Intensive Care Unit Readmission during Childhood after Preterm Birth with Respiratory Failure

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

Study design We studied preterm newborns (birth weight 500-1250 g) 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 male subjects (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 per day; 95% CI 1.00-1.01). In the first year after birth hospitalization, children readmitted to an ICU incurred greater 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, require extensive health care resources, and incur high treatment costs. *(J Pediatr 2014;164:749-55)*.

Early preterm birth (<34 weeks' gestational age at birth) is associated with late morbidities such as chronic lung disease (CLD), neurologic impairment, and a high risk for hospital readmission in the first years of life.[1-4] During the first year of life, rates of rehospitalization 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 a significant use of resources, great 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 intensive care unit (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 500-1250 g) who required mechanical ventilation at birth and

CLD	Chronic lung disease
ICH	Intracranial hemorrhage
ICU	Intensive care unit
iNO	Inhaled nitric oxide
LOS	Length of stay
NDI	Neurodevelopmental impairment
NICU	Neonatal intensive care unit

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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 ≤34 weeks' gestation, weighed 500-1250 g, were <48 hours 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 <48 hours 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 year corrected age, survival and other postdischarge 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 3 months during the first year of the patient's life and every 6 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 randomized controlled trial and postdischarge follow-up were conducted with institutional review board 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 Hospital Cost Reports and multiplied 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 infants and unit costs from the Centers for Medicare and Medicaid Services 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 test, χ^2 test, or Fisher exact tests. Subjects were censored at the last date when vital status was known. Proportions are reported on the basis of 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 $P \leq .30$ in the univariate analysis. We assumed statistical significance at $P < .05$.

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 attributable to trial enrollment before institutional research board 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 because of 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 one-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 3 deaths occurred during follow-up before data were censored; all had ICU readmissions. More than 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