 9 (13%) were confirmed to have bacteremia, 4 (6%) had been diagnosed with NEC, and 10 (15%) had IVH. Stratified data of these characteristics by birth weight are presented in Table 1. Of 21 VLBW infants, 80% had been ventilated, 47% had any oxygen use, 35% had a history of IVH, and 33% had confirmed bacteremia. Of 20 LBW infants, 16% had been ventilated, 39% had any oxygen use, and 5% had a history of IVH. Of 26 NBW infants, 23% had been ventilated, 13% had any oxygen use, 8% had a history of IVH, and 8% had confirmed bacteremia.

Characteristics Associated With Age at Readmission With RSV

Medical and sociodemographic characteristics of infants readmitted with RSV were analyzed in relation to their age at readmission with RSV within 90, 125, and 180 days after discharge from the NICU. No significant relationship was found between oxygen use (including duration of use) and presumed bacteremia to age at readmission with RSV for any of the three cutoff points. However, four medical characteristics were found to be significantly associated with age at readmission with RSV.

As shown in Tables 2 and 3, crude (unadjusted) results revealed that ventilator use was significantly associated with younger age at readmission with RSV. Infants who had been ventilated had more than three times the odds of being readmitted with RSV infection within 90 days of being discharged from the NICU compared with infants who had not been ventilated (OR = 3.06; 95% CI: 1.09,8.62; $P = .03$). When the cutoff for age at readmission with RSV was changed to 125 days, the results indicated that infants who had been ventilated at birth had nearly five times the odds of being readmitted with RSV within 125 days of being discharged from the NICU compared with infants who had not been ventilated at birth (OR = 4.84; 95% CI: 1.6,14.1; $P = .003$).

Diagnosis with bacteremia also was found to be significantly associated with younger age at readmission with RSV (Tables 3 and 4). Infants with bacteremia had over seven times the odds of being readmitted with RSV within 125 days of being discharged from the NICU (OR = 7.78; 95% CI: 1.47,41.19; $P = .02$) and more than four times the odds of being readmitted with RSV within 180 days of being discharged from the NICU (OR = 4.32; 95% CI: 1.1,17.3; $P = .05$) compared with infants who had not been diagnosed with bacteremia.

A third predictor that was significantly associated with younger age at readmission with RSV was IVH. Infants with IVH had more than five times the odds of being readmitted with RSV within 90 days of being discharged from the NICU (OR = 5.12; 95% CI: 1.2,23.6; $P = .04$) and more than 4.5 times the odds of being readmitted with RSV within 125 days of being discharged from the NICU (OR = 4.66; 95% CI: 1.1,20.1; $P = .03$) compared with infants who did not have IVH (Tables 2 and 3). Another predictor that was associated with younger age at readmission with RSV was NEC. As indicated in Table 4, this association was borderline significant when using 180 days as the cutoff point. Infants who were diagnosed with NEC had 9.6 times the odds of being admitted within 180 days of being discharged from the NICU compared with infants who were diagnosed with NEC (95% CI: 1.3,70.5; $P = .05$). Thus, ventilator use, bacteremia, IVH, and NEC all were associated with younger age at readmission with RSV.

In addition to medical characteristics, sociodemographic characteristics such as sex, race, gestational age, and birth weight were examined in relation to age at readmission with RSV. Sex, race, and gestational age were not significantly associated with younger age at readmission with RSV. However, NBW was significantly related to younger age at readmission with RSV, regardless of which cutoff point was used to assess the association ($P = .001$ for 90, 125, and 180 days, respectively).

When significant medical (ventilator use at birth, confirmed bacteremia, IVH, and NEC) and sociodemographic (birth weight) characteristics were modeled to simultaneously examine their effects on age at readmission with RSV using stepwise logistic regression analysis for 90, 125, and 180 days after NICU discharge, the findings suggested that only NBW was a significant predictor of younger age at readmission with RSV. Although there was no significant association between any of these characteristics and readmission with RSV by 90 and 180 days after NICU discharge, NBW infants were nearly five times more likely to be readmitted within 125 days after NICU discharge than were LBW infants after adjusting for ventilator use at birth, bacteremia, IVH, and NEC (OR = 4.72, 95% CI: 1.3,17.6, $P = .02$).

TABLE 1. Medical Characteristics of 67 Rehospitalized Infants

Birth Weight (n)*	Ventilator Use (%)	Oxygen Use (%)	IVH (%)*	Bacteremia† (%)
VLBW (n = 21)	80	47	35	33
LBW (n = 20)	16	39	5	0
NBW (n = 26)	23	13	8	8

* VLBW (<1500 g), LBW (1500–2499 g), NBW (≥2500 g).
† Confirmed.

DISCUSSION

The purpose of this study was to determine the incidence of rehospitalization with RSV within a 3-year follow-up among infants discharged from the NICU and to examine associations between age at readmission and medical and sociodemographic characteristics among infants rehospitalized with RSV after NICU discharge to identify those most

TABLE 2. Factors Associated With Age at Readmission With RSV Infection Within 90 Days After NICU Discharge

Factor	Readmitted by 90 Days		OR	95% CI	P Value*
	<90 n (%)	≥90 n (%)			
Ventilator use					
Yes	16 (67)	8 (33)	3.06	(1.09,8.62)	.03
No	17 (40)	26 (60)			
IVH					
Yes	8 (80)	2 (20)	5.12	(1.12,23.63)	.04
No	25 (44)	32 (56)			
Birth weight					
NBW	15 (58)	11 (42)	—	—	.001
LBW	15 (75)	5 (25)			
VLBW	4 (19)	17 (81)			

* Estimated using Fisher's exact test or χ^2 test based on cell sizes.

TABLE 3. Factors Associated With Age at Readmission With RSV Infection Within 125 Days After NICU Discharge

Factor	Readmitted by 125 Days		OR	95% CI	*P* Value*
	<125 n (%)	≥125 n (%)			
Ventilator use					
Yes	15 (63)	9 (37)	4.84	(1.60,14.1)	.003
No	11 (26)	32 (74)			
IVH					
Yes	7 (70)	3 (30)	4.66	(1.08,20.10)	.03
No	19 (33)	38 (67)			
Birth weight					
NBW	22 (85)	4 (15)	—	—	.001
LBW	15 (75)	5 (25)			
VLBW	4 (19)	17 (81)			
Bacteremia†					
Yes	7 (78)	2 (22)	7.78	(1.47,41.19)	.01
No	18 (31)	40 (69)			

* Estimated using Fisher's exact test or χ^2 test based on cell sizes.
† Confirmed.

TABLE 4. Factors Associated With Age at Readmission With RSV Infection Within 180 Days After NICU Discharge

Factor	Readmitted by 180 Days		OR	95% CI	*P* Value*
	<180 n (%)	≥180 n (%)			
Bacteremia†					
Yes	5 (56)	4 (44)	4.32	(1.1,18.5)	.05
No	13 (22)	45 (78)			
NEC					
Yes	3 (75)	1 (25)	9.6	(1.3,70.5)	.05
No	15 (24)	48 (76)			
Birth Weight					
NBW	25 (96)	1 (4)	—	—	.001
LBW	16 (80)	4 (20)			
VLBW	8 (38)	13 (62)			

* Estimated using Fisher's exact test or χ^2 test based on cell sizes.
† Confirmed.

likely to have benefited from administration of RSV immune globulin. Of 2506 NICU discharges during a 3-year period, only 67 infants (2.7%) were readmitted with RSV. When stratified by birth weight, 6.4% of VLBW infants, 2.8% of LBW infants, and 1.7% of NBW infants were readmitted with RSV infection. These findings differ from those in the literature, which report a 22% rate of RSV readmission among LBW premature infants.[27] This inconsistency is most likely attributable to biases that result from sampling. However, several efforts were undertaken in this study to minimize such biases. Our institution's infection control policy requires systematic screening for RSV of all hospitalized children who are ≤2 years old during the RSV season (November to April). Thus, children who tested positive for RSV at admission would have been cross-classified using our selected ICD-9 codes and included in our study sample, even if their primary discharge diagnosis was not RSV-related. In addition, to decrease the probability of excluding infants with true RSV infection who may have falsely tested negative, we broadened

the diagnostic criteria used to identify infants with RSV-type symptoms such as respiratory distress or viral illness. This is more likely to have resulted in overestimating the incidence of RSV-related readmissions. Another factor that could explain the observed low incidence of hospitalization with RSV could be that some infants with RSV sought care at other medical institutions and, thus, they would not have been included in our study sample. Although we cannot rule out this possibility, several reasons make it unlikely that this occurrence would have altered our findings significantly. Our institution is the only tertiary care center in our county, and the nearest other tertiary care center is in a neighboring county >40 miles away. The two closest community hospitals have no pediatrics-specific intensive care units, no pediatric subspecialists, and no house officers or residency programs, thereby limiting their ability to care for infants with RSV-related inpatient needs. Furthermore, a university-conducted survey at our institution of more than 50 randomly selected community pediatricians with privileges at more than one institution revealed that all preferred to readmit NICU graduates with respiratory distress to University Medical Center at Stony Brook rather than to any other county-located institutions. In addition, our institution has managed care contracts with more than 25 health insurance companies to meet the hospitalization needs of their enrollees.

We examined medical and sociodemographic characteristics of our study sample in relation to age at readmission with RSV by 90 days after discharge from NICU, by 125 days, and by 180 days. Significant characteristics associated with younger age at readmission with RSV were the presence of bacteremia, IVH, and NEC, as well as ventilation use. After simultaneously adjusting for the effects of ventilator use, bacteremia, IVH, and NEC, NBW was the only significant factor associated with younger age at readmission with RSV, with infants who weighed >2500 g being nearly five times more likely to have been readmitted with RSV within 125 days of initial discharge from the NICU compared with LBW infants.

Although our results concurred with those reported previously[23,27] in that we found preterm infants were more likely to be readmitted with RSV than full-term infants, our rates of readmission were significantly lower. In addition, we found no significant association between LBW and younger age at readmission among NICU infants rehospitalized with RSV. Based on these data, the cost of RSVIG therapy (estimated at $4000 to $5000 for a full RSV season[28]) and the logistic difficulties associated with RSV–IVIG treatment, prophylactic treatment for all premature infants may not be warranted.

This study's findings must be viewed in light of its potential limitations. The small sample size, the nonrandom selection of the study site, and the selected study period may have led to results with limited generalizability. However, to the extent that we could assess the external validity of our findings, we compared our data with comparable data available from other published studies on VLBW infants admitted to the NICU. We found little difference in the medical characteristics of VLBW infants in our study compared with those presented in a large cohort study of VLBW NICU infants.[29] Eighty percent of our VLBW infants had been ventilated, compared with 79% reported in the literature.[29] Other characteristics including rates of oxygen use, NEC, bacteremia, and IVH were also similar.

Despite its limitations, this study contributes to our existing knowledge of hospitalization rates with RSV infection after NICU discharge. Furthermore, it provides a basis for future research that can focus on identifying characteristics that may be predictive of RSV-related hospitalizations in an effort to better target RSV prophylactic treatment.

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