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INTENSIVE CARE UNIT READMISSION DURING CHILDHOOD FOLLOWING PRETERM BIRTH WITH RESPIRATORY FAILURE

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Abstract

Objective—To determine the incidence and risk factors for intensive care unit (ICU) readmission among preterm infants who required mechanical ventilation at birth.

Study design—We studied preterm newborns (birth weight 500–1250 grams) who required mechanical ventilation at birth and were enrolled in a multicenter trial of inhaled nitric oxide therapy. Patients were assessed up to 4.5 years of age via annual in-person evaluations and structured telephone interviews. Univariate and multivariable analyses of baseline and birth hospitalization predictors of ICU readmission were performed.

Results—Of 512 subjects providing follow-up data, 58% were readmitted to the hospital (51% of these had multiple readmissions, averaging 3.9 readmissions per subject), 19% were readmitted to an ICU, and 12% required additional mechanical ventilation support. In univariate analyses, ICU readmission was more common among males (OR 2.01; 95% CI, 1.27–3.18), infants with grade 3–4 intracranial hemorrhage (OR 2.13; 95% CI, 1.23–3.69), increasing duration of birth hospitalization (OR 1.01 per day; 95% CI: 1.00–1.02), and prolonged oxygen therapy (OR 1.01

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*A list of the PrONox Investigators is available at www.jpeds.com (Appendix).

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per day; 95% CI 1.00–1.01). In the first year after birth hospitalization, children readmitted to an ICU incurred higher health care costs (median \$69,700 vs. \$30,200 for subjects admitted to the ward and \$9600 for subjects never admitted).

Conclusions—Small preterm infants who were mechanically ventilated at birth have substantial risk for readmission to an ICU and late mechanical ventilation, using extensive health care resources and incurring high costs.

Keywords

preterm infants; bronchopulmonary dysplasia; intensive care; mechanical ventilation; inhaled nitric oxide; rehospitalization

Early preterm birth (< 34 weeks gestational age at birth) is associated with late morbidities such as chronic lung disease (CLD), neurological impairment, and a high risk for hospital readmission in the first years of life [1–4]. During the first year of life, rehospitalization rates increase with decreasing gestational age at birth, ranging from 13% in infants born at 35 weeks gestation to 31% in infants born at 25 weeks gestation [5]. Up to 50% of preterm infants with CLD are readmitted to the hospital during the first or second year of life [6–8]. Rehospitalization results in significant resource use, large financial burden, and increased stress for families, especially if the rehospitalization involves admission to an intensive care unit (ICU).

Characterization of late morbidities incurred by preterm infants associated with readmission to the hospital and admission to an ICU may guide allocation of health service resources and the design and implementation of appropriate preventive strategies. Although the rate of rehospitalization of preterm infants has been described, the rate of preterm infants admitted to the ICU has not been sufficiently evaluated. Moreover, there are limited data about resource use, including mechanical ventilation, and financial burden of preterm infants readmitted to the ICU. These data may serve as useful prognostic information for families as they are discharged from the neonatal ICU (NICU). Therefore, the aim of this study was to determine the incidence and risk factors for readmission to the ICU among preterm infants mechanically ventilated at birth enrolled in a randomized controlled trial of prophylactic inhaled nitric oxide (iNO) [9]. This trial enrolled 793 infants (birth weight 500–1250g) who required mechanical ventilation at birth and were randomized to receive low dose iNO or placebo. We studied the outcomes of these premature newborns up to 4.5 years of chronological age to determine the impact of preterm birth on late admissions to the ICU.

METHODS

Between March 2001 and June 2005, 793 subjects were enrolled at 16 US centers [9]. Subjects were born at 24–34 weeks gestation, weighed 500 to 1250 g, were < 48h old, and required mechanical ventilation. Exclusion criteria included lethal congenital anomalies, congenital heart disease, active pulmonary hemorrhage, unevacuated pneumothorax, or expected mechanical ventilation duration of < 48h from birth. Subjects were randomized to 5 parts per million iNO or placebo for 21 days or until extubation, stratified by center and birth weight. The primary outcome was death or CLD (supplemental oxygen or mechanical

ventilation and abnormal chest radiograph) at 36 weeks of postmenstrual age. The trial demonstrated no difference in the primary outcome of CLD at 36 weeks' postmenstrual age or death with iNO. At 1 y corrected age, survival and other post-discharge outcomes were not different by treatment arm, although there were significant neurodevelopment and pulmonary morbidities [10]. In addition, total costs for the treatment groups were similar. As part of the trial, most parents consented to a Long-term Outcomes study[10], in which we obtained detailed hospital bills and conducted structured telephone interviews every three months during the first year of life and every six months thereafter up until 4.5 years of age or until the end of the study period (December 2007). We collected data on hospital readmissions and outpatient resource use via scripted questions at each interview. We solicited dates of deaths from parents and/or study sites. Interviewers remained blinded through follow-up. The RCT and post-discharge follow-up were conducted with institutional review board (IRB) approval from each participating site and the University of Pittsburgh.

Cost Estimates

For birth hospitalization costs, we multiplied hospital charges from detailed hospital bills by department- and institution-specific ratios of costs-to-charges from the 2000–2005 Centers for Medicare and Medicaid Services (CMS) Hospital Cost Reports, multiplying them by 1.17 to reflect additional physician costs [11–13]. To estimate readmission hospital costs, we used the average costs for comparable hospital days from the hospital bills of subjects in study hospitals. To estimate rehospitalization costs, we multiplied average costs of ward days and ICU days with and without mechanical ventilation from hospital bills by the durations of the different types of days during rehospitalization. To estimate costs of other resources used, we applied costs from 2001 Medicaid Data on outpatient medication use in very low birth weight (VLBW) babies and unit costs from the CMS Medicare fee schedule. We estimated costs of lost work by multiplying time from enrollment to return to work by US average age- and sex-specific daily wage rates [14, 15].

Statistical Analyses

We adjusted costs to year 2012 US dollars using the Consumer Price Index [16]. We compared groups by Mann-Whitney U, chi-square, or Fisher exact tests. Subjects were censored at the last date when vital status was known. Proportions are reported based on the number of subjects available at each time point. Univariate and multivariable logistic regression analyses were conducted to identify baseline and birth hospitalization variables predictive of ICU readmission. No adjustments were made for subjects from multiple birth gestations. Although neurodevelopmental impairment (NDI) was determined at 1 year of age, it was included in the analyses because preterm birth and events during the birth hospitalization contribute to NDI. The multivariable model included covariates which had p-values less than or equal to 0.30 in the univariate analysis. We assumed statistical significance at $p < 0.05$.

RESULTS

Parents of 652 infants (82.2%) consented to enrollment in the Long-term Outcomes cohort (n=332 iNO, n=320 placebo). Lack of participation was due to trial enrollment before IRB

approval for the Long-term Outcomes study (n=52, 6.6%) and parent refusal (n=89, 11.2%). As reported previously, Long-term Outcomes subjects had similar birth weights and gestational ages as trial subjects who did not enroll [10]. Of the 652 consenting families, post-NICU data were available for 512 infants (Table I). Data were available for 171 infants through the full 4.5 years of follow-up due to a combination of loss to follow-up and subjects that were enrolled toward the end of the trial not reaching that age when the study was completed (only 249 subjects reached the 4.5 year follow-up time point when study was completed).

More than half (57.8%, n=296) of subjects were readmitted to the hospital at least once during the follow-up period. Of those readmitted, nearly one-third (n=96) were readmitted to an ICU, and one-fifth (n=61) required mechanical ventilation (Figure; available at www.jpeds.com). The percentage of subjects readmitted to the hospital and ICU decreased with increasing age. Of subjects readmitted to the hospital, the majority (51.3%, n=152) had multiple readmissions; subjects with multiple readmissions averaged 3.9 readmissions during the follow-up period. Among subjects admitted to an ICU, 51% required multiple hospital readmissions. Subjects readmitted to an ICU had an average of 13.6 ICU days during the study period (Table I). Despite the high number of readmissions, only three deaths occurred during follow-up before data were censored; all had ICU readmissions. Over three-quarters of subjects who required ICU admission (78.1%, n=75) were admitted to the ICU in the first year of life. A similar proportion of subjects who required mechanical ventilation support (77.0%, n=47) received it in the first year of life. Subjects who required mechanical ventilation had an average of 11.6 days on mechanical ventilation.

By univariate analysis, the only baseline subject characteristic associated with both hospital and ICU readmission was male sex ($P = 0.01$ and 0.001 , respectively; Table II). Birth weight stratum was not significantly associated with hospital readmission ($P = 0.06$), but was associated with readmission to an ICU ($P = 0.04$). Other baseline characteristics that were not significantly associated with readmission included gestational age, race, Apgar scores, oxygenation index (OI), early evidence of intracranial hemorrhage (ICH), and surfactant treatment. In addition, treatment group assignment was not associated with hospital or ICU readmission, neither all inclusive nor by birth weight stratum.

We compared data from the birth hospitalization for subjects who were never readmitted to the hospital to those who were exclusively readmitted to the hospital ward and to those who were readmitted to an ICU to determine which therapies and morbidities were associated with hospital ward and/or ICU readmission (Table III). The median duration for both mechanical ventilation and oxygen use during the NICU course was significantly higher among patients readmitted exclusively to the hospital ward and for those with an ICU readmission than those without a readmission. ICH, determined at NICU discharge, was more common among subjects with an ICU readmission (38.4% vs. 30.4% among those without a hospital readmission, $P = 0.006$), and severe ICH (grade 3–4, periventricular leukomalacia, or ventriculomegaly) was much more common (30.2% vs. 15.0%). Birth hospitalization length of stay was also significantly longer among readmitted patients.

In univariate analyses (Table IV), males were more likely to be readmitted to an ICU. ICU readmission was more common with increasing duration of supplemental oxygen, with grade 3–4 ICH, and increasing duration of birth hospitalization. In multivariable analyses, only sex and final ICH status remained significant predictors of ICU readmission (Table IV). The diagnosis of CLD and treatment with iNO had no impact on readmission to the ICU.

Post-NICU resource use by readmission status and year of life are listed in Table V (available at www.jpeds.com). The median inpatient costs incurred by subjects who required ICU readmission were at least 4 fold higher than those incurred by subjects readmitted to a non-ICU hospital ward. Subjects requiring ICU readmission and mechanical ventilation during the first year of life incurred median inpatient costs \$120,900 (IQR: \$44,400 – \$270,600), and those requiring ICU readmission without the need for mechanical ventilation incurred median inpatient costs of \$26,300 (\$19,300 – \$55,300). This trend continued through the entire follow-up period (data not shown). Among the groups of patients who did not require hospital admission, those requiring admission only to the hospital ward, and those requiring admission to an ICU, there was an incremental increase in home oxygen use, days on home oxygen, number of emergency department (ED) visits, and the costs of care. The percentage of subjects utilizing home health care was relatively consistent between the groups in the first year of life, but in subsequent years, a smaller percentage of infants who were readmitted to an ICU utilized home health care compared with the other groups. Subjects not requiring hospital readmission had relatively fewer outpatient physician visits than the subjects in the other groups.

DISCUSSION

We studied subjects enrolled in a large, multi-center RCT of iNO in preterm infants who were mechanically ventilated at birth to determine the incidence and risk factors for readmission to an ICU after NICU discharge. Consistent with previous studies [3, 5–8], we found that the majority of infants were readmitted to the hospital at least once in the first 4.5 years of life. Among the infants who were readmitted to the hospital, more than half required multiple readmissions. Nearly 1 in 5 early preterm infants requiring mechanical ventilation in the first days of life were readmitted to an ICU after discharge from the NICU, and over 1 in 10 required late mechanical ventilation support. These data provide important and tangible prognostic information for parents and caregivers, and may be used to reinforce the implementation of existing preventive strategies. ICU readmissions and the need for late mechanical ventilation are significant morbidities incurred by preterm infants. Thus, it is important to understand which infants are at greatest risk in order to develop more effective preventive strategies. Although the data collected as part of this inhaled NO trial revealed several statistically significant risk factors for ICU readmission including birth weight, male sex, length of respiratory support, ICH, and NICU LOS, the differences between groups with and without these risk factors were too small for them to serve as clear clinical predictors. It should be noted that these results may not be generalizable to preterm infants who do not require mechanical ventilation at birth or to preterm infants outside the birth weight range included in this study (500–1250g).

Prediction of hospital readmission and its associated morbidities are important both in terms of the quality of life for the infants and their families as well as the cost to the public. Although it has been well-reported that preterm infants are at high risk for rehospitalization [6, 8, 17–20], few studies have examined the incidence of readmission to an ICU in this population. A single center study following 217 infants born at 24 to 28 weeks' gestation from 1987 to 1992 found a rehospitalization rate of 48% and ICU readmission rate of 6% during the 18 month follow-up period. There were no differences in the rates of readmission to the hospital or to the ICU among patients with and without BPD, although patients with moderate or severe BPD spent more days in the hospital [3].

Previous studies found hospital readmission rates in preterm infants ranging from 15–50%, depending on the inclusion criteria for degree of prematurity or birth weight [5, 8, 17, 19–21]. The rehospitalization rate for patients enrolled in this trial was 43.4% in the first year of life and 57.8% during the 4.5 year follow-up, which is consistent with other studies with similar enrollment criteria [17, 19, 20, 22, 23]. The finding that almost 30% of subjects required multiple hospital readmissions, averaging 3.9 admissions over the study period, is remarkable and demonstrates a high degree of morbidity in these infants. The risk factors for hospital readmission that have been previously identified [8, 17, 19, 20] are similar to those we identified for readmission to the ICU. One notable difference is the lack of CLD as a risk factor for either hospital or ICU readmission in our study. A possible reason for the difference is that the incidence of CLD was much higher in this trial (67% vs. 10–30%) compared with the incidence of CLD in the studies that identified it as a risk factor. The high incidence of CLD in this trial is likely due in part to the fact that only infants who were mechanically ventilated in the first days of life were eligible for the trial.

Even though we found small but statistically significant differences in birth hospitalization LOS between groups, we did not find significant differences in the costs incurred during the birth hospitalization. One possible reason for this discrepancy is that the variance in hospital costs was large, limiting statistical power to detect differences. Another possible reason is that the majority of costs for the birth hospitalization are typically related to support received soon after birth, so small differences in LOS for these long stay patients may not translate to statistically significant cost differences.

ICU readmission was associated with substantially higher inpatient costs than hospital readmission without an ICU stay. Subjects requiring at least one episode of mechanical ventilation and an ICU admission incurred the majority of these costs. Further, the inpatient costs represented a large proportion of the total costs for these children. Previous studies have demonstrated that the primary reason for hospital readmission is respiratory illness [3, 5, 20, 24]. We have previously shown that among children under age 2 readmitted to the ICU for respiratory illness, preterm infants had longer ICU and hospital lengths of stay, utilized more hospital resources, and incurred higher total hospital charges compared with full term infants [25]. Mechanical ventilation support is a major component of both the cost and morbidities associated with severe acute respiratory illness in preterm infants. Although data detailing the reasons for hospital or ICU readmission were not available for this study, the impact of the need for mechanical ventilatory support suggests that recurrent and/or acute respiratory illnesses may be among the most costly morbidities for preterm infants and

could have a major impact on quality of life. Thus, given the high costs of ICU readmission, these data should be used to reinforce adherence to present guidelines for preventative care in these infants, especially those focusing on respiratory care. Additionally, infants with ICH and/or NDI appear to be at the higher risk of these morbidities, so targeted intervention strategies with this group of infants may have higher impact.

The results of this original trial of iNO involving 793 infants (500–1250 g) by Kinsella et al [9] found no difference in the primary outcome of CLD at 36 weeks' postmenstrual age or death with iNO. However, CLD was significantly lower with iNO among subjects with birth weights of 1000 to 1250 g. Subjects treated with iNO had a significantly lower rate of grade 3 or 4 intracranial hemorrhage (ICH), periventricular leukomalacia, or ventriculomegaly and a trend toward improved survival. The follow-up study found that these short-term benefits did not persist at 1 year of life [10]. Effects among birth weight subgroups were inconsistent. The data examined here show that iNO as administered in this study did not impact readmission to the hospital or the ICU, further demonstrating that short-term, proxy end points may not be reliable estimates of long-term effect. Thus, prolonged evaluation of therapies used in preterm infants is required to determine long-term risks and benefits, which can potentially have great impact on the design of clinical trials and comparative effectiveness research.

This study has several limitations. All post discharge resource use including days of mechanical ventilation were acquired through care-giver recall during telephone interviews, which is subject to inaccuracies and recall bias. Parent recall was found to be a reliable source of information regarding children's acute health care use [26, 27], and we sought to maximize reliability through simple questions and frequent interviews. Calculating costs from detailed billing data by using department specific cost-to-charge ratios is labor intensive, but it correlates well with detailed time-and-motion cost accounting strategies [28]. Loss to follow-up raises the potential of informative censoring. However, we had high follow-up rates, and there were not consistent differences in baseline characteristics between subjects with and without missing data. Yet, the decreasing numbers of respondents over time may limit the generalizability of the data from the latter time points. Additionally, data were not available to evaluate the reasons for readmission and mechanical ventilation use or any specific preventive strategies that were employed, limiting the ability to make inferences about post NICU discharge risk factors or the types of illnesses that lead to ICU readmissions. Finally, because the current study population involved infants with birth weights 500–1250g requiring mechanical ventilation in the first days of life, these results may not be generalizable to preterm infants who do not require mechanical ventilation at birth. However, our results provide important prognostic information for parents and health care providers, and underscore the need for better predictors of late morbidity and improved preventive strategies.

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Abbreviations

CLD	Chronic lung disease
CMS	Centers for Medicare and Medicaid Services
g	Grams
iNO	Inhaled nitric oxide
IQR	Interquartile range
IRB	Institutional review board
ICH	Intracranial hemorrhage
LOS	Length of stay
NDI	neurodevelopmental impairment
OI	Oxygenation Index
SGA	small for gestational age
RCT	Randomized, controlled trial
VLBW	Very low birth weight

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Appendix

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Hospital and ICU Readmission Rates

Figure.

Hospital and ICU readmission rates among preterm infants. Bars indicate the percentage of infants by year of age requiring readmission to the hospital and the ICU, as well as the percentage requiring mechanical ventilation. Numbers above bars represent the absolute number of infants.

Table 1**Hospital readmissions**

	To 1 y of age n=512	1 to 2 y of age n=455	2 to 3 y of age n=412	3 to 4.5 y of age n=282	Total n=512
Number of subjects readmitted to a hospital (%)	222 (43.4%)	144 (31.7%)	104 (25.2%)	53 (18.8%)	296 (57.8%)
Number of hospital readmissions	363	173	139	67	742
Number of subjects readmitted to an ICU (%)	75 (14.7%)	35 (7.7%)	22 (5.3%)	10 (3.6%)	96 (18.8%)
Mean ICU days per subject (SD)	11.1 (18.0)	8.0 (12.2)	6.1 (9.5)	5.7 (8.4)	13.6 (19.2)
Number of subjects readmitted with MV (%)	47 (9.2%)	20 (4.4%)	11 (2.7%)	6 (2.1%)	61 (11.9%)
Mean days of MV per subject (SD)	9.3 (17.7)	8.3 (17.6)	6.6 (11.6)	5.1 (7.9)	11.6 (21.3)

Table 2

Baseline characteristics of subjects with and without readmissions

	Subjects without a readmission (n=216)	Subjects readmitted only to the ward (n=201)	p ¹	Subjects with at least one ICU readmission (n=95)	p ²
Birth weight, g, mean (SD)	827.8 (182.3)	812.6 (187.1)	0.16	801.9 (192.2)	0.16
Birth weight, g, median (IQR)	807.5 (687.0–941.0)	780.0 (680.0–915.0)		743.0 (673.0–922.0)	
Birth weight strata, n (%)			0.06		0.04
500–749 g	78 (36.1)	88 (43.8)		49 (51.6)	
750–999 g	97 (44.9)	75 (37.3)		31 (32.6)	
1000–1250 g	41 (19.0)	38 (18.9)		15 (15.8)	
Gestational age, weeks, mean (SD)	26.0 (1.8)	26.0 (1.9)	0.65	25.7 (1.7)	0.24
Gestational age, weeks, median (IQR)	26.0 (25.0–27.0)	26.0 (25.0–27.0)		25.0 (24.0–27.0)	
Sex, n (%)			0.01		0.001
Female	124 (57.4)	101 (50.3)		35 (36.8)	
Male	92 (42.6)	100 (49.7)		60 (63.2)	
Race/Ethnicity, n (%)			0.53		0.26
African-American	42 (19.4)	48 (23.9)		17 (17.9)	
Caucasian	139 (64.4)	127 (63.1)		68 (71.6)	
Hispanic	29 (13.4)	22 (11.0)		6 (6.3)	
Asian / Other	6 (2.8)	4 (2.0)		4 (4.2)	
Apgar score at 1 minute, median (IQR)	4.0 (2.0–6.0)	4.0 (2.0–6.0)	0.82	4.5 (2.0–6.0)	0.69
Apgar score at 5 minutes, median (IQR)	7.0 (5.0–8.0)	7.0 (6.0–8.0)	0.82	7.0 (5.0–8.0)	0.94
Baseline OI, mean (SD)	4.8 (3.6)	5.0 (4.1)	0.95	5.6 (6.7)	0.85
Baseline OI, median (IQR)	3.9 (2.7–5.6)	3.8 (2.7–5.5)		3.9 (2.8–5.5)	
Baseline ICH, n (%)			0.83		0.37
Grades 1–2	35 (16.4)	33 (16.5)		19 (20.4)	
Grades 3–4	10 (4.7)	9 (4.5)		7 (7.5)	
SGA, n (%)			0.23		0.66
SGA	11 (5.1)	17 (8.5)		6 (6.3)	
Not SGA	205 (94.9)	184 (91.5)		89 (93.7)	
Surfactant, n (%)			0.99		0.83
Received surfactant	175 (81.0)	164 (81.6)		76 (80.0)	

	Subjects without a readmission (n=216)	Subjects readmitted only to the ward (n=201)	p ¹	Subjects with at least one ICU readmission (n=95)	p ²
Did not receive surfactant	41 (19.0)	37 (18.4)		19 (20.0)	
Treatment group, n (%)					
iNO	111 (51.4)	109 (54.2)	0.55	51 (53.7)	0.71
Placebo	105 (48.6)	92 (45.8)		44 (46.3)	
Treatment group by weight strata, n (%)					
500–749 g			0.62		0.67
iNO	40 (51.3)	48 (54.5)		27 (55.1)	
Placebo	38 (48.7)	40 (45.5)		22 (44.9)	
750–999 g			0.25		0.41
iNO	48 (49.5)	43 (57.3)		18 (58.1)	
Placebo	49 (50.5)	32 (42.7)		13 (41.9)	
1000–1250 g			0.30		0.29
iNO	23 (56.1)	18 (47.4)		6 (40.0)	
Placebo	18 (43.9)	20 (52.6)		9 (60.0)	

iNO – subjects treated with inhaled nitric oxide; SGA – small for gestational age; SD – standard deviation; g – grams; IQR – interquartile range; OI – oxygenation index; ICH – intracranial hemorrhage

p¹ values are for comparison between subjects without a readmission vs. subjects with any readmission (with or without ICU stay)

p² values are for comparison between subjects without a readmission vs. subjects with an ICU readmission

Table 3

NICU course of subjects with and without readmissions

	Subjects without a readmission (n=216)	Subjects readmitted only to the ward (n=201)	Subjects with at least one ICU readmission (n=95)	p ¹	p ²
Ventilator days, median (IQR)	35 (10–54)	39 (19–56)	45 (29–66)	0.005	0.001
Oxygen days, median (IQR)	79 (55–101)	84 (63–105)	92 (68–110)	0.04	0.01
Prophylactic Indocin, n (%)	70 (32.4)	65 (32.3)	25 (26.3)	0.63	0.28
PDA, n (%) ^a				0.30	0.78
	123 (73.6)	124 (79.5)	55 (75.3)		
Sepsis, n (%)	68 (31.5)	66 (32.8)	38 (40.4)	0.37	0.13
NEC, n (%)	19 (8.8)	18 (9.0)	12 (12.6)	0.62	0.30
Postnatal steroid treatment, n (%)	124 (57.4)	125 (62.2)	58 (61.1)	0.31	0.55
CLD at 36 weeks, n (%)	147 (68.1)	129 (64.2)	68 (71.6)	0.72	0.54
Oxygen at hospital discharge, n (%)	139 (65.3)	132 (66.3)	62 (68.9)	0.66	0.54
Bronchodilators, steroids, or diuretics at 36 weeks, n (%)	89 (43.6)	93 (47.4)	47 (51.6)	0.26	0.20
Final ICH, n (%)				0.21	0.006
None	144 (69.6)	115 (63.2)	53 (61.6)		
Grades 1–2	32 (15.4)	37 (20.3)	7 (8.2)		
Grades 3–4, PVL, or ventriculomegaly	31 (15.0)	30 (16.5)	26 (30.2)		
Neurologic exam at discharge, n (%)				0.36	0.56
Normal	174 (80.9)	152 (76.4)	71 (75.5)		
Suspect	27 (12.6)	35 (17.6)	15 (16.0)		
Abnormal	14 (6.5)	12 (6.0)	8 (8.5)		
Birth hospitalization LOS, median (IQR)	88 (71–108)	92 (75–110)	99 (81–126)	0.006	0.001
Birth hospitalization cost, median (IQR) ^b	219 (138–309)	213 (147–290)	222 (139–320)	0.68	0.33

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Number of post-birth hospitalization deaths, n (%)	Subjects without a readmission (n=216)	Subjects readmitted only to the ward (n=201)	p ¹	Subjects with at least one ICU readmission (n=95)	p ²
	0 (0.0)	0 (0.0)	0.27	3 (3.2)	0.03

NICU - neonatal intensive care unit; **PDA** - patent ductus arteriosis; **CLD** - chronic lung disease; **SD** - standard deviation; **g** - grams; **IQR** - interquartile range; **OI** - oxygenation index; **ICH** - intracranial hemorrhage

p¹ values are for comparison between subjects without a readmission vs. subjects with any readmission (with or without ICU stay)

p² values are for comparison between subjects without a readmission vs. subjects with an ICU readmission

^a PDA is absent or missing for all patients who were enrolled in PRONox and survived to discharge from birth hospital.

^b Costs are presented in thousands of 2012 US dollars.

Univariate and multivariable analysis of baseline and birth hospitalization predictors of ICU readmission

Table 4

Variable	Univariate			Multivariable ^a		
	OR	95% CI	p ^b	OR	95% CI	p ^b
Birth weight, unit size 100g	0.95	0.84–1.07	0.38	NA		
Birth weight strata, vs. 500–749 g			0.11 ^c			0.37 ^c
750–999 g	0.61	0.37–1.00	0.05	0.62	0.31–1.21	0.16
1000–1250 g	0.64	0.34–1.22	0.17	0.74	0.25–2.18	0.58
Gestational age, unit size 1 week	0.90	0.79–1.03	0.12	1.03	0.83–1.28	0.78
Gender, male vs. female	2.01	1.27–3.18	0.003	1.86	1.04–3.35	0.04
Race, vs. White			0.22 ^c			0.55 ^c
Black	0.74	0.41–1.32	0.31	0.81	0.39–1.70	0.58
Hispanic	0.46	0.19–1.12	0.09	0.49	0.18–1.35	0.17
Asian/Other	1.57	0.48–5.14	0.46	1.11	0.26–4.70	0.89
Apgar score at 1 minute, 1 unit	0.98	0.89–1.08	0.66	NA		
Apgar score at 5 minutes, 1 unit	1.03	0.92–1.15	0.60	NA		
Baseline OI, 1 unit	1.03	0.99–1.08	0.20	1.02	0.97–1.08	0.41
Baseline ICH, vs. none			0.30 ^c			0.30 ^c
Grades 1–2	1.36	0.77–2.42	0.29	1.80	0.84–3.90	0.13
Grades 3–4	1.80	0.73–4.45	0.20	0.90	0.24–3.30	0.87
SGA ^d	0.94	0.38–2.33	0.89	NA		
NDI ^d	1.80	1.12–2.92	0.02	1.50	0.78–2.86	0.22
Surfactant, receive vs. not receive	0.92	0.53–1.61	0.77	NA		
Treatment group, iNO vs. placebo	1.04	0.66–1.62	0.87	NA		
Ventilator days, unit 1 day	1.00	1.00–1.01	0.14	1.00	0.99–1.01	0.84
Oxygen days, unit 1 day	1.01	1.00–1.01	0.003	1.00	0.99–1.01	0.69
Prophylactic Indocin ^d	0.75	0.45–1.23	0.25	0.57	0.27–1.20	0.14
PDA ^d	NA			NA		
Air leak ^d	NA			NA		
Sepsis ^d	1.43	0.90–2.27	0.13	1.35	0.73–2.48	0.34

Variable	Univariate			Multivariable ^a		
	OR	95% CI	p ^b	OR	95% CI	p ^b
NEC ^d	1.48	0.74–2.96	0.27	1.10	0.41–2.94	0.85
Postnatal steroid treatment ^d	1.06	0.67–1.67	0.81	NA		
CLD at 36 weeks ^d	1.29	0.79–2.10	0.31	NA		
Oxygen at hospital discharge ^d	1.15	0.71–1.88	0.57	NA		
Bronchodilators, steroids, or diuretics at 36 weeks ^d	1.28	0.81–2.02	0.29	1.12	0.60–2.09	0.73
Final ICH, vs. none			0.004^c			0.04^c
Grades 1–2	0.49	0.23–1.02	0.06	0.38	0.15–0.95	0.04
Grades 3–4, PVL, or ventriculomegaly	2.13	1.23–3.69	0.01	1.67	0.80–3.48	0.17
Neurologic exam at discharge, vs. normal			0.70 ^c			
Suspect	1.11	0.60–2.06	0.74	NA		
Abnormal	1.41	0.61–3.25	0.42	NA		
Birth hospitalization LOS, unit size 1 day	1.01	1.00–1.02	0.001	1.01	1.00–1.02	0.06
Birth hospitalization cost, unit size \$1000	1.00	1.00–1.00	0.11	1.00	1.00–1.00	0.83

SGA – small for gestational age; **NDI** – neurodevelopmental impairment; **g** – grams; **OI** – oxygenation index; **ICH** – intracranial hemorrhage; **PDA** – patent ductus arteriosus; **NEC** – necrotizing enterocolitis; **CLD** – chronic lung disease; **PVL** – periventricular leukomalacia

^a Multivariable analysis included covariates which had p-values less than or equal to 0.30 in the univariate analysis

^b p-value for Chi-square test of significance for covariate in predicting ICU readmission vs. no ICU readmission

^c p-value for Wald global test of significance

^d Present vs. Absent

Table 5

Post-NICU resource use by readmission status and year of life

	Home oxygen use, n (%)	Days on home oxygen, Median (IQR)	Home health care, n (%)	Outpatient physician visits per subject, Median (IQR)	ED visits per subject, Median (IQR)	Readmission hospital costs ^a , Median (IQR)	Outpatient costs ^b , Median (IQR)	Lost wages from work, Median (IQR)	Total costs, Median (IQR)
Year 1, N=479									
No readmissions, n=266	165 (62.7)	26 (0–91)	148 (55.6)	9 (6–13)	0 (0–1)	NA	3.9 (2.5–6.1)	1.3 (0–13.3)	9.6 (4.2–28.5)
Readmission only to ward, n=141	104 (74.8)	45 (0–126)	83 (58.9)	11 (8–18)	1 (0–3)	8.7 (3.7–12.0)	5.6 (3.5–8.7)	1.5 (0–15.1)	30.2 (12.6–59.7)
At least one ICU readmission, n=72	56 (77.8)	82 (3–161)	40 (55.6)	11 (8–18)	2 (0–3)	40.9 (15.7–113.3)	6.9 (4.4–11.6)	1.6 (0–17.4)	69.7 (34.1–132.7)
p-value	0.01 ^c	0.002 ^c	0.81	0.003 ^c	<0.001 ^{cd}	<0.001 ^{cde}	<0.001 ^{cd}	0.50	<0.001 ^{cde}
Year 2, N=436									
No readmissions, n=198	125 (63.8)	26 (0–91)	121 (61.1)	16 (11–22)	0 (0–1)	NA	6.4 (3.8–11.9)	1.4 (0.0–14.4)	16.7 (6.0–42.2)
Readmission only to ward, n=163	122 (76.3)	45 (1–130)	100 (61.4)	20 (14–28)	2 (1–4)	10.0 (5.0–20.0)	9.8 (6.1–16.3)	2.5 (0.2–17.1)	36.2 (17.3–65.1)
At least one ICU readmission, n=75	61 (81.3)	90 (6–223)	41 (54.7)	20 (13–31)	3 (1–5)	61.1 (23.7–149.9)	14.9 (7.4–27.0)	6.8 (0.2–25.7)	109.6 (57.1–217.8)
p-value	0.004 ^{cd}	<0.001 ^{cd}	0.57	<0.001 ^{cd}	<0.001 ^{cd}	<0.001 ^{cde}	<0.001 ^{cde}	0.06	<0.001 ^{cde}
Year 3, N=346									
No readmissions, n=139	87 (63.5)	22 (0–91)	80 (57.6)	20 (14–29)	1 (0–2)	NA	8.3 (4.6–17.8)	1.7 (0.2–15.0)	19.1 (6.9–50.5)
Readmission only to ward, n=147	115 (79.3)	49 (6–150)	87 (59.2)	24 (19–37)	3 (1–5)	10.0 (5.0–22.6)	13.1 (8.0–27.1)	3.0 (0.3–20.6)	43.1 (22.7–86.3)
At least one ICU readmission, n=60	47 (78.3)	82 (4–275)	31 (51.7)	26 (20–46)	4 (1–7)	45.9 (26.0–133.3)	24.4 (12.3–42.6)	6.2 (0.5–28.8)	116.0 (65.7–247.8)
p-value	0.01 ^c	0.001 ^{cd}	0.61	<0.001 ^{cd}	<0.001 ^{cd}	<0.001 ^{cde}	<0.001 ^{cde}	0.11	<0.001 ^{cde}
Year 4, N=171									
No readmissions, n=61	41 (69.5)	30 (0–91)	23 (37.7)	23 (15–32)	1 (0–2)	NA	8.8 (4.7–17.6)	1.9 (0.2–11.7)	19.4 (7.2–41.4)
Readmission only to ward, n=77	56 (75.7)	60 (1–160)	31 (40.3)	31 (24–50)	4 (2–7)	10.0 (5.0–22.6)	20.4 (10.1–37.0)	4.1 (0.5–16.1)	53.2 (30.8–80.0)
At least one ICU readmission, n=33	22 (66.7)	66 (0–221)	11 (34.4)	36 (25–53)	3 (1–7)	45.9 (22.9–129.3)	32.9 (18.0–51.6)	7.6 (0.7–47.3)	111.8 (74.2–250.9)
p-value	0.57	0.23	0.84	<0.001 ^{cd}	<0.001 ^{cd}	<0.001 ^{cde}	<0.001 ^{cd}	0.14	<0.001 ^{cde}

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^pCosts are presented in thousands of 2012 US dollars.

^qOutpatient costs do not include costs for medications or RSV immune globulin

^cPost hoc pairwise comparison with Bonferroni adjustment was significant for “No readmissions” vs. “Readmission only to ward”

^dPost hoc pairwise comparison with Bonferroni adjustment was significant for “No readmissions” vs. “At least one ICU readmission”

^ePost hoc pairwise comparison with Bonferroni adjustment was significant for “Readmission only to ward” vs. “At least one ICU readmission”

NA - Not applicable