JAMA Pediatrics | Original Investigation

Effect of Inhaled Nitric Oxide on Survival Without Bronchopulmonary Dysplasia in Preterm Infants
A Randomized Clinical Trial

Shabih U. Hasan, MD, DCH, FRCPC; Jim Potenziano, PhD; Girija G. Konduri, MD; Jose A. Perez, MD; Krisa P. Van Meurs, MD; M. Whit Walker, MD, MS; Bradley A. Yoder, MD; for the Newborns Treated With Nitric Oxide (NEWNO) Trial Group

IMPORTANCE Bronchopulmonary dysplasia (BPD) occurs in approximately 40% of infants born at younger than 30 weeks' gestation and is associated with adverse pulmonary and neurodevelopmental outcomes.

OBJECTIVE To test whether administration of inhaled nitric oxide to preterm infants requiring positive pressure respiratory support on postnatal days 5 to 14 improves the rate of survival without BPD.

DESIGN, SETTING, AND PARTICIPANTS This intent-to-treat study was a randomized clinical trial performed at 33 US and Canadian neonatal intensive care units. Participants included 451 neonates younger than 30 weeks' gestation with birth weight less than 1250 g receiving mechanical ventilation or positive pressure respiratory support on postnatal days 5 to 14. Enrollment spanned from December 23, 2009, to April 23, 2012, and neurodevelopmental outcome studies were completed by April 4, 2014.

INTERVENTIONS Placebo (nitrogen) or inhaled nitric oxide initiated at 20 ppm was decreased to 10 ppm between 72 and 96 hours after starting treatment and then to 5 ppm on day 10 or 11. Infants remained on the 5-ppm dose until completion of therapy (24 days).

MAIN OUTCOMES AND MEASURES The primary outcome was the rate of survival without BPD at 36 weeks' postmenstrual age (PMA). Secondary outcomes included BPD severity, postnatal corticosteroid use, respiratory support, survival, and neurodevelopmental outcomes at 18 to 24 months' PMA.

RESULTS In total, 222 infants (52.3% male [n = 116]) received placebo, and 229 infants (50.2% male [n = 115]) received inhaled nitric oxide. Their mean (SD) gestation was 25.6 (1.5) vs 25.6 (1.4) weeks, and their mean (SD) birth weight was 750 (164) vs 724 (160) g. Survival without BPD at 36 weeks' PMA was similar between the placebo and inhaled nitric oxide groups (31.5% [n = 70] vs 34.9% [n = 80]) (odds ratio, 1.17; 95% CI, 0.79-1.73). Rates for severe BPD (26.6% [55 of 207] vs 20.5% [43 of 210]) and postnatal corticosteroid use for BPD (41.0% [91 of 222] vs 41.5% [95 of 229]) and the mean (SD) days of positive pressure respiratory support (55 [40] vs 54 [42]), oxygen therapy (88 [41] vs 91 [59]), and hospitalization (105 [37] vs 108 [54]) were equivalent between the 2 groups. No differences in the incidence of common morbidities were observed. Respiratory outcomes on discharge to home, at 1 year, and at age 18 to 24 months' PMA and neurodevelopmental assessments at 18 to 24 months' PMA did not differ between groups.

CONCLUSIONS AND RELEVANCE Inhaled nitric oxide, initiated at 20 ppm on postnatal days 5 to 14 to high-risk preterm infants and continued for 24 days, appears to be safe but did not improve survival without BPD at 36 weeks' PMA or respiratory and neurodevelopmental outcomes at 18 to 24 months' PMA.

TRIAL REGISTRATION clinicaltrials.gov Identifier: NCT00931632

JAMA Pediatr. doi:10.1001/jamapediatrics.2017.2618
Published online September 25, 2017.

Supplemental content

Author Affiliations: Author affiliations are listed at the end of this article.

Group Information: The members of the Newborns Treated With Nitric Oxide (NEWNO) Trial Group appear at the end of the article.

Corresponding Author: Shabih U. Hasan, MD, DCH, FRCPC, Department of Pediatrics, Cumming School of Medicine, University of Calgary, 3330 Hospital Dr NW, Calgary, AB T2N 4N1, Canada (hasans@ucalgary.ca).

With modern neonatal care, approximately 40% of survivors with gestational age (GA) younger than 30 weeks develop bronchopulmonary dysplasia (BPD).[1] Prevention and treatment of evolving BPD is an important clinical concern because it is associated with long-term pulmonary disease[2,3] and neurodevelopmental impairment.[4,5]

Inhaled nitric oxide is a pulmonary vasodilator approved for treatment of hypoxic respiratory failure in term and near-term infants with clinical or echocardiographic evidence of pulmonary hypertension based on results from 2 randomized clinical trials.[6,7] Interest in inhaled nitric oxide use in preterm infants increased as animal studies[8-11] demonstrated a wide array of beneficial effects on lung parenchyma, bronchi, and pulmonary vasculature. However, randomized clinical trials[12-17] assessing inhaled nitric oxide efficacy for preventing BPD in preterm infants have yielded mixed results. Trials in preterm infants are broadly categorized based on inclusion criteria, entry in the first 3 days for high oxygenation index (rescue), routine use in intubated preterm infants (prophylactic), and later enrollment for increased BPD risk (prevention).[18] Only 2 studies demonstrated reduction in BPD. One was a single-center study[12] of prophylactic inhaled nitric oxide in preterm infants. The second study, the Nitric Oxide (to Prevent) Chronic Lung Disease (NO CLD) trial,[16] found that inhaled nitric oxide therapy improved survival without BPD at 36 weeks' postmenstrual age (PMA). The NO CLD trial focused on BPD prevention using a starting dose of 20 ppm and delaying start of treatment until 7 to 21 days after birth. By treating only those infants requiring mechanical ventilation for at least 7 days after birth, infants with developing lung disease and at very high risk for BPD were targeted.[19] Post hoc analyses indicated that inhaled nitric oxide had the greatest benefit in infants when starting treatment on postnatal days 7 to 14, with no advantage for those infants starting later than day 14 after birth.[16] Furthermore, infants treated with inhaled nitric oxide received less bronchodilators, inhaled corticosteroids, systemic corticosteroids, diuretics, and supplemental oxygen after discharge.[20] However, the cohort treated with inhaled nitric oxide had no reduction in hospitalizations,[20] and the rate of neurodevelopmental impairment at age 2 years was similar to the placebo group.[21] The hypothesis of the present study was that administration of inhaled nitric oxide to infants younger than 30 weeks' gestation with birth weight less than 1250 g receiving mechanical ventilation or positive pressure respiratory support on postnatal days 5 to 14 would decrease the incidence of BPD at 36 weeks' PMA.

Key Points

Question Does inhaled nitric oxide initiated on postnatal days 5 to 14 and continued for 24 days improve survival without bronchopulmonary dysplasia in preterm infants younger than 30 weeks' gestation?

Findings In this randomized clinical trial of 451 infants, no differences were observed in mortality, incidence of bronchopulmonary dysplasia, or respiratory or neurodevelopmental outcomes between the placebo and inhaled nitric oxide groups at 36 weeks' postmenstrual age, 1 year, or 18 to 24 months' postmenstrual age.

Meaning This study provides evidence that inhaled nitric oxide administration does not improve survival without bronchopulmonary dysplasia or neurodevelopmental outcomes in very preterm infants.

Methods

This randomized clinical trial was performed at 33 US and Canadian neonatal intensive care units (NICUs) (listed in the Group Information section at the end of the article). Enrollment in this multicenter, double-masked, and placebo-controlled trial spanned from December 23, 2009, until April 23, 2012, and neurodevelopmental outcome studies were completed by April 4, 2014.

The protocol, protocol amendments, and informed consent forms were reviewed and approved by the institutional review board at each study site. The trial protocol is in Supplement 1. Written informed consent was obtained from the parents or legal representative.

Eligibility Criteria

Inclusion criteria were as follows: (1) GA younger than 30 weeks; (2) birth weight less than 1250 g; (3) postnatal age of 5 to 14 days at study entry; and (4) requirement of mechanical ventilation or, for those weighing 800 g or less, positive pressure respiratory support (including continuous positive airway pressure [CPAP]) for primary respiratory insufficiency. Exclusion criteria were the following: (1) presence of any life-threatening cranial, cardiac, thoracic, or chromosomal anomalies; (2) congenital diaphragmatic hernia; (3) bilateral grade 4 intraventricular hemorrhage; (4) dependence on right-to-left shunting to maintain systemic circulation; (5) prior exposure to inhaled nitric oxide therapy; or (6) use of another investigational agent. A head ultrasound scan was obtained for all infants after 72 hours of life and before start of study gas (placebo or inhaled nitric oxide).

Randomization and Interventions

Eligible infants were block randomized in groups of 4 to treatment with placebo or inhaled nitric oxide using an interactive voice response system and stratified by NICU and GA at birth (<27 vs 27 to <30 weeks' GA). Twins and triplets were assigned to the same treatment arm. Infants received either inhaled nitric oxide (INOmax; INO Therapeutics) or placebo (100% grade 5 nitrogen gas) for 24 days. The INOvent delivery system (INO Therapeutics) had a metal face plate covering nitric oxide and nitrogen dioxide monitors. The INOvent delivery system was calibrated by an unmasked respiratory therapist within 24 hours of study drug initiation, and the system remained locked at all times after study drug initiation except to make changes to study gas administration. The unmasked respiratory therapists were not involved in direct infant care, whereas all personnel providing direct care were masked to treatment assignment.

Placebo (nitrogen) or inhaled nitric oxide was initiated at 20 ppm and was decreased to 10 ppm between 72 and 96 hours after starting treatment and then to 5 ppm on day 10 or 11. Infants remained on the 5 ppm dose until completion of therapy (24 days). If infants were extubated before completion of 24 days of therapy, study gas was administered via nasal CPAP or nasal cannula to complete the assigned treatment period. Treatment with open-label inhaled nitric oxide was not allowed at any time unless individuals were withdrawn from the study. Because this trial was an intent-to-treat study, data from withdrawn participants were included in the analysis. The infants whose legal guardian withdrew informed consent before the primary outcome and were alive were not assessed for BPD using the timed oxygen reduction test.[22] However, they were imputed as having BPD.

Nitrogen dioxide and methemoglobin levels were monitored during study drug administration. The study drug was discontinued if nitrogen dioxide levels exceeded 3 ppm or methemoglobin levels exceeded 5% on 2 samples 6 hours apart or if levels exceeded 5 ppm or 7.5%, respectively, on a single reading.

Outcome Measures

The primary outcome was the rate of survival without BPD at 36 weeks' PMA. Diagnosis of BPD was assessed at 36 weeks' PMA (±3 days) using the physiologic assessment of BPD.[22] Infants who were receiving CPAP or had a fraction of inspired oxygen (F_{IO_2}) concentration of at least 0.3 were classified as having BPD. Infants who were off ventilatory support with F_{IO_2} concentration less than 0.3 or were receiving CPAP with room air at 36 weeks' PMA underwent a timed oxygen reduction test[22] to determine if BPD was present. Bronchopulmonary dysplasia severity among survivors, as determined by level of support given to maintain arterial oxygen saturation of at least 90%, was classified according to the National Institutes of Health criteria[23] as none or mild, moderate, or severe. Secondary outcomes included the following: (1) duration of CPAP; (2) duration of oxygen therapy and birth hospitalization; (3) proportion of infants who received postnatal corticosteroids during their birth hospitalization; (4) proportion of infants receiving respiratory medications, inhaled or systemic corticosteroids, and oxygen therapy; and (5) proportion of infants requiring hospitalization for respiratory illness or any reason. Survival to follow-up at 1 year and 18 to 24 months' PMA was assessed as an additional efficacy measure. To assess long-term effects, respiratory status at 1 year and 18 to 24 months' PMA and neurodevelopmental outcomes at 18 to 24 months' PMA were also investigated.

Safety Assessments

The incidence of all adverse events (AEs) and their severity were monitored throughout the course of treatment. Serious AEs occurring during the follow-up period were summarized at defined follow-up visits. Other safety evaluations included the incidence of elevated nitrogen dioxide and methemoglobin levels. An independent safety monitoring committee met periodically to review the unmasked safety data. All data were verified by United BioSource Corporation, an independent contract research organization.

Follow-up at 1 Year and 18 to 24 Months' PMA

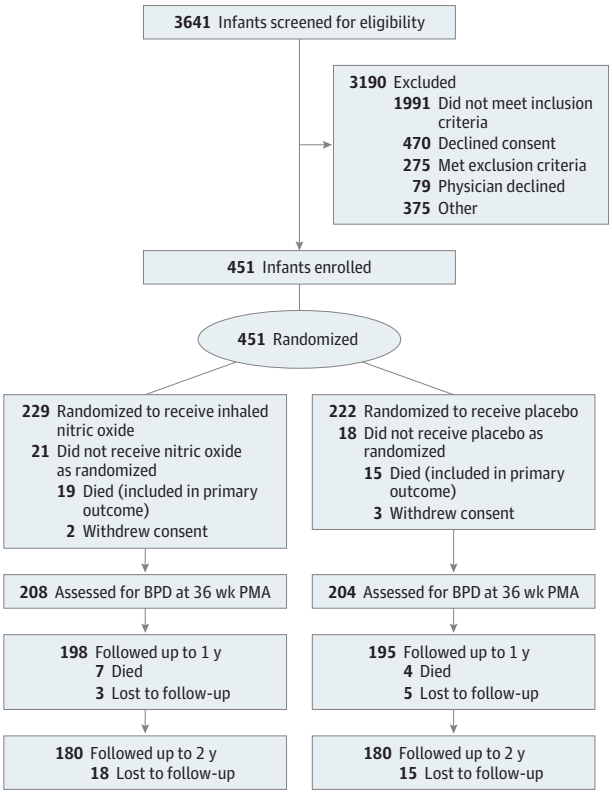
After assessment at 36 weeks' PMA, all infants were to be seen at 1-year corrected age for assessment of respiratory outcomes. Neurodevelopmental and respiratory assessments were performed at 18 to 24 months' PMA. At the 12-month follow-up, recorded variables included the following: survival, somatic growth measurements (weight, length, and head circumference), vital signs, medical history review, complete physical examination, vision assessment (including retinopathy of prematurity treatment), oxygen therapy at discharge home or follow-up visit, hospitalization or emergency department visit history, medications, and respiratory syncytial virus prophylaxis. Neurodevelopmental outcomes were assessed at 18 to 24 months' PMA using the Bayley Scales of Infant and Toddler Development, Third Edition (BSID-III),[24] which included assessments of cognitive, receptive, and expressive communication skills. The BSID-III was administered by certified examiners. Neurodevelopmental impairment was defined as any one of the following: BSID-III cognitive score less than 85, Gross Motor Function Classification System level of at least 2, moderate to severe cerebral palsy, any visual loss in one or both eyes, or any hearing impairment.

Statistical Analysis

Based on the outcome of infants randomized to nitric oxide therapy on postnatal days 7 to 14 in the NO CLD trial (n = 112),[16] we calculated that a sample size of 450 infants (225 per group) would provide 90% power to detect a 15% absolute difference (28% vs 43%) in the rate of survival without BPD at a type I error rate of 5%. Measurements from the same birth (ie, twins and triplets) were considered repeat measurements. The generalized estimating equation model with a logit link was used for analysis of the primary outcome and other binary response variables, and an exchangeable working correlation structure was used. A mixed-effects model with random intercepts was used to analyze continuous outcome variables. All models were adjusted for GA strata because GA was used to stratify randomization. To allow comparison with other published randomized trials of inhaled nitric oxide to prevent BPD, post hoc analyses were planned for subgroups based on birth weight, GA, sex, postnatal age at study entry, maternal race, and mode of respiratory support at study entry. These analyses were performed by including group by treatment interactions in the regression model. For an interaction term with more than 2 categories (birth weight or maternal race), a multivariable Wald test was performed to evaluate equality of treatment across groups.

A gatekeeping procedure was used to handle multiplicity for the primary and secondary comparisons. The Fisher exact test was used for between-group comparisons of AE incidences. A significance level of 2-sided $P < .05$ was set for all between-group comparisons. Efficacy analyses were performed on the intent-to-treat population, which included all randomized infants. Safety analyses were performed on the study population, which included all randomized infants who received the study drug. Statistical analyses were performed using a software program (SAS, versions 9.2 and 9.4; SAS Institute Inc).

Figure. CONSORT Study Diagram



BPD indicates bronchopulmonary dysplasia; CONSORT, Consolidated Standards of Reporting Trials; and PMA, postmenstrual age.

Results

A total of 3641 infants who met birth weight and GA at birth criteria were assessed for eligibility; 3190 of these infants were deemed ineligible (**Figure**). Of the 451 neonates enrolled, 222 were randomized to receive placebo, and 229 were randomized to receive inhaled nitric oxide. There were 186 singletons, 15 sets of twins, and 2 sets of triplets in the placebo group. There were 191 singletons, 16 sets of twins, and 2 sets of triplets in the inhaled nitric oxide group.

In the placebo group, 15 infants died, and informed consent was withdrawn for 3 infants, leaving 204 infants for BPD assessment at 36 weeks' PMA (Figure). In the inhaled nitric oxide group, 19 infants died, and informed consent was withdrawn for 2 infants, leaving 208 infants for BPD assessment at 36 weeks' PMA. The 5 infants whose parents withdrew consent were imputed as having BPD because they could not be assessed for BPD. Therefore, the total numbers of infants who survived to 36 weeks' PMA were 207 in the placebo group and 210 in the inhaled nitric oxide group.

There were 2 clinically relevant imbalances between the placebo and inhaled nitric oxide groups: a larger proportion of infants of maternal white race were enrolled in the inhaled nitric oxide group compared with the placebo group, and rupture of membranes for more than 7 days occurred in a higher proportion of infants in the inhaled nitric oxide group compared with the placebo group (**Table 1**). No other relevant imbalances were observed in baseline characteristics between groups.

The proportion of infants who survived to 36 weeks' PMA without BPD was similar between the placebo and inhaled nitric oxide groups. The proportion of infants who survived to 36 weeks' PMA or had a BPD diagnosis at 36 weeks' PMA also did not differ between groups (**Table 2**). Post hoc analyses of primary outcome data for selected subgroups of study infants demonstrated no significant interactions with birth weight, GA, sex, postnatal age at study entry, maternal race, or mode of respiratory support at study entry. Subgroup analysis of infants born at 27 to less than 30 weeks' GA showed no significant difference in the rate of BPD-free survival at 36 weeks' PMA between infants randomized to placebo vs inhaled nitric oxide (28.3% [13 of 46] vs 47.6% [20 of 42]). Subgroup analysis of infants born at younger than 27 weeks' GA also showed no difference in the rate of BPD-free survival at 36 weeks' PMA between infants randomized to placebo vs inhaled nitric oxide (32.4% [57 of 176] vs 32.1% [60 of 187]). Rates for severe BPD were similar between the placebo (55 of 207 [26.6%]) and inhaled nitric oxide (43 of 210 [20.5%]) groups (odds ratio, 0.71; 95% CI, 0.45-1.12).

There were no differences between groups in the incidence of common complications of prematurity, including sepsis, patent ductus arteriosus, necrotizing enterocolitis, retinopathy of prematurity (any stage), intraventricular hemorrhage (any grade), and pulmonary air leak (eTable in Supplement 2). None of the infants receiving inhaled nitric oxide had a significant elevation in nitrogen dioxide or methemoglobin level.

Respiratory support outcomes and other respiratory morbidities at the time of discharge to home and follow-up at 1 year or 18 to 24 months' PMA did not differ between groups (**Table 3**). As expected, given the degree of prematurity, the infants had a long duration of CPAP, oxygen therapy, and hospitalization. Severity of BPD and postnatal corticosteroid use were also similar between groups. Of the 417 infants who survived to 36 weeks' PMA, outcome data were available for 412 (98.8%). Eleven infants (4 in the placebo group and 7 in the inhaled nitric oxide group) died after the 36-week assessment but before age 1 year. Of the remaining 401 infants, 393 (98.0%) were evaluated at 1 year, and 360 (89.8%) were evaluated at the follow-up assessment at 18 to 24 months' PMA.

Neurodevelopmental assessment, including BSID-III examination at the follow-up at 18 to 24 months' PMA, was completed on 331 infants (167 in the placebo group and 164 in the inhaled nitric oxide group); no significant differences were found between groups (**Table 4**). The percentage of infants with severe (BSID-III cognitive score <70) or moderate (BSID-III cognitive score of 70-84) cognitive disability was similar between groups. Overall, 33.5% (111 of 331) of the infants had normal cognitive ability, defined as a BSID-III cognitive score of at least 100. Overall, 17.8% (64 of 360) of the infants had neurodevelopmental impairment, 5.0% (18 of 360) had moderate to severe cerebral palsy, 13.3% (48 of 360) had vision

Table 1. Demographics and Baseline Characteristics of Study Infants[a]

Variable	Placebo (n = 222)	Inhaled Nitric Oxide (n = 229)
Birth weight, g		
Mean (SD)	750 (164)	724 (160)
<750, No./total No. (%)	119/221 (53.8)	139/229 (60.7)
750-999, No./total No. (%)	82/221 (37.1)	71/229 (31.0)
≥1000, No./total No. (%)	20/221 (9.0)	19/229 (8.3)
Gestational age at birth, wk		
Mean (SD)	25.6 (1.5)	25.6 (1.4)
<27, No. (%)	176 (79.3)	187 (81.7)
27 to <30, No. (%)	46 (20.7)	42 (18.3)
Male sex, No. (%)	116 (52.3)	115 (50.2)
Maternal race, No. (%)		
Black	62 (27.9)	55 (24.0)
Hispanic	48 (21.6)	40 (17.5)
White	85 (38.3)	120 (52.4)
Other	27 (12.2)	14 (6.1)
Antenatal corticosteroid use, No./total No. (%)	186/216 (86.1)	199/223 (89.2)
Cesarean delivery, No./total No. (%)	144/218 (66.1)	154/229 (67.2)
Intrauterine growth restriction, No./total No. (%)	41/221 (18.6)	54/221 (24.4)
Rupture of membranes for >7 d, No. (%)	9 (4.1)	24 (10.5)
Suspected chorioamnionitis, No./total No. (%)	41/203 (20.2)	55/216 (25.5)
Surfactant use, No./total No. (%)	220/220 (100)	229/229 (100)
Vitamin A use, No./total No. (%)	36/220 (16.4)	30/229 (13.1)
Apgar score, mean (range), min		
1	4 (0-9)	4 (0-9)
5	6 (1-9)	6 (1-10)
Age at start of treatment, d		
Mean (SD)	9.9 (2.8)	9.5 (2.9)
<7, No./total No. (%)	45/220 (20.4)	54/229 (23.6)
7-14, No./total No. (%)	175/220 (79.5)	175/229 (76.4)
Respiratory severity score, mean (SD)[b]	3.0 (1.9)	2.9 (2.0)
Mode of respiratory support at study entry, No./total No. (%)		
High-frequency ventilation	51/220 (23.2)	65/228 (28.5)
Conventional ventilation	123/220 (55.9)	118/228 (51.8)
Nasal CPAP	18/220 (8.2)	29/228 (12.7)
Other	28/220 (12.7)	16/228 (7.0)

Abbreviation: CPAP, continuous positive airway pressure.

[a] Denominators listed in the table reflect the number of patients with available data for that variable.

[b] Calculated as the fraction of inspired oxygen (FIO_2) concentration times the mean airway pressure (cm H_2O).

impairment, and 5.2% (18 of 346) had hearing impairment, with no differences between groups.

Discussion

In high-risk preterm infants requiring mechanical ventilation or positive pressure respiratory support on postnatal days 5 to 14, inhaled nitric oxide (initiated at 20 ppm and administered in decreasing doses over 24 days) did not increase the likelihood of survival without BPD at 36 weeks' PMA vs placebo. No significant between-group differences were observed in secondary outcomes measured or AE rates. No significant differences were found in respiratory outcomes at 1 year or 18 to 24 months' PMA or in neurodevelopmental outcomes assessed at 18 to 24 months' PMA.

We hypothesized that initiating inhaled nitric oxide treatment later, at a higher dose, and for a longer period than in studies reported by Kinsella et al,[15] Mercier et al,[17] Schreiber et al,[12] and Van Meurs et al[13] would improve the primary outcome of survival without BPD at 36 weeks' PMA. We expected our results to be similar to the NO CLD trial reported by Ballard et al.[16] That trial included high-risk preterm infants aged 7 to 21 days requiring mechanical ventilation or positive pressure respiratory support. They reported a 16% relative increase in survival without BPD in the group treated with inhaled nitric oxide. Post hoc analysis suggested that the outcome difference for the whole study was attributed to the subgroup enrolled between ages 7 and 14 days, with a 75% relative increase in survival without BPD in the group treated with inhaled nitric oxide. Our study was designed to confirm the efficacy of inhaled nitric oxide to improve survival without BPD by

Table 2. Primary and Secondary Subgroup Analyses for Survival Without Bronchopulmonary Dysplasia (BPD) at 36 Weeks' Postmenstrual Age (PMA)[a]

Variable	No./Total No. (%)		Odds Ratio (95% CI)	*P* Value[b]
	Placebo	Inhaled Nitric Oxide		
Primary Outcome				
Survival without BPD	70/222 (31.5)	80/229 (34.9)	1.17 (0.79-1.73)	NA
Survival to 36 wk PMA	207/222 (93.2)	210/229 (91.7)	0.80 (0.40-1.62)	NA
BPD in survivors to 36 wk PMA	137/207 (66.2)	130/210 (61.9)	0.83 (0.56-1.24)	NA
Post Hoc Subgroup Analyses[c]				
Birth weight, g				
<750	29/119 (24.4)	41/139 (29.5)	1.30 (0.73-2.29)	.19
750-999	33/82 (40.2)	26/71 (36.6)	0.86 (0.45-1.61)	
≥1000	8/20 (40.0)	13/19 (68.4)	3.29 (0.88-12.25)	
Gestational age at birth, wk				
<27	57/176 (32.4)	60/187 (32.1)	0.99 (0.63-1.54)	.08
27 to <30	13/46 (28.3)	20/42 (47.6)	2.31 (0.99-5.37)	
Sex				
Female	40/106 (37.7)	39/114 (34.2)	0.85 (0.49-1.48)	.12
Male	30/116 (25.9)	41/115 (35.7)	1.60 (0.90-2.83)	
Maternal race				
Black	22/62 (35.5)	25/55 (45.5)	1.51 (0.73-3.13)	.23
Hispanic	17/48 (35.4)	13/40 (32.5)	0.89 (0.35-2.24)	
White	27/85 (31.8)	36/120 (30.0)	0.91 (0.50-1.66)	
Other	4/27 (14.8)	6/14 (42.9)	4.34 (0.93-20.19)	
Age at study entry, d				
<7	16/45 (35.6)	20/54 (37.0)	1.07 (0.46-2.49)	.85
7-14	54/175 (30.9)	60/175 (34.3)	1.17 (0.75-1.82)	
Respiratory support at start of treatment				
Mechanical ventilation	61/202 (30.2)	64/199 (32.2)	1.10 (0.72-1.68)	.86
Nasal CPAP	9/18 (50.0)	16/29 (55.2)	1.23 (0.38-3.99)	

Abbreviations: CPAP, continuous positive airway pressure; NA, not applicable.

[a] No significant difference between groups for any outcome assessment. Denominators listed in the table reflect the number of patients with available data for that variable.

[b] Wald *P* value evaluating equality of treatment effects across groups.

[c] Post hoc subgroup analyses data denote survival without BPD.

Table 3. Respiratory Support Outcomes and Other Morbidities at the Time of Discharge to Home and at 18 to 24 Months' Postmenstrual Age[a]

Variable	Placebo	Inhaled Nitric Oxide
Outcome Assessment at Discharge to Home	**(n = 222)**	**(n = 229)**
Duration of any airway pressure support, mean (SD), d[b]	55 (40)	54 (42)
Duration of oxygen therapy, mean (SD), d[c]	88 (41)	91 (59)
Duration of hospitalization, mean (SD), d[d]	105 (37)	108 (54)
Postnatal corticosteroid use for BPD, No. (%)	91 (41.0)	95 (41.5)
Outcome Assessment at 18-24 mo PMA, No. (%)	**(n = 180)**	**(n = 180)**
Any respiratory medication use	96 (53.3)	95 (52.8)
Postnatal corticosteroid use	41 (22.8)	34 (18.9)
Oxygen therapy use	12 (6.7)	3 (1.7)
Hospitalization for respiratory illness	56 (31.1)	51 (28.3)
Any respiratory medication use, oxygen therapy use, hospitalization for respiratory illness, or death	109 (60.6)	103 (57.2)

Abbreviations: BPD, bronchopulmonary dysplasia; PMA, postmenstrual age.

[a] No significant difference between groups for any outcome assessment.

[b] Among 220 infants in the placebo group and 229 infants in the inhaled nitric oxide group.

[c] Among 212 infants in the placebo group and 207 infants in the inhaled nitric oxide group.

[d] Among 203 infants in the placebo group and 201 infants in the inhaled nitric oxide group.

replicating the NO CLD subgroup enrolled between ages 7 and 14 days. Reasons for the inconsistency in efficacy outcomes in our study vs results reported in the NO CLD trial[16] are unclear. The NO CLD trial was not powered to assess the primary outcome in the subgroup enrolled between ages 7 and 14 days, whereas our study was powered specifically for that purpose and included twice as many infants in each treatment arm.

Comparison of the NO CLD trial[16] and our study population did not reveal differences in sex allocation, proportion of infants receiving noninvasive pressure support at randomization, or exposure to antenatal corticosteroids or postnatal surfactant therapy. There were no identifiable differences in reported rates of secondary outcomes or AEs except for retinopathy of prematurity. Notably, the rate of survival without BPD reported in the NO CLD trial (44%)[16] was higher than

Table 4. BSID-III Assessment and Other Neurodevelopmental Outcomes at 18 to 24 Months' Postmenstrual Age[a]

Variable	Placebo (n = 180)	Inhaled Nitric Oxide (n = 180)
Death or NDI, No. (%)	53 (29.4)	56 (31.1)
Death before assessment, No. (%)	19 (10.6)	26 (14.4)
NDI, No./total No. (%)	34/180 (18.9)	30/180 (16.7)
Cognitive scale, mean (SD)		
Composite score	90.9 (15.6)	91.3 (15.5)
Scaled score	8.1 (3.2)	8.3 (3.0)
Receptive and expressive communication, mean (SD)		
Composite score	82.6 (15.2)	85.5 (16.3)
Scaled score	13.8 (5.3)	14.8 (5.6)
Overall cognitive disability, No./total No. (%)		
Severe, BSID-III cognitive score <70	12/167 (7.2)	13/164 (7.9)
Moderate, BSID-III cognitive score of 70-84	33/167 (19.8)	26/164 (15.9)
Mild, BSID-III cognitive score of 85-99	64/167 (38.3)	72/164 (43.9)
None, BSID-III cognitive score ≥100	58/167 (34.7)	53/164 (32.3)
Gross Motor Function Classification System level ≥2	8/170 (4.7)	8/171 (4.7)
Moderate to severe cerebral palsy, No./total No. (%)	11/180 (6.1)	7/180 (3.9)
Seizures, No./total No. (%)	9/173 (5.2)	2/173 (1.2)
Any vision impairment, No./total No. (%)	25/180 (13.9)	23/180 (12.8)
Any hearing impairment, No./total No. (%)	10/173 (5.8)	8/173 (4.6)

Abbreviations: BSID-III, Bayley Scales of Infant and Toddler Development, Third Edition; NDI, neurodevelopmental impairment.

[a] No significant difference between groups for any outcome assessment.

that seen in other similar cohorts, such as the control group in the recently published Trial of Late Surfactant (TOLSURF) (32%)[25] and our study (34.9%). Despite numerous improvements in neonatal care leading to better survival and lower rates for many major morbidities, recent data from the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Neonatal Research Network[1] show no significant improvement in BPD rates among infants of 23 to 28 weeks' GA over the past 2 decades; in fact, BPD rates appear to have increased.

Within our study, we identified clinically relevant imbalances between treatment groups for maternal race and presence of prolonged rupture of membranes. Ruptured membrane data were not reported in the NO CLD trial.[16] However, the overall percentage of such cases in our study (7.3% [33 of 451]) is unlikely to have a major effect on the primary outcome. The discrepancy in maternal race is important to consider. We report a small (10%) but nonsignificant increase in survival without BPD among infants of black race treated with inhaled nitric oxide. In post hoc analysis, the NO CLD trial[16] also reported improved survival without BPD among black infants treated with inhaled nitric oxide, with a 20% difference between inhaled nitric oxide and placebo groups. Even in the early entry study subgroup, the relative benefit was limited only to the nonwhite population, with no significant relative benefit in white infants. Survival without BPD was also noted to be higher in the inhaled nitric oxide trial by Schreiber et al,[12] with a predominantly black (70%) study population. The trial by Kinsella et al[11] did not report a post hoc analysis by maternal race, and the European Union Nitric Oxide (EUNO) trial[17] had very low inclusion rates (11%) for black infants. The individual patient meta-analysis by Askie and colleagues,[26] which included 3298 preterm infants from 11 randomized trials, indicated no overall benefit for inhaled nitric oxide in preventing death or BPD, but it suggested a possible subgroup benefit among nonwhite preterm infants (relative risk, 0.93; 95% CI, 0.86-1.00). Plausible biologic differences in genetic polymorphisms within the nitric oxide metabolic pathway[27,28] could contribute to the noted increased risk of cardiovascular disease, including pulmonary hypertension, in blacks.[29] Increasingly, evidence from single-nucleotide polymorphisms and genome-wide analyses show important risk association of specific preterm infants for development of BPD and pulmonary vascular disease.[30-32] As the concept of personalized genomic medicine advances, focused investigation of specific higher-risk subpopulations of premature infants may be indicated, including those who might benefit from inhaled nitric oxide or other therapies.[33-35]

The 1-year respiratory outcomes from the NO CLD trial[16] and our study are difficult to compare. Within both studies, there was considerable variability across NICUs in respiratory medication use, oxygen therapy, and rehospitalization. Although the NO CLD trial reported lower rates of bronchodilator, corticosteroid, and diuretic use in the group treated with inhaled nitric oxide, use of bronchodilators and diuretics was higher at 1 year than in either arm of our study. In the NO CLD trial,[20] which included infants enrolled between ages 7 and 21 days, there was significantly lower use of bronchodilators in infants treated with inhaled nitric oxide (40%) vs placebo (54%), but rates were higher compared with both arms of our study (21.1% [83 of 393]). It is unclear why infants treated with inhaled nitric oxide on postnatal days 7 to 14 in the NO CLD trial had higher survival without BPD than similarly managed infants in our trial.

Lack of treatment effect in our trial is similar to other multicenter trials designed to prevent BPD.[13-15,17] Our follow-up studies at 1 year and 18 to 24 months' PMA mirror data from other multicenter trials,[21,36] demonstrating no significant

effect on neurodevelopmental outcomes or evidence for any other safety issues. To our knowledge, only one trial (by Mestan and colleagues[37]) reported improved neurodevelopmental outcomes for infants aged 2 years treated with inhaled nitric oxide; however, this difference was not sustained at school age.[38]

Limitations

Our study has some limitations. It is important to note that there was inadequate power for any subgroup comparisons because the sample size was derived only for the primary outcome of survival without BPD across the entire study population. We acknowledge that, with multiple centers contributing varying numbers of patients, differences in other care practices could have affected the primary outcome. However, such variation should have been minimized by the masking and randomization process.

Conclusions

In summary, inhaled nitric oxide (initiated at 20 ppm on postnatal days 5 to 14 to high-risk premature infants and continued for 24 days) appears to be safe but did not improve survival without BPD at 36 weeks' PMA or respiratory and neurodevelopmental outcomes at 18 to 24 months' PMA. These findings are consistent with meta-analyses and the National Institutes of Health consensus statement,[18,26,39-41] in which prophylactic but delayed use of inhaled nitric oxide does not appear to prevent BPD.

ARTICLE INFORMATION

Accepted for Publication: June 25, 2017.

Published Online: September 25, 2017. doi:10.1001/jamapediatrics.2017.2618

Author Affiliations: Department of Pediatrics, Cumming School of Medicine, University of Calgary, Alberta Children's Hospital Research Institute, Calgary, Alberta, Canada (Hasan); Mallinckrodt Pharmaceuticals, Hampton, New Jersey (Potenziano); Department of Pediatrics, Medical College of Wisconsin, Milwaukee (Konduri); Department of Neonatology, Winnie Palmer Hospital, Pediatrix Medical Group, Orlando, Florida (Perez); Department of Pediatrics, Stanford University School of Medicine, Palo Alto, California (Van Meurs); Lucile Packard Children's Hospital Stanford, Palo Alto, California (Van Meurs); Division of Neonatology, Department of Pediatrics, University of South Carolina School of Medicine, Greenville (Walker); Department of Pediatrics, University of Utah School of Medicine, Salt Lake City (Yoder).

Author Contributions: Dr Hasan had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Potenziano, Perez, Walker, Yoder.
Acquisition, analysis, or interpretation of data: Hasan, Potenziano, Konduri, Van Meurs, Yoder.
Drafting of the manuscript: Hasan, Potenziano, Konduri, Perez, Van Meurs, Yoder.
Critical revision of the manuscript for important intellectual content: Hasan, Potenziano, Van Meurs, Walker, Yoder.
Statistical analysis: Potenziano.
Obtained funding: Potenziano.
Administrative, technical, or material support: Hasan, Perez, Yoder.
Study supervision: Hasan, Potenziano, Konduri, Perez, Yoder.

Conflict of Interest Disclosures: Dr Konduri reported receiving an honorarium for participation in a roundtable meeting in April 2015 that was supported by a grant from Mallinckrodt Pharmaceuticals. Dr Perez reported serving on a speakers bureau for Mallinckrodt Pharmaceuticals. Dr Van Meurs reported serving on an advisory panel to Mallinckrodt Pharmaceuticals. Dr Yoder reported serving as a consultant to Mallinckrodt Pharmaceuticals. No other disclosures were reported.

Funding/Support: This study was sponsored by Mallinckrodt Pharmaceuticals.

Role of the Funder/Sponsor: United BioSource Corporation, an independent contract research organization, was solely responsible for administration of the clinical trial and verification of the data points. The study was supervised by the Newborns Treated With Nitric Oxide (NEWNO) Trial Group steering committee and was overseen by an independent data safety monitoring board. James S. Baldassarre, MD, an Ikaria Therapeutics (now Mallinckrodt Pharmaceuticals) employee at the time of the study, was a member of the steering committee. Shannon Escalante, MS, of Mallinckrodt Pharmaceuticals, was responsible for the statistical analysis; however, she neither participated in the verification of the data from the investigational sites (performed by United BioSource Corporation) nor in the data interpretation or writing of the manuscript.

Group Information: The members of the Newborns Treated With Nitric Oxide (NEWNO) Trial Group were the following: *Arizona:* Gregory Carl Martin, MD (Phoenix Children's Hospital, Phoenix) and Jeanne P. Zenge, MD (St Joseph's Hospital and Medical Center, Phoenix); *California:* John Cleary, MD (Children's Hospital of Orange County Research Institute, Orange), Yomna Adly Ibrahim, MD (Loma Linda University School of Medicine, Loma Linda), Amy L. Kimball, MD (Rady Children's Specialists of San Diego, San Diego), Maynard R. Rasmussen, MD (Sharp Mary Birch Hospital for Women and Newborns, San Diego), and Krisa P. Van Meurs, MD (Stanford University School of Medicine, Palo Alto); *Connecticut:* James I. Hagadorn, MD (Connecticut Children's Medical Center, Hartford) and Shabnam Lainwala, MD, PhD (Connecticut Children's Medical Center, Hartford); *Florida:* Terri L. Ashmeade, MD, MS, CPHQ (Department of Pediatrics, Morsani College of Medicine, University of South Florida, Tampa), Jose A. Perez, MD (Department of Neonatology, Pediatrix Medical Group, Winnie Palmer Hospital, Orlando), and Lewis P. Rubin, MD (deceased, replaced by Terri Ashmeade, MD, MS, CPHQ) (University of South Florida College of Medicine, Tampa); *Georgia:* Chantrapa Bunyapen, MD (Medical College of Georgia, Augusta); *Illinois:* Bhagya Lakshmi Puppala, MD (Lutheran General Children's Hospital, Park Ridge); *Indiana:* Gregory M. Sokol, MD (Indiana University School of Medicine, Riley Hospital for Children at IU Health, Indianapolis); *Kentucky:* Tonya W. Robinson, MD (University of Louisville, Louisville); *Minnesota:* Raul F. Cifuentes, MD (Hennepin County Medical Center at University of Minnesota, Minneapolis); *New Jersey:* Eduardo R. Bautista, MD (Jersey Shore University Medical Center, Neptune), Surasak Puvabanditsin, MD (Robert Wood Johnson University Hospital, New Brunswick), and Shyan Sun, MD (Saint Barnabas Medical Center, Livingston); *New York:* Mamta Fuloria, MD (Montefiore Medical Center-Weiler Division, Bronx), Sergio G. Golombek, MD, MPH (Maria Fareri Children's Hospital at Westchester Medical Center, Valhalla), and Nazeeh Hanna, MD (Winthrop University Hospital, Mineola); *North Carolina:* Stephen Downer Kicklighter, MD (WakeMed, Raleigh); *Ohio:* Minda Te, MD (Mercy Children's Hospital, Toledo); *Oklahoma:* Michael R. Gomez, MD (Saint Francis Children's Hospital, Tulsa); *South Carolina:* M. Whit Walker, MD, MS (University of South Carolina School of Medicine, Greenville); *South Dakota:* Mohammed Akram Khan, MD (Sanford Children's Hospital, Sioux Falls); *Texas:* Jonathan Henry Nedrelow, MD (Cook Children's Medical Center, Fort Worth); *Utah:* Robert DiGeronimo, MD (University of Utah School of Medicine, Salt Lake City); *Virginia:* Archana Jayaram, MD (Virginia Commonwealth University, Richmond); *Wisconsin:* Jeffery S. Garland, MD (Wheaton Franciscan Healthcare, Milwaukee) and Girija G. Konduri, MD (Children's Hospital of Wisconsin and Medical College of Wisconsin, Milwaukee); *Canada:* Georges Caouette, BSc, MD, FRCPC (Centre Hospitalier Universitaire de Québec, Québec, Québec), and Shabih U. Hasan, MD, DCH, FRCPC (University of Calgary, Calgary, Alberta).

Additional Contributions: James S. Baldassarre, MD, formerly of Ikaria Therapeutics (now Mallinckrodt Pharmaceuticals), provided input to the study concept and design. Michael Morren, MBA, RPh, of Peloton Advantage, and Shylin Miljan, of the University of Calgary, provided editorial support. None received compensation. We thank United BioSource Corporation for their role in the conduct of the study. We also thank the respiratory therapists, study coordinators, registered nurses, and other allied health professionals, as well as the Newborns Treated With Nitric Oxide (NEWNO) Trial Group, for their contributions to the study. Finally, we thank all of the parents and guardians and infants who participated in the study.

REFERENCES

1. Stoll BJ, Hansen NI, Bell EF, et al; Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network. Trends in care practices, morbidity, and mortality of extremely preterm neonates, 1993-2012. *JAMA*. 2015;314(10):1039-1051.

2. Vrijlandt EJ, Boezen HM, Gerritsen J, Stremmelaar EF, Duiverman EJ. Respiratory health in prematurely born preschool children with and without bronchopulmonary dysplasia. *J Pediatr*. 2007;150(3):256-261.

3. Northway WH Jr, Moss RB, Carlisle KB, et al. Late pulmonary sequelae of bronchopulmonary dysplasia. *N Engl J Med*. 1990;323(26):1793-1799.

4. Wood NS, Costeloe K, Gibson AT, Hennessy EM, Marlow N, Wilkinson AR; EPICure Study Group. The EPICure study: associations and antecedents of neurological and developmental disability at 30 months of age following extremely preterm birth. *Arch Dis Child Fetal Neonatal Ed*. 2005;90(2):F134-F140.

5. Vohr BR, Wright LL, Poole WK, McDonald SA. Neurodevelopmental outcomes of extremely low birth weight infants <32 weeks' gestation between 1993 and 1998. *Pediatrics*. 2005;116(3):635-643.

6. Neonatal Inhaled Nitric Oxide Study Group. Inhaled nitric oxide in full-term and nearly full-term infants with hypoxic respiratory failure [published correction appears in *N Engl J Med*. 1997;337:434]. *N Engl J Med*. 1997;336(9):597-604.

7. Clark RH, Kueser TJ, Walker MW, et al; Clinical Inhaled Nitric Oxide Research Group. Low-dose nitric oxide therapy for persistent pulmonary hypertension of the newborn. *N Engl J Med*. 2000;342(7):469-474.

8. Roberts JD Jr, Roberts CT, Jones RC, Zapol WM, Bloch KD. Continuous nitric oxide inhalation reduces pulmonary arterial structural changes, right ventricular hypertrophy, and growth retardation in the hypoxic newborn rat. *Circ Res*. 1995;76(2):215-222.

9. McCurnin DC, Pierce RA, Chang LY, et al. Inhaled NO improves early pulmonary function and modifies lung growth and elastin deposition in a baboon model of neonatal chronic lung disease. *Am J Physiol Lung Cell Mol Physiol*. 2005;288(3):L450-L459.

10. Bland RD, Albertine KH, Carlton DP, MacRitchie AJ. Inhaled nitric oxide effects on lung structure and function in chronically ventilated preterm lambs. *Am J Respir Crit Care Med*. 2005;172(7):899-906.

11. Kinsella JP, Parker TA, Galan H, Sheridan BC, Halbower AC, Abman SH. Effects of inhaled nitric oxide on pulmonary edema and lung neutrophil accumulation in severe experimental hyaline membrane disease. *Pediatr Res*. 1997;41(4, pt 1):457-463.

12. Schreiber MD, Gin-Mestan K, Marks JD, Huo D, Lee G, Srisuparp P. Inhaled nitric oxide in premature infants with the respiratory distress syndrome. *N Engl J Med*. 2003;349(22):2099-2107.

13. Van Meurs KP, Wright LL, Ehrenkranz RA, et al; Preemie Inhaled Nitric Oxide Study. Inhaled nitric oxide for premature infants with severe respiratory failure. *N Engl J Med*. 2005;353(1):13-22.

14. Field D, Elbourne D, Truesdale A, et al; INNOVO Trial Collaborating Group. Neonatal ventilation with inhaled nitric oxide vs ventilatory support without inhaled nitric oxide for preterm infants with severe respiratory failure: the INNOVO multicentre randomised controlled trial (ISRCTN 17821339). *Pediatrics*. 2005;115(4):926-936.

15. Kinsella JP, Cutter GR, Walsh WF, et al. Early inhaled nitric oxide therapy in premature newborns with respiratory failure. *N Engl J Med*. 2006;355(4):354-364.

16. Ballard RA, Truog WE, Cnaan A, et al; NO CLD Study Group. Inhaled nitric oxide in preterm infants undergoing mechanical ventilation [published correction appears in *N Engl J Med*. 2007;357:1444-1445]. *N Engl J Med*. 2006;355(4):343-353.

17. Mercier JC, Hummler H, Durrmeyer X, et al; EUNO Study Group. Inhaled nitric oxide for prevention of bronchopulmonary dysplasia in premature babies (EUNO): a randomised controlled trial. *Lancet*. 2010;376(9738):346-354.

18. Barrington KJ, Finer N. Inhaled nitric oxide for respiratory failure in preterm infants. *Cochrane Database Syst Rev*. 2010;(12):CD000509.

19. Laughon MM, Langer JC, Bose CL, et al; Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network. Prediction of bronchopulmonary dysplasia by postnatal age in extremely premature infants. *Am J Respir Crit Care Med*. 2011;183(12):1715-1722.

20. Hibbs AM, Walsh MC, Martin RJ, et al. One-year respiratory outcomes of preterm infants enrolled in the Nitric Oxide (to Prevent) Chronic Lung Disease trial. *J Pediatr*. 2008;153(4):525-529.

21. Walsh MC, Hibbs AM, Martin CR, et al; NO CLD Study Group. Two-year neurodevelopmental outcomes of ventilated preterm infants treated with inhaled nitric oxide. *J Pediatr*. 2010;156(4):556-561.e1.

22. Walsh MC, Wilson-Costello D, Zadell A, Newman N, Fanaroff A. Safety, reliability, and validity of a physiologic definition of bronchopulmonary dysplasia. *J Perinatol*. 2003;23(6):451-456.

23. Ehrenkranz RA, Walsh MC, Vohr BR, et al; National Institutes of Child Health and Human Development Neonatal Research Network. Validation of the National Institutes of Health consensus definition of bronchopulmonary dysplasia. *Pediatrics*. 2005;116(6):1353-1360.

24. Bayley N. *Bayley Scales of Infant and Toddler Development: Technical Manual*. 3rd ed. San Antonio, TX: Psychological Corp, Pearson Education Inc; 2005.

25. Ballard RA, Keller RL, Black DM, et al; TOLSURF Study Group. Randomized trial of late surfactant treatment in ventilated preterm infants receiving inhaled nitric oxide. *J Pediatr*. 2016;168:23-29.e4.

26. Askie LM, Ballard RA, Cutter GR, et al; Meta-analysis of Preterm Patients on Inhaled Nitric Oxide Collaboration. Inhaled nitric oxide in preterm infants: an individual-patient data meta-analysis of randomized trials. *Pediatrics*. 2011;128(4):729-739.

27. Mason RP, Kalinowski L, Jacob RF, Jacoby AM, Malinski T. Nebivolol reduces nitroxidative stress and restores nitric oxide bioavailability in endothelium of black Americans. *Circulation*. 2005;112(24):3795-3801.

28. Tanus-Santos JE, Desai M, Deak LR, et al. Effects of endothelial nitric oxide synthase gene polymorphisms on platelet function, nitric oxide release, and interactions with estradiol. *Pharmacogenetics*. 2002;12(5):407-413.

29. Hernández-Díaz S, Van Marter LJ, Werler MM, Louik C, Mitchell AA. Risk factors for persistent pulmonary hypertension of the newborn. *Pediatrics*. 2007;120(2):e272-e282.

30. Trittmann JK, Peterson E, Rogers LK, et al. Plasma asymmetric dimethylarginine levels are increased in neonates with bronchopulmonary dysplasia-associated pulmonary hypertension. *J Pediatr*. 2015;166(2):230-233.

31. Bhattacharya S, Zhou Z, Yee M, et al. The genome-wide transcriptional response to neonatal hyperoxia identifies Ahr as a key regulator. *Am J Physiol Lung Cell Mol Physiol*. 2014;307(7):L516-L523.

32. Li J, Yu KH, Oehlert J, et al. Exome sequencing of neonatal blood spots and the identification of genes implicated in bronchopulmonary dysplasia. *Am J Respir Crit Care Med*. 2015;192(5):589-596.

33. Copland IB, Post M. Understanding the mechanisms of infant respiratory distress and chronic lung disease. *Am J Respir Cell Mol Biol*. 2002;26(3):261-265.

34. Solomon BD, Pineda-Alvarez DE, Hadley DW, et al; NISC Comparative Sequencing Program. Personalized genomic medicine: lessons from the exome. *Mol Genet Metab*. 2011;104(1-2):189-191.

35. McEvoy CT, Jain L, Schmidt B, Abman S, Bancalari E, Aschner JL. Bronchopulmonary dysplasia: NHLBI Workshop on the Primary Prevention of Chronic Lung Diseases. *Ann Am Thorac Soc*. 2014;11(suppl 3):S146-S153.

36. Durrmeyer X, Hummler H, Sanchez-Luna M, et al; European Union Nitric Oxide Study Group. Two-year outcomes of a randomized controlled trial of inhaled nitric oxide in premature infants. *Pediatrics*. 2013;132(3):e695-e703.

37. Mestan KK, Marks JD, Hecox K, Huo D, Schreiber MD. Neurodevelopmental outcomes of premature infants treated with inhaled nitric oxide. *N Engl J Med*. 2005;353(1):23-32.

38. Patrianakos-Hoobler AI, Marks JD, Msall ME, Huo D, Schreiber MD. Safety and efficacy of inhaled nitric oxide treatment for premature infants with respiratory distress syndrome: follow-up evaluation at early school age. *Acta Paediatr*. 2011;100(4):524-528.

39. Allen MC, Donohue P, Gilmore M, et al. Inhaled nitric oxide in preterm infants. *Evid Rep Technol Assess (Full Rep)*. 2010;(195):1-315.

40. Cole FS, Alleyne C, Barks JD, et al. NIH Consensus Development Conference statement: inhaled nitric-oxide therapy for premature infants. *Pediatrics*. 2011;127(2):363-369.

41. Kumar P; Committee on Fetus and Newborn; American Academy of Pediatrics. Use of inhaled nitric oxide in preterm infants. *Pediatrics*. 2014;133(1):164-170.