Inhaled Nitric Oxide Use and Outcomes in Critically Ill Children With a History of Prematurity

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BACKGROUND: Inhaled nitric oxide (INO) is used to treat hypoxic respiratory failure without clear evidence of benefit. Future trials to evaluate its use will be designed based on an understanding of the populations in which this therapy is provided and with outcomes based on patient characteristics, for example, a history of premature birth. METHODS: This was a multicenter prospective observational study that evaluated subjects in the pediatric ICU who were treated with INO for a respiratory indication, excluding those treated in the neonatal ICU or treated for birth-related disease. We used logistic regression to evaluate characteristics associated with mortality and duration of mechanical ventilation. Specifically, we compared subjects born early preterm (<32 weeks post-conceptual age), late preterm (32–37 weeks post-conceptual age), and full term. RESULTS: A total of 163 children (median age [interquartile range], 1.8 [0.7–6.0] y) were included, 41 (25.2%) had a history of preterm birth (18 born early preterm and 23 born late preterm). INO was initiated for less-severe lung disease in the early preterm versus late preterm versus full-term subjects (median mean airway pressures, 16 vs 19 vs 19 cm H_2O; $P = .03$), although the oxygenation index and oxygenation saturation index did not differ. The early preterm subjects had more ventilator-free days (median, 18.0, 7.0, 4.5 d; $P = .02$) and lower 28-d mortality (0, 26.1, 32.0%; $P = .007$). Lower respiratory tract disease, but not a history of prematurity, was independently associated with lower mortality. CONCLUSIONS: INO was used differently in early preterm subjects. Clinical trials that evaluate INO use should have standardized oxygenation deficit thresholds for initiation of therapy and should consider stratifying by early preterm status. *Key words: pediatric; Acute Respiratory Distress Syndrome; critical care outcomes; nitric oxide; right ventricular failure; pulmonary hypertension; infant; premature.*
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Introduction

Infants born preterm, especially early preterm (<32 weeks post conceptual age at birth) are at risk for impaired pulmonary angiogenesis and alveolarization. The arrested pulmonary development results in simplification of the distal lung air space, which causes a reduction of the alveolar-capillary surface area limiting gas exchange.[1] Bronchopulmonary dysplasia, the chronic lung disease of infancy that occurs in preterm neonates who have required mechanical ventilation and oxygen therapy for acute respiratory distress at birth, is characterized by a prolonged need for supplemental oxygen, with recurrent respiratory exacerbations and frequent hospitalizations.[2-9] However, manifestations of disease are highly variable. In addition, up to 25% of children with moderate or severe bronchopulmonary dysplasia have concomitant pulmonary hypertension[10,11] and altered pulmonary vascular regulation, which result in ventilation-perfusion mismatch with subsequent acute pulmonary insults.[12,13] For these reasons, formerly preterm children are at risk of profound hypoxemia with acute respiratory infections later in childhood.[1,14-17] Compared with patients who were born at term, patients born preterm, including those born late preterm (32–37 weeks post-conceptual age at birth), are more frequently admitted to the pediatric ICU with respiratory

illnesses, and incur longer and more resource-intensive hospitalizations.[5]

Acute pulmonary insults (eg, lower respiratory tract infections) can lead to severe hypoxemia and acute pulmonary hypertension that require mechanical ventilation support. Inhaled nitric oxide (INO) is a therapy often used to treat pulmonary vascular disease and severe ventilation-perfusion mismatch associated with acute hypoxemic respiratory failure during pediatric critical illness.[18,19] The continued controversy surrounding the potential effectiveness of INO use in patients who are critically ill has led intensivists to contemplate a targeted trial to evaluate its efficacy. To optimally design a trial, it is important to understand the following: (1) the pattern of usage across the population of patients with respiratory failure, and (2) the incidence of likely outcome measures (eg, mortality), particularly across key subgroups, such as formerly premature infants who may display differential responses to the therapy. The objectives of this study were to (1) characterize INO use for respiratory failure in children who are critically ill based on their history of prematurity, and (2) delineate outcomes based on a history of prematurity to inform a future clinical trial. We tested the hypothesis that patients with a history of preterm birth have differing indications and thresholds of pulmonary support for which INO is initiated compared with patients with a history of full-term birth.

QUICK LOOK

Current knowledge

Inhaled nitric oxide (INO) is a controversial therapy often used to treat pulmonary vascular disease and severe ventilation-perfusion mismatch associated with acute hypoxemic respiratory failure during pediatric critical illness. A high proportion of children afflicted with these severe illnesses have a history of preterm birth and may respond differently to treatment with INO due to impaired pulmonary angiogenesis and alveolarization. Intensivists continue to contemplate a targeted trial to evaluate the efficacy of INO.

What this paper contributes to our knowledge

Children with a history of an early preterm birth who were treated with INO for a respiratory indication more often had direct pulmonary injury, were initiated on INO at a less-severe stage of respiratory impairment, and experienced better outcomes compared with the children with a history of late preterm or full-term birth. Patients with a history of prematurity represent a key subgroup in future trials to evaluate the efficacy of this therapy in acute respiratory failure.

Methods

This was a secondary analysis of a previously published prospective observational cohort study that enrolled consecutive subjects treated with INO in the pediatric ICU or Cardiac ICU of the 8 Collaborative Pediatric Critical Care Research Network institutions between October 15, 2015 and October 31, 2016.[18] Eligible subjects were < 18 years of age, were on mechanical ventilation, and received INO in the pediatric ICU or Cardiac ICU. We did not

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The authors have disclosed no conflicts of interest.

Supplementary material related to this paper is available at http://www.rcjournal.com.

Drs Maddux and Mourani contributed equally to this work.

The study was conducted at the 8 sites of the Eunice Kennedy Shriver National Institute of Child Health and Human Development Collaborative Pediatric Critical Care Research Network, including Children's Hospital Colorado (Aurora, CO), Children's National Health System (Washington, DC), Children's Hospital of Philadelphia (Philadelphia, PA), Children's Hospital of Pittsburgh (Pittsburgh, PA), Nationwide Children's Hospital (Columbus, OH), Children's Hospital of Michigan (Detroit, MI), Benioff Children's Hospital (San Francisco, CA), and Mattel Children's Hospital (Los Angeles, CA).

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evaluate patients who had received INO while in the neonatal ICU and excluded those who had received INO for lung disease related to complications at birth, specifically newborns with congenital diaphragmatic hernia, meconium aspiration syndrome, or persistent pulmonary hypertension of the newborn, to exclude patients for whom INO was used to treat perinatal lung disease. We also excluded patients for whom INO was started at an outside institution or were previously enrolled in the study. For the current analysis, we excluded patients administered INO for a cardiac indication and included only subjects administered INO for a respiratory indication. In addition, we classified the subjects based on their birth history: early preterm if born $<$ 32 weeks post-conceptual age, late preterm if born between 32 and 37 weeks post-conceptual age, and full term if born $>$ 37 weeks post-conceptual age. The project was approved with a waiver of informed consent by the responsible institutional review board for every clinical site and the data coordinating center at the University of Utah. INO use in pediatric ARDS is considered off-label because it has not been approved by the U.S. Food and Drug Administration for this indication.

The clinical care team dictated ventilator management and administration of INO. Data collection techniques were previously described.[18] Briefly, data were extracted from the medical record by trained research coordinators. Data collection began at the time of INO initiation and continued daily until 28 days, discharge from the ICU, or death. Admission data included demographics; hospitalization diagnoses; comorbidities; and pre-hospital technology dependence, defined as dependence on oxygen, tracheostomy, ventilator, or chronic vascular access before hospitalization. We collected, daily, the use of ICU technologies (eg, extracorporeal membrane oxygenation, renal replacement therapies), cardiac arrests, echocardiogram evaluations, medications to treat pulmonary hypertension, and mechanical ventilation data. We collected all changes to mechanical ventilator settings, blood gas measurements, and changes to the INO dose immediately before INO initiation and for the next 48 h. In addition, we collected hourly pulse oximetry and end-tidal carbon dioxide measurements. Based on the methods of the parent study, the a priori definition of clinician responsiveness to oxygenation improvement after INO initiation was defined as a decrease in the fraction of inspired oxygen to $\leq$ 0.6 by 24 h after INO initiation. The etiology of pediatric ARDS was defined as direct pulmonary injury (eg, lower respiratory tract infections and aspiration) or indirect pulmonary injury (eg, sepsis and trauma). A Functional Status Scale score was designated by trained research staff at admission, reflective of pre-illness baseline and at ICU discharge or 28 d, whichever came first.[20] New ICU morbidity was defined as an increase in the Functional Status Scale score of $\geq$3 points.[21]

Counts and percentages for nominal variables were reported, whereas medians and interquartile ranges (IQR) were used to summarize interval variables. The premature status was treated nominally in all statistical tests. Owing to small counts across prematurity status and non-normal variable distributions in many clinical measures, non-parametric tests of association were selected. One subject remained hospitalized at the end of the study. The stay data for this subject was truncated at study end ($>$8 months after admission). Time-to-event analyses included time-to-INO discontinuation among the subjects who survived the hospitalization. The time to INO discontinuation was marked as the number of calendar days between INO initiation and the last known date of INO administration, ICU discharge, or the end of ICU data collection per study protocol (28 d), whichever occurred first. Kaplan-Meier curves were plotted to show INO attrition on the study, whereas a Cox proportional hazards model was used to evaluate INO discontinuation likelihood among early preterm and late preterm subjects compared with full-term subjects. We used univariable logistic regression models to evaluate for patient and clinical characteristics associated with in-hospital mortality. Factors with univariable association were evaluated in multivariable analyses by using a bidirectional stepwise variable selection process, with criteria $P < .20$ to enter the multivariable model and $P < .10$ to remain. We reported the odds ratio (OR) estimates and 95% CIs of the univariable analyses and the stepwise variable selection. All analyses were performed by using SAS 9.4 (SAS Institute, Cary, North Carolina). We did not make adjustments for multiple comparisons, and we considered $P < .05$ to be statistically significant.

Results

Cohort Characteristics

The parent study included 571 subjects who were critically ill and who were treated with INO.[18] Herein, we reported the results of the 163 children treated with INO for a respiratory indication (Fig. 1). The median (IQR) age of the study was 1.8 (0.7–6.0) y; 56.4% were boys (Table 1). Forty-one subjects (25.2%) had a history of preterm birth, including 18 early preterm subjects. Nearly all the subjects ($n = 160$ [98%]) were treated at a hospitalization separate from their birth hospitalization, including all 18 early preterm (100%) and 23 late preterm (100%) subjects. The early preterm and late preterm subjects were younger than the subjects with a history of term birth (median [IQR], 0.8 [0.5–1.7] y vs 0.9 [0.5–1.9] y vs 2.9 [0.9–7.8] y, respectively; $P = .002$). The distribution of chronic diagnoses differed across the groups of subjects with a higher portion of the early preterm and late preterm subjects with a preexisting chronic condition (early preterm [$n = 18$ {100%}] vs late preterm [$n = 19$ {82.6%}] vs full term [$n = 86$ {70.5%}]; $P = .01$). Thirteen early preterm subjects

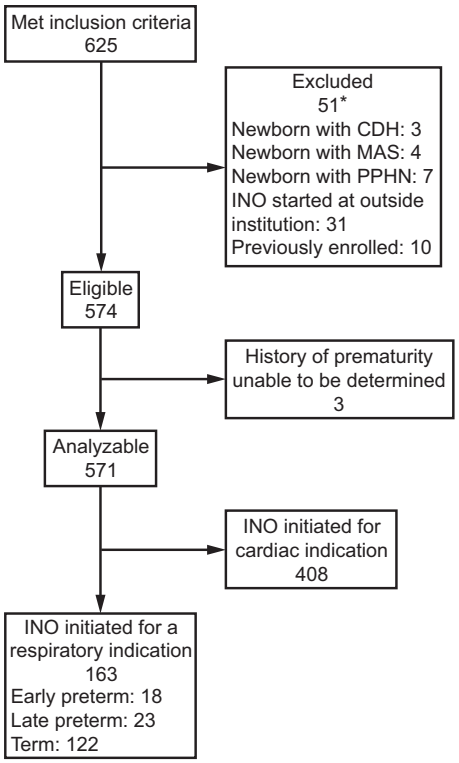

Fig. 1. Flow chart. *Subjects may have more than one reason for exclusion. INO = inhaled nitric oxide; CDH = congenital diaphragmatic hernia; MAS = meconium aspiration syndrome; PPHN = primary pulmonary hypertension of the newborn.

(72.2%) and 2 late preterm subjects (8.7%) were reported to have bronchopulmonary dysplasia. Pre-hospital technology dependence was most frequent in the early preterm subjects compared with the late preterm and full-term subjects (55.6, 43.5, and 23.8%, respectively; $P = .008$). Eleven subjects (6.7%) had a diagnosis of chronic pulmonary hypertension before hospitalization. This was most frequent in early preterm subjects compared with late preterm and full-term subjects (22.2, 13.0, and 3.3%, respectively; $P = .007$).

INO Use and Indication

Nearly all the subjects were given INO for respiratory failure without evidence of elevated pulmonary arterial pressure ($n = 146$ [90.0%]), and this did not differ based on prematurity status (Table 2). The etiology of respiratory failure differed by prematurity status, with the early preterm subjects more frequently presenting with direct pulmonary injury compared with the late preterm and full-term subjects (81.3, 59.1, and 43.3%, respectively; $P = .009$). The early preterm subjects had lower mean airway pressures compared with late preterm and full-term subjects at the time of INO initiation (median, 16.0, 19.0, and 19.0 cm H_2O, respectively; $P = .03$) (Table 3). Although the early preterm subjects were ventilated with higher tidal volumes (median, 9.4, 7.5, and 7.5 mL/kg, respectively; $P = .036$), peak inspiratory pressures were not significantly different (median, 30.0, 32.0, 32.0 cm H_2O, respectively; $P = .33$). The oxygenation index and oxygenation saturation index variables did not differ at the time of INO initiation by prematurity history. However, a large portion of the subjects did not have the necessary variables available to calculate this metric (Table 3). There were no differences in echocardiogram abstractions at INO initiation or during the study period based on prematurity status (Supplementary Table 1 [see the supplementary materials at http://www.rcjournal.com]).

Fifteen subjects (9.2%) were initiated on INO before mechanical ventilation. The remaining subjects had INO initiated after mechanical ventilation, the timing of which did not differ based on prematurity status (Table 1). There was no difference in the time to discontinuation of INO among the survivors based on prematurity status ($P = .45$) (Fig. 2). Five children with a history of chronic pulmonary hypertension were initiated on INO for respiratory failure: 4 without elevated pulmonary arterial pressure, and one with elevated pulmonary arterial pressure (Supplementary Table 2 [see the supplementary materials at http://www.rcjournal.com]). Four of these 5 subjects had an echocardiogram during the 12 h before INO initiation.

Outcomes

One hundred thirty-nine subjects (85.3%) displayed an improvement in oxygenation after INO initiation, and the clinician responded to oxygenation improvement as measured by a decrease in F_{IO_2} to ≤ 0.6 by 24 h after INO initiation in 97 subjects (59.9%) (Table 4). Neither the oxygenation improvement nor the clinician responsiveness differed by prematurity status. The early preterm subjects had the most ventilator-free days compared with the late preterm and full-term subjects (median, 18.0, 7.0, and 4.5 d, respectively; $P = .02$). ICU lengths of stay were similar among the groups (Table 4). The early preterm subjects had a lower 28-d mortality rate compared with the late preterm and full-term subjects (0.0, 26.1, and 32.0%, respectively; $P = .007$).

Factors associated with increased mortality in univariable analysis were a history of term (vs preterm) birth (OR 2.77 [95% CI 1.14–7.82]), older chronological age (OR 1.08 [95% CI 1.01–1.16]), and indirect lung injury due to sepsis that resulted in pediatric ARDS versus indirect lung injury due to a non-sepsis etiology that resulted in pediatric ARDS (OR 1.67 [95% CI 0.69–4.11]) (Table 5). Lower respiratory tract disease as the etiology of respiratory

Table 1. Demographics and INO Use

Characteristic	Overall ($N = 163$)	Birth History			P
		Early Preterm ($n = 18$)	Late Preterm ($n = 23$)	Term ($n = 122$)	
Demographics					
Boys, *n* (%)	92 (56.4)	12 (66.7)	14 (60.9)	66 (54.1)	.57*
Race, *n* (%)					.057*
White	86 (52.8)	6 (33.3)	12 (52.2)	68 (55.7)	
Black or African American	48 (29.4)	11 (61.1)	6 (26.1)	31 (25.4)	
Other or unknown	29 (17.8)	1 (5.6)	5 (21.7)	23 (18.9)	
Age, median (IQR) y	1.8 (0.7–6.0)	0.8 (0.5–1.7)	0.9 (0.5–1.9)	2.9 (0.9–7.8)	.002†
Ethnicity, *n* (%)					.37*
Hispanic or Latino	20 (12.3)	2 (11.1)	3 (13.0)	15 (12.3)	
Not Hispanic or Latino	139 (85.3)	16 (88.9)	18 (78.3)	105 (86.1)	
Unknown or not reported	4 (2.5)	0 (0)	2 (8.7)	2 (1.6)	
Any chronic diagnosis, *n* (%)‡	123 (75.5)	18 (100)	19 (82.6)	86 (70.5)	.01*
Chromosomal defect	31 (19.0)	2 (11.1)	7 (30.4)	22 (18.0)	.29*
Oncologic diagnosis	21 (12.9)	0 (0.0)	1 (4.3)	20 (16.4)	.056*
BPD	15 (9.2)	13 (72.2)	2 (8.7)	0 (0)	<.001*
Bone marrow transplantation	8 (4.9)	0 (0)	0 (0)	8 (6.6)	.47*
Organ transplantation	1 (0.6)	0 (0)	1 (4.3)	0 (0)	.25*
Congenital cardiovascular disease	18 (11.0)	1 (5.6)	3 (13.0)	14 (11.5)	.78*
Pre-hospital technology dependence, *n* (%)	49 (30.1)	10 (55.6)	10 (43.5)	29 (23.8)	.008*
Chronic pulmonary hypertension, *n* (%)	11 (6.7)	4 (22.2)	3 (13.0)	4 (3.3)	.007*
Chronic pulmonary hypertension treatment, *n* (%)§	8 (72.7)	3 (75.0)	3 (100)	2 (50.0)	.70*
Cardiac arrest in 12 h before INO initiation, *n* (%)	19 (11.7)	1 (5.6)	2 (8.7)	16 (13.1)	.77*
INO use, *n* (%)					
Echocardiogram 12 h before INO	34 (20.9)	3 (16.7)	4 (17.4)	27 (22.1)	.85*
Echocardiogram on any study day	113 (69.3)	11 (61.1)	18 (78.3)	84 (68.9)	.49*
Cardiac catheterization before INO	2 (1.2)	0 (0)	0 (0)	2 (1.6)	>.99*
Location of INO initiation, *n* (%)					.13*
Pediatric ICU	148 (90.8)	18 (100)	19 (82.6)	111 (91.0)	
Cardiac ICU	14 (8.6)	0 (0)	3 (13.0)	11 (9.0)	
Other	1 (0.6)	0 (0)	1 (4.3)	0 (0)	
Hospital admission to INO initiation, median (IQR) h	65.8 (24.5–168.0)	62.7 (38.8–108.5)	46.1 (21.8–153.7)	67.8 (27.4–211.7)	.66†

(Continued)

Table 1. Continued

Characteristic	Overall ($N = 163$)	Birth History			P
		Early Preterm ($n = 18$)	Late Preterm ($n = 23$)	Term ($n = 122$)	
Time from the start of mechanical ventilation to INO initiation, median (IQR) h[¶]	30.0 (5.4–88.4)	42.0 (12.8–100)	35.6 (8.0–85.3)	28.0 (5.3–88.2)	.81[†]
Initial dose of INO, median (IQR) ppm	20.0 (20.0–20.0)	20.0 (20.0–20.0)	20.0 (20.0–20.0)	20.0 (20.0–20.0)	.85[†]
Last recorded INO dose, median (IQR) ppm[‖]	2.0 (1.5–2.0)	2.0 (1.0–2.0)	2.0 (1.5–2.0)	2.0 (2.0–2.0]	.51[†]
Time on continuous INO, median (IQR) d	4.0 (2.0–8.0)	5.0 (2.0–15.0)	6.0 (4.0–14.0)	4.0 (1.0–7.0)	.049[†]

* The Fisher exact test (Monte Carlo approximation for tables larger than 2 × 2).
† The Kruskal-Wallis test.
‡ Only select chronic diagnoses are listed; the subjects may have had multiple chronic diagnoses.
§ Percentages were calculated with the subjects with chronic pulmonary hypertension as the denominator.
‖ The INO dose was recorded for the first 48 h; the subjects not discontinuing INO or who died within the first 48 h of INO use were excluded.
¶ The subjects who were started on INO before mechanical ventilation were excluded ($n = 15$: 1 early preterm, 6 late preterm, 8 full term).
INO = inhaled nitric oxide
BPD = bronchopulmonary dysplasia
IQR = interquartile range

dysfunction was protective against mortality (OR 0.30 [95% CI 0.12–0.73]). In multivariable analysis, lower respiratory tract disease as the etiology of respiratory dysfunction, not a history of preterm birth, was independently associated with a lower mortality risk (OR 0.35 [95% CI 0.14–0.87]; $P < .001$).

Table 2. Primary Diagnoses

Diagnosis	Overall ($N = 163$ [100%])	Birth History			P
		Early Preterm ($n = 18$ [11%])	Late Preterm ($n = 23$ [14%])	Term ($n = 122$ [75%])	
Primary indication for INO initiation					.09*
Respiratory failure without elevated pulmonary artery pressure	146 (90)	14 (78)	20 (87)	112 (92)	
Other[†]	16 (10)	4 (22)	3 (13)	9 (7)	
Unknown	1 (1)	0 (0)	0 (0)	1 (1)	
Direct pulmonary injury[‡]	78/158 (49)	13/16 (81.3)	13/22 (59.1)	52/120 (43.3)	.009*
Primary respiratory dysfunction					.02*
ALI/ARDS non-pulmonary etiology	80 (49)	3 (17)	9 (39)	68 (56)	
Non-sepsis	40 (25)	1 (6)	3 (13)	36 (30)	
Sepsis	40 (25)	2 (11)	6 (26)	32 (26)	
ALI/ARDS pulmonary etiology	83 (51)	13 (72)	13 (57)	52 (43)	
Aspiration	10 (6)	0 (0)	2 (9)	8 (7)	
Lower respiratory tract disease (bacterial)	11 (7)	1 (6)	0 (0)	10 (8)	
Lower respiratory tract disease (viral, not RSV)	39 (24)	6 (33)	8 (35)	25 (20)	
Lower respiratory tract disease (RSV)	18 (11)	6 (33)	3 (13)	9 (7)	
Asthma	3 (2)	1 (6)	0 (0)	2 (2)	
Other or unknown	2 (1)	1 (6)	1 (4)	0 (0)	

Data are number (%) unless otherwise noted.
* The Fisher exact test (Monte Carlo approximation for tables larger than 2 × 2).
† Includes 6 subjects with respiratory failure and elevated pulmonary arterial pressure, 6 with preexisting pulmonary hypertension, and 4 additional subjects with other indications, including hypoxia after cardiac arrest, new pulmonary hypertension, right-ventricular dysfunction, and to decrease sickling.
‡ Summary of those with ARDS due to direct pulmonary injury; the denominator includes only those with ARDS.
INO = inhaled nitric oxide
ALI = acute lung injury
RSV = respiratory syncytial virus

Table 3. Ventilation and Gas Exchange at the Time of INO Initiation*

Characteristic	Birth History			*P*
	Early Preterm (*n* = 18)	Late Preterm (*n* = 23)	Term (*n* = 122)	
Ventilation type, *n* (%)†				.51‡
Conventional	16/140 (11.4)	19/140 (13.6)	105/140 (75.0)	
High frequency oscillatory ventilation	0/15 (0)	2/15 (13.3)	13/15 (86.7)	
Not invasively ventilated	1/4 (25.0)	2/4 (5.0)	1/4 (25.0)	
NA	1/4 (25.0)	0/4 (0)	3/4 (75.0)	
P_{aO_2} *n*; median (IQR) mm Hg	6; 56.0 (51.3–63.0)	11; 76.3 (64.8–82.0)	89; 63.0 (54.1–78.0)	.08§
Exhaled tidal volume, *n*; median (IQR) mL/kg	12; 9.4 (8.0–1.7)	16; 7.5, (6.6–8.5)	76; 7.5 (6.2–9.2)	.036§
Mean airway pressure, *n*; median (IQR) cm H_2O	14; 16.0 (12.0–18.0)	19; 19.0 (14.0–21.0)	97; 19.0 (15.0–25.0)	.03§
F_{IO_2} *n*; median (IQR)	18; 0.9 (0.7–1.0)	23; 1.0 (0.6–1.0)	120; 0.9 (0.7–1.0)	.89§
S_{pO_2} *n*; median (IQR) %	15; 92.0 (88.0–97.0)	20; 92.5 (89.5–97.5)	115; 93.0 (9.0, 97.0)	.99§
Amplitude, *n*; median (IQR) cm H_2O‖	0; ND	2; 54.0 (38.0–70.0)	13; 52.0 (45.0–60.0)	.80§
PEEP, *n*; median (IQR) cm H_2O	16; 10.0 (8.0–10.5)	19; 10.0 (6.0–12.0)	104; 10.0–(8.0–12.0)	.62§
Peak inspiratory pressure, *n*; median (IQR) cm H_2O	16; 3.0 (27.5–33.0)	19; 32.0 (28.0–36.0)	97; 32.0 (27.0–38.0)	.33§
Dynamic compliance, *n*; median (IQR) mL/cm H_2O/kg¶	12; 0.5 (0.4–0.6)	15; 0.3 (0.3–0.4)	74; 0.4 (0.3–0.5)	.069§
End tidal carbon dioxide, *n*; median (IQR) mm Hg	9; 46.0 (38.0–54.0)	10; 49.0 (41.0–54.0)	75; 36.0 (29.0–49.0)	.047§
Oxygenation index, *n*; median (IQR)	6; 15.4 (11.8–18.2)	10; 20.0 (15.4–23.0)	71; 23.8 (15.6–39.1)	.13§
Oxygenation saturation index, *n*; median (IQR)**	11; 15.9 (9.6–18.6)	14; 15.7 (11.2–23.0)	76; 18.5 (13.1–23.2)	.16§

* If a parameter value was not entered at INO initiation, then the closest previous value to initiation was used; ventilation parameters up to 6 h before INO initiation were used; data were collected only with changes in ventilation parameters; thus, variables collected up to 6 h before INO initiation reflected the same parameters at the time of initiation, otherwise new parameters would have been recorded in the database.
† Row percentages are reported.
‡ The Fisher exact test.
§ The Kruskal-Wallis test.
‖ Patients on high-frequency oscillatory ventilation only.
¶ Exhaled tidal volume/(peak inspiratory pressure positive end expiratory pressure).
** Oxygenation Saturation Index = (F_{IO_2} × mean airway pressure)/S_{pO_2}.
INO = inhaled nitric oxide
NA = not available
IQR = interquartile range
ND = no data

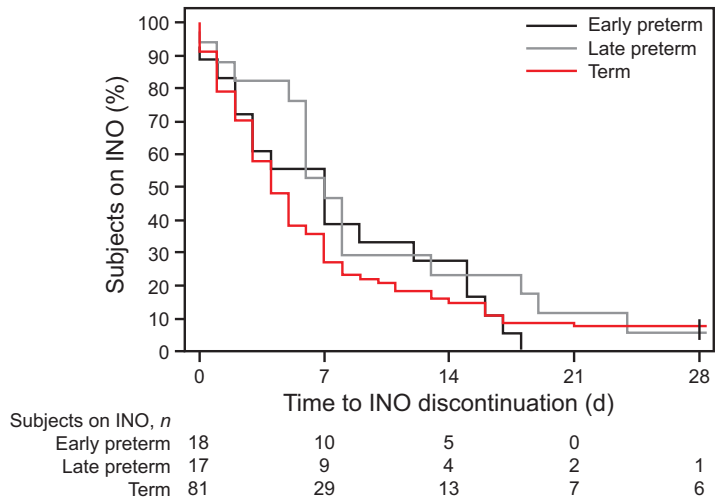

Fig. 2. Time to discontinuation of inhaled nitric oxide (INO). Among survivors, there was no difference in the duration of treatment with INO based on prematurity status (log rank test, *P* = .45).

Table 4. Outcomes Based on Birth History

Outcome	Birth History			*P*
	Early Preterm ($n = 18$)	Late Preterm ($n = 23$)	Term ($n = 122$)	
Oxygenation improvement on INO, *n* (%)*				.54†
Yes	17 (10.0)	19 (90.5)	103 (90.4)	
No	0 (0)	2 (9.5)	11 (9.6)	
Clinician response to improvement, *n* (%)‡				.39†
Timely	10 (58.8)	12 (66.7)	75 (73.5)	
None or delayed	7 (41.2)	6 (33.3)	27 (26.5)	
ECMO use after day 0, *n* (%)	1 (5.6)	4 (17.4)	19 (15.6)	.53†
Ventilator-free days, median (IQR)§	18.0 (6.0–20.0)	7.0 (0.0–13.0)	4.5 (0.0–17.0)	.02‖
Duration of mechanical ventilation, median (IQR) days §	10.0 (8.0–22.0)	16.0 (12.0–22.0)	13.0 (8.0–23.0)	.47‖
Cardiac arrest after day 0, *n* (%)	0 (0)	3 (13.0)	15 (12.3)	.36†
CVVH/dialysis use after day 0, *n* (%)	0 (0)	5 (21.7)	19 (15.6)	.12†
ICU, *n* (%)				
Mortality	0 (0)	6 (26.1)	39 (32.0)	.007†
New morbidity (survivors)	2 (11.1)	4 (23.5)	16 (19.3)	.61†
ICU Length of Stay, median [IQR]				
Overall	18.0 (11.0–35.0)	23.0 (11.0–73.0)	18.0 (1.0–35.0)	.48‖
Survivors	18.0 (11.0–35.0)	23.0 (16.0–43.0)	20.0 (13.0–39.0)	.46‖
Non-survivors	ND	17.5 (1.0–85.0)	10.0 (5.0–31.0)	.83‖
Day 28 mortality, *n* (%)	0 (0)	6 (26.1)	39 (32.0)	.007†
Hospital mortality, *n* (%)	0 (0)	6 (26.1)	41 (33.6)	.004†
Hospital length of stay, median (IQR)				
Overall	29.5 (21.0–50.0)	36.0 (20.0–97.0)	26.0 (14.0–51.0)	.39‖
Survivors	29.5 (21.0–50.0)	40.0 (23.0–97.0)	30.0 (22.0–54.0)	.39‖
Non-survivors	ND	20.5 (1.0–85.0)	15.0 (7.0–43.0)	.98‖

* Percentages do not include subjects for whom oxygenation improvement was indeterminate ($n = 11$).
† The Fisher exact test.
‡ Percentages are of the subjects with oxygenation improvement.
§ Ventilator-free days and mechanical ventilation days were unable to be assessed in 15 subjects (2 early preterm, 5 late preterm, and 8 full term) and 27subjects (2 early preterm, 6 late preterm, and 19 full term), respectively.
‖ Kruskal-Wallis test.
ECMO = extracorporeal membrane oxygenation
IQR = interquartile range
CVVH =continuous venovenous hemofiltration
INO = inhaled nitric oxide
ND = no data

Discussion

In this multicenter observational study, we found that nearly one fourth of the subjects who were critically ill and treated with INO for a respiratory indication had a history of preterm birth. The characteristics of the early preterm subjects treated with INO differed in regard to chronological age and preexisting chronic conditions. In addition, the early preterm subjects treated with INO for a respiratory indication were initiated on treatment at a lower severity of lung disease and, more frequently, had lung disease due to direct pulmonary injury. These findings have important implications for an INO trial design: (1) preterm patients are a critical cohort of patients treated with INO for a respiratory indication and should not be a priori excluded from future trials to evaluate efficacy of INO, and (2) it is necessary to adjust study procedures through stratification or altering physiologic inclusion criteria (eg, lower oxygenation index (OI) for enrolling early preterm subjects). In relation to outcomes, the early preterm subjects had more ventilator-free days and lower mortality compared with the late preterm and full-term subjects, which suggests that stratification of enrollment based on prematurity status or primary etiology of respiratory failure may be an important component of the study design.

The high proportion of the preterm subjects in the subset of our cohort given INO for a respiratory indication was consistent with other reports that suggest that patients with a history of preterm birth have a higher risk of severe respiratory disease in childhood.[5,22] In a retrospective cohort of children who were critically ill and <2 y old, preterm children accounted for nearly one third of the subjects admitted to a pediatric ICU with respiratory illness and their admissions resulted in longer pediatric ICU and hospital lengths of stay compared with subjects with a history of term birth.[5,6] The

Table 5. Stepwise Selection Process to Identify Risk Factors for Mortality

Parameter	% Missing	Univariable Models		Step 1		Step 2	
		OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
Prematurity	0		.02		.02		.10
Preterm		Ref.		Ref.		Ref.	
Term		2.77 (1.14–7.82)		2.77 (1.14–7.82)		2.26 (0.87–6.68)	
Age, per year		1.08 (1.01–1.16)	.03	NA		NA	
Hospital admission to INO initiation, per day	1	1.01 (0.99–1.02)	.32	NA		NA	
Race	0		.26	NA		NA	
White		Ref.					
Black or African American		1.78 (0.82–3.85)					
Other or unknown		0.88 (0.31–2.28)					
Chromosomal defect	0		.32	NA		NA	
No		Ref.					
Yes		0.63 (0.24–1.53)					
Cardiovascular disease, congenital	0		.85	NA		NA	
No		Ref.					
Yes		0.90 (0.27–2.55)					
Pre-hospital technology dependence	0		.38	NA		NA	
No		Ref.					
Yes		1.39 (0.66–2.89)					
At least one echo cardiogram obtained on study	0		.83	NA		NA	
No		Ref.					
Yes		1.09 (0.52, 2.33)					
Primary respiratory dysfunction	0		<.001	NA			<.001
ALI/ARDS non-pulmonary etiology, non-sepsis		Ref.				Ref.	
ALI/ARDS non-pulmonary etiology, sepsis		1.67 (0.69–4.11)				1.82 (0.74–4.57)	
Lower respiratory tract disease		0.30 (0.12–0.73)				0.35 (0.14–0.87)	

OR = odds ratio
Ref. = reference
INO = inhaled nitric oxide
ALI = acute lung injury
NA = not applicable

finding in our study that INO therapy for a respiratory indication was started earlier in the hospitalization and on lower levels of mechanical ventilation support in early preterm subjects suggests that, in these patients, treatment may be initiated for a concern of new or worsening pulmonary hypertension in addition to hypoxemia.

When designing a trial to evaluate the efficacy of INO for acute respiratory failure, the physiologic or ventilatory inclusion criteria will need to take into account the variation in practice for initiation of INO based on prematurity status given that our results suggest that clinicians have a lower threshold for INO initiation in children with a history of early prematurity. If a single threshold for treatment initiation is selected, then equipoise may be compromised in the trial, such that, in children with a history of prematurity, intensivists may feel it is inappropriate to withhold INO until higher levels of pulmonary support most frequently deemed appropriate for children born at term. Likewise, simply lowering the threshold of pulmonary support for INO initiation may not improve clinician equipoise when applied to subjects with a history of full-term birth or may not demonstrate a treatment effect, given the overall favorable outcomes for these patients. Alternatively, the use of 2 thresholds of pulmonary support for study inclusion based on birth age will complicate analysis of results.

There is ongoing debate about the efficacy of INO in pediatric ARDS and continued variability in its use across institutions, despite multiple clinical trials that did not reveal an improvement in mortality.[23-26] When considering selection of the primary outcome for a future clinical trial, the distribution of events among trial subjects is of primary importance. Given that ~1 in 4 patients treated with INO for respiratory failure has a history of preterm birth, this population is a key driver of event rates. The results of our study were similar to the findings reported in the Pediatric Acute Respiratory Distress Syndrome Incidence and Epidemiology study,[27] which included > 700 children with pediatric ARDS enrolled across 145 pediatric ICUs internationally. This study reported a higher proportion of children with a history of prematurity in survivors versus non-

survivors (19.9% vs 11.6%; $P = .031$).[27] Again, similar to our study, they reported that a direct lung injury that triggered pediatric ARDS (pneumonia) was more common among the survivors versus non-survivors (67% vs 43%; $P < .001$), and an indirect lung injury triggering pediatric ARDS (sepsis) was less common among the survivors versus non-survivors (16.2% vs 33.9%; $P < .001$), respectively. Given the strong association between direct lung injury and lower mortality, it will be important to evaluate the complex interaction between direct versus indirect lung injury across children with a history of prematurity versus those born full term. In addition, alternative longer-term outcomes may be important to consider because patients with a history of prematurity who have a direct lung injury may be at lower risk of mortality, but they may disproportionately have long-term sequelae associated with persistent and repetitive lung damage either due to the primary insult or associated with ventilatory support.[28-32]

The ability to draw conclusions related to INO use in hypoxic respiratory failure is limited due to the observational study design and the inherent selection bias introduced by the clinician-driven decision to initiate INO. The decision to initiate INO in this cohort may vary based on clinician, severity of lung disease, and patients' comorbidities. Our study had incomplete clinical data, including missing echocardiographic data due to the use of only clinically obtained echocardiographic data and incomplete ventilator data. In addition, we did not exclude subjects with intracardiac shunts from the oxygenation index/oxygenation saturation index analyses. Also, this was a secondary analysis that specifically evaluated subjects with a history of early and late premature birth in this cohort of subjects who were critically ill and in whom INO therapy was used, and we were not likely powered to detect differences in clinically meaningful outcomes, such as mortality, new morbidities, and the duration of mechanical ventilation.

Conclusions

A high proportion of the subjects who received INO have a history of prematurity and will represent a key subgroup in future trials evaluating efficacy of this therapy in acute respiratory failure. However, the early preterm subjects who received INO for a respiratory indication more often had direct pulmonary injury, were initiated on INO at a less-severe stage of respiratory impairment, and experienced better outcomes compared with late preterm and full-term subjects. If future trials to study the use of INO in hypoxic respiratory failure are pursued, it will be important to standardize oxygenation thresholds for initiation of therapy, with thoughtful consideration of the differential initiation thresholds noted in early preterm subjects, and perhaps stratify trial enrollment based on prematurity status.

REFERENCES

1. Balinotti JE, Chakr VC, Tiller C, Kimmel R, Coates C, Kisling J, et al. Growth of lung parenchyma in infants and toddlers with chronic lung disease of infancy. Am J Respir Crit Care Med 2010;181(10):1093-1097.
2. Bastek JA, Sammel MD, Paré E, Srinivas SK, Posencheg MA, Elovitz MA. Adverse neonatal outcomes: examining the risks between preterm, late preterm, and term infants. Am J Obstet Gynecol 2008;199(4):367.e1-e8.
3. Engle WA, Tomashek KM, Wallman C, Committee on Fetus and Newborn, American Academy of Pediatrics. "Late-preterm" infants: a population at risk. Pediatrics 2007;120(6):1390-1401.
4. Grégoire MC, Lefebvre F, Glorieux J. Health and developmental outcomes at 18 months in very preterm infants with bronchopulmonary dysplasia. Pediatrics 1998;101(5):856-860.
5. Gunville CF, Sontag MK, Stratton KA, Ranade DJ, Abman SH, Mourani PM. Scope and impact of early and late preterm infants admitted to the PICU with respiratory illness. J Pediatr 2010;157(2):209-214.e1.
6. Mourani PM, Kinsella JP, Clermont G, Kong L, Perkins AM, Weissfeld L, et al. Intensive care unit readmission during childhood after preterm birth with respiratory failure. J Pediatr 2014;164(4):749-755.e3.
7. Furman L, Baley J, Borawski-Clark E, Aucott S, Hack M. Hospitalization as a measure of morbidity among very low birth weight infants with chronic lung disease. J Pediatr 1996;128(4):447-452.
8. Smith VC, Zupancic JAF, McCormick MC, Croen LA, Greene J, Escobar GJ, Richardson DK. Rehospitalization in the first year of life among infants with bronchopulmonary dysplasia. J Pediatr 2004;144(6):799-803.
9. Higano NS, Spielberg DR, Fleck RJ, Schapiro AH, Walkup LL, Hahn AD, et al. Neonatal pulmonary magnetic resonance imaging of bronchopulmonary dysplasia predicts short-term clinical outcomes. Am J Respir Crit Care Med 2018;198(10):1302-1311.
10. Al-Ghanem G, Shah P, Thomas S, Banfield L, El Helou S, Fusch C, Mukerji A. Bronchopulmonary dysplasia and pulmonary hypertension: a meta-analysis. J Perinatol 2017;37(4):414-419.
11. Arjaans S, Zwart EAH, Ploegstra M-J, Bos AF, Kooi EMW, Hillege HL, Berger RMF. Identification of gaps in the current knowledge on pulmonary hypertension in extremely preterm infants: a systematic review and meta-analysis. Paediatr Perinat Epidemiol 2018;32(3):258-267.
12. Kjellberg M, Björkman K, Rohdin M, Sanchez-Crespo A, Jonsson B. Bronchopulmonary dysplasia: clinical grading in relation to ventilation/perfusion mismatch measured by single photon emission computed tomography. Pediatr Pulmonol 2013;48(12):1206-1213.
13. Svedenkrans J, Stoecklin B, Jones JG, Doherty DA, Pillow JJ. Physiology and predictors of impaired gas exchange in infants with bronchopulmonary dysplasia. Am J Respir Crit Care Med 2019;200(4):471-480.
14. Northway WH Jr, Rosan RC, Porter DY. Pulmonary disease following respirator therapy of hyaline-membrane disease. Bronchopulmonary dysplasia. N Engl J Med 1967;276(7):357-368.
15. Jobe AH, Bancalari E. Bronchopulmonary dysplasia. Am J Respir Crit Care Med 2001;163(7):1723-1729.
16. Bancalari E, Claure N, Sosenko IRS. Bronchopulmonary dysplasia: changes in pathogenesis, epidemiology and definition. Semin Neonatol 2003;8(1):63-71.
17. Jobe AH. The new bronchopulmonary dysplasia. Curr Opin Pediatr 2011:23(2):167-172.
18. Berger JT, Maddux AB, Reeder RW, Banks R, Mourani PM, Berg RA, et al. Inhaled nitric oxide use in pediatric hypoxemic respiratory failure. Pediatr Crit Care Med 2020;21(8):708-719.

19. Klinger JR. The nitric oxide/cGMP signaling pathway in pulmonary hypertension. Clin Chest Med 2007;28(1):143-167, ix.
20. Pollack MM, Holubkov R, Glass P, Dean JM, Meert KL, Zimmerman J, et al. Functional status scale: new pediatric outcome measure. Pediatrics 2009;124(1):e18-28.
21. Pollack MM, Holubkov R, Funai T, Berger JT, Clark AE, Meert K, et al. Simultaneous prediction of new morbidity, mortality, and survival without new morbidity from pediatric intensive care: a new paradigm for outcomes assessment. Crit Care Med 2015;43(8):1699-1709.
22. Mourani PM, Mandell EW, Meier M, Younoszai A, Brinton JT, Wagner BD, et al. Early pulmonary vascular disease in preterm infants is associated with late respiratory outcomes in childhood. Am J Respir Crit Care Med 2019;199(8):1020-1027.
23. Adhikari NKJ, Dellinger RP, Lundin S, Payen D, Vallet B, Gerlach H, et al. Inhaled nitric oxide does not reduce mortality in patients with acute respiratory distress syndrome regardless of severity: systematic review and meta-analysis. Crit Care Med 2014;42(2):404-412.
24. Bhalla AK, Yehya N, Mack WJ, Wilson ML, Khemani RG, Newth CJL. The association between inhaled nitric oxide treatment and ICU mortality and 28-day ventilator-free days in pediatric acute respiratory distress syndrome. Crit Care Med 2018;46(11):1803-1810.
25. Bronicki RA, Fortenberry J, Schreiber M, Checchia PA, Anas NG. Multicenter randomized controlled trial of inhaled nitric oxide for pediatric acute respiratory distress syndrome. J Pediatr 2015;166(2):365-369.e1.
26. Gupta P, Richardson T, Hall M, Bertoch D, Hebbar KB, Fortenberry JD, Wetzel RC. Effect of inhaled nitric oxide on outcomes in children with acute lung injury: propensity matched analysis from a linked database. Crit Care Med 2016;44(10):1901-1909.
27. Khemani RG, Smith L, Lopez-Fernandez YM, Kwok J, Morzov R, Klein MJ, et al. Paediatric Acute Respiratory Distress Syndrome Incidence and Epidemiology (PARDIE): an international, observational study. Lancet Respir Med 2019;7(2):115-128.
28. Boucher V, Mathy C, Lacroix J, Émériaud G, Jouvet P, Tse SM. Post-discharge respiratory outcomes of children with acute respiratory distress syndrome. Pediatr Pulmonol 2020;55(2):468-473.
29. Keim G, Watson RS, Thomas NJ, Yehya N. New morbidity and discharge disposition of pediatric acute respiratory distress syndrome survivors. Crit Care Med 2018;46(11):1731-1738.
30. Keim G, Yehya N, Spear D, Hall MW, Loftis LL, Alten JA, et al. Development of persistent respiratory morbidity in previously healthy children after acute respiratory failure. Crit Care Med 2020;48 (8):1120-1128.
31. Quasney MW, Löápez-Fernandez YM, Santschi M, Watson RS, Pediatric Acute Lung Injury Consensus Conference Group. The outcomes of children with pediatric acute respiratory distress syndrome: proceedings from the Pediatric Acute Lung Injury Consensus Conference. Pediatr Crit Care Med 2015;16(5 Suppl 1): S118-S131.
32. Yagiela LM, Barbaro RP, Quasney MW, Pfarr MA, Ursu DC, Prosser LA, Odetola FO. Outcomes and patterns of healthcare utilization after hospitalization for pediatric critical illness due to respiratory failure. Pediatr Crit Care Med 2019;20(2):120-127.