



**NATIONAL INSTITUTES OF HEALTH
CONSENSUS DEVELOPMENT CONFERENCE STATEMENT**

NIH Consensus Development Conference:
Inhaled Nitric Oxide Therapy for Premature Infants
October 27–29, 2010

National Institutes of Health (NIH) consensus and state-of-the-science statements are prepared by independent panels of health professionals and public representatives on the basis of (1) the results of a systematic literature review prepared under contract with the Agency for Healthcare Research and Quality (AHRQ), (2) presentations by investigators working in areas relevant to the conference questions during a 2-day public session, (3) questions and statements from conference attendees during open discussion periods that are part of the public session, and (4) closed deliberations by the panel during the remainder of the second day and morning of the third. This statement is an independent report of the panel and is not a policy statement of the NIH or the Federal Government.

The statement reflects the panel's assessment of medical knowledge available at the time the statement was written. Thus, it provides a "snapshot in time" of the state of knowledge on the conference topic. When reading the statement, keep in mind that new knowledge is inevitably accumulating through medical research.

Introduction

Premature birth is a major public health problem in the United States and internationally. Despite clinical, educational, and scientific efforts, the frequency of preterm birth has risen in the United States from 10.6 percent in 1990 to 12.7 percent in 2007. Worldwide, approximately 13 million infants are born prematurely every year. Infants born at or before 32 weeks gestation (2 percent of all births in the United States in 2007) are at extremely high risk for death in the neonatal period or for pulmonary, visual, and neurodevelopmental morbidities with lifelong consequences, including bronchopulmonary dysplasia (BPD, a form of chronic lung disease seen in premature infants), retinopathy of prematurity (ROP, the leading cause of blindness in children in the developed world), and brain injury. Reduced lung function associated with prematurity may persist throughout childhood and adolescence. Neurodevelopmental problems—including cerebral palsy, blindness, hearing loss, and learning disabilities—create lifelong challenges for many of these children and their families. Risks for adverse outcomes increase with decreasing gestational age. The economic costs to care for these infants are also substantial (estimated at \$26 billion in 2005 in the United States). In addition, the emotional and indirect economic costs for families are substantial. Unfortunately, however, the multifactorial biological, behavioral, and environmental causes and the heterogeneity of preterm birth make it extremely unlikely that all premature births can be prevented.

Over the past 20 years, continuing advances in high-risk obstetrical management and neonatal intensive care have resulted in increased survival of extremely premature infants. For example, based on recent Cochrane reviews, administration of antenatal steroids to women with impending premature birth reduces the risk of in-hospital neonatal death by 23 percent, neonatal respiratory distress syndrome by 34 percent, and cerebroventricular hemorrhage by 46 percent.

Exogenous surfactant administered to premature infants to either treat or prevent respiratory distress syndrome improves respiratory function and reduces risk of in-hospital death by 32 to 40 percent. After demonstration of efficacy and safety in multiple randomized controlled trials (RCTs), both of these interventions have been adopted into clinical practice.

Many clinical practices integrated into the care of these infants have been inadequately studied for safety and efficacy, with potentially serious consequences; yet, the smallest and sickest infants are the most vulnerable to adverse effects of the treatments they receive. The broad boundaries of accepted clinical practices in neonatal intensive care units lead to practice variations among centers. Large variations among centers in outcomes of premature infants, including BPD and adverse neurodevelopmental outcomes, persist after adjusting for risk factors such as gestational age, sex, and disease severity. The extent to which these differences in outcomes are due to differences in care practices or in patient characteristics is poorly understood. Clearly, the need for strategies to improve outcomes for this high-risk population is great, and this need has prompted testing of new therapies with the potential to decrease pulmonary and other complications of prematurity. Inhaled nitric oxide (iNO) emerged as one such therapy.

Nitric oxide is a gas that is ubiquitously produced in the human body. It serves as a signaling molecule with numerous regulatory effects on multiple human organ systems, including blood vessels, the lung, the heart, the nervous system, the immune system, and stem cells, and on the development of cancer. First discovered as a factor that relaxes resistance in blood vessels in 1980, nitric oxide was recognized by *Science* as the “Molecule of the Year” in 1992. The scientists who discovered its important role in diverse disease processes, including atherosclerosis, diabetes, impotence, and hypertension, were recognized with the Nobel Prize for Medicine or Physiology in 1998. More than 85,000 independent scientific articles about nitric oxide have been published since 1980. Over the past decade, the efficacy of nitric oxide in reducing blood vessel resistance and its easy administration via endotracheal tube to infants with respiratory distress led to trials in term and near-term newborns suffering from persistent pulmonary hypertension, a condition that results from failure of normal fetal lung blood vessel relaxation immediately following birth. Prior to iNO trials, many infants severely affected with pulmonary hypertension were treated using extracorporeal membrane oxygenation (ECMO), an invasive heart-lung bypass system, as a short-term strategy (up to 14 days) to improve survival by “buying time” for lung blood vessel resistance to decrease spontaneously. ECMO therapy is expensive, not widely available, and associated with considerable morbidity (e.g., bleeding). Large, placebo-controlled trials showed that nitric oxide decreases death or the need for ECMO in term and near-term infants with persistent pulmonary hypertension and led the Food and Drug Administration (FDA) to approve iNO as a therapy for that disease.

Findings from a substantial body of experimental work in developing animals and other model systems suggest that nitric oxide may enhance lung growth and reduce lung inflammation independently of its effects on blood vessel resistance. Although this work demonstrates biologic plausibility and the results of RCTs in term and near-term infants were positive, combined evidence from the 14 RCTs of iNO treatment in premature infants ≤ 34 weeks gestation have shown equivocal effects on pulmonary outcomes, survival, and neurodevelopmental outcomes. Despite these equivocal results, the off-label use of iNO has increased substantially. Controversy

about its use in premature infants has been fueled by the refusal of some third-party payers to cover the substantial costs for iNO administration (up to \$3,000 a day).

To provide healthcare professionals, families, and the general public with a responsible assessment of currently available data regarding the benefits and risks of iNO in premature infants, the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, the National Heart, Lung, and Blood Institute, and the Office of Medical Applications of Research of the National Institutes of Health convened a Consensus Development Panel that included experts in the fields of neonatology, pediatric pulmonology, pediatric neurology, perinatal epidemiology, ethics, neurodevelopmental follow-up, nursing, and family-centered care to review available data, to hear scientific summaries from investigators involved in this field, and to solicit input from the general public. A Planning Committee developed six questions to be addressed by the Consensus Development Panel.

As part of a comprehensive data review, an independent group, the Johns Hopkins University Evidence-based Practice Center (JHU EPC), generated a systematic review of all available human studies concerning use of iNO in premature infants. This review (available at <http://www.ahrq.gov/clinic/tp/inoinftp.htm>), along with an as yet unpublished, updated Cochrane review and an unpublished individual patient data meta-analysis (the Meta-Analysis of Preterm Patients on Inhaled Nitric Oxide [MAPPiNO] IPD meta-analysis), provided the Panel with summaries of the available evidence from these trials. One of the published trials, and therefore the JHU EPC systematic review, included infants of 34 weeks gestation. The Panel's review of the published evidence is therefore based on infants ≤ 34 weeks gestation. Its recommendations for clinical use of iNO, however, are limited to infants < 34 weeks to avoid contradiction and confusion with the FDA's labeled indications for iNO use.

Combining results of studies is complicated by differences in dose, timing, and duration of iNO administration, inclusion criteria (e.g., gestational age, chronologic age, severity of lung disease) of infants studied, and diversity of neurodevelopmental and pulmonary outcome measures. Where applicable, the Panel chose to follow the Cochrane review approach of subdividing the 14 trials into 3 clinically relevant groups based on characteristics of the participating infants and specific treatment strategies: early routine (initiation at < 3 days, routine use in intubated infants), early rescue (initiation at < 3 days based on oxygenation status), and later rescue (initiation at > 3 days based on BPD risk).

Many of the trials and meta-analyses examined results in clinical or demographic subgroups. When treatment effects differ across subgroups, however, as they did in some of the iNO studies, it is unwise to make firm inferences about subgroup differences when those differences are observed post hoc. Post hoc analysis of treatment effects in specific subgroups (e.g., dose of iNO, gestational age, early versus late initiation of treatment), whether within or across trials, is prone to false-positive results. The Consensus Development Panel therefore considered the subgroup results of these analyses as hypothesis-generating, rather than hypothesis-testing, and used them as a basis for recommending future research directions.

The six questions considered by the Consensus Development Panel are listed below and addressed in the following sections.

1. Does inhaled nitric oxide therapy increase survival and/or reduce the occurrence or severity of bronchopulmonary dysplasia among premature infants who receive respiratory support?
2. Are there short-term risks of inhaled nitric oxide therapy among premature infants who receive respiratory support?
3. Are there effects of inhaled nitric oxide therapy on long-term pulmonary and/or neurodevelopmental outcomes among premature infants who receive respiratory support?
4. Does the effect of inhaled nitric oxide therapy on bronchopulmonary dysplasia and/or death or neurodevelopmental impairment vary across subpopulations of premature infants?
5. Does the effect of inhaled nitric oxide therapy on bronchopulmonary dysplasia and/or death or neurodevelopmental impairment vary by timing of initiation, mode of delivery, dose and duration, or concurrent therapies?
6. What are the future research directions needed to better understand the risks, benefits, and alternatives to nitric oxide therapy for premature infants who receive respiratory support?

Terminology surrounding disease processes in premature infants has been used in inconsistent ways. For clarity throughout this document, the Panel has chosen to define the following terms:

- *Premature infant*: The International Classification of Diseases (ICD) has eliminated the term “prematurity,” because its prior definition was based on birth weight. This term is commonly used and understood as a synonym for preterm birth, defined by ICD as a gestational age at birth <37 completed weeks. Because the questions posed to the Panel used *premature infant*, this term is used throughout this consensus statement as a synonym for preterm infant. In this document, “near term” is used as it reflects the specific language in the FDA-approved label for inhaled nitric oxide. The Panel recognizes that “late preterm” is currently used to describe infants at 34 and up to 36 weeks and 6 days gestation.
- *Bronchopulmonary dysplasia (BPD)*: First described in 1967, BPD is a heterogeneous lung disease observed in premature infants and diagnosed within the first months of life. The clinical picture and definition of BPD have evolved substantially since its first description, complicating comparisons of studies that use BPD as an outcome. In analyzing the studies of iNO discussed in this report, the Panel decided to follow the definitions of BPD used by the researchers who designed the different clinical trials.

- *Cerebroventricular hemorrhage (CVH)*: This term is used as an inclusive term to refer to the spectrum of hemorrhagic brain injury most typically occurring in the first week of life in very premature infants. The location of hemorrhage may be periventricular, intraventricular, or intraparenchymal. Most studies report both the presence of any brain hemorrhage and severe hemorrhage. Severe hemorrhage most often refers to a large intraventricular hemorrhage or hemorrhage into white matter that surrounds the ventricles.
- *White matter injury (WMI)*: WMI is a spectrum of brain pathology that includes (1) the classic lesion of periventricular leukomalacia (PVL), which comprises focal cystic damage to white matter tracts (made of nerve axons that connect different brain regions covered by the insulating substance, myelin), and (2) diffuse, noncystic lesions that result in disturbances in myelination.

1. Does inhaled nitric oxide therapy increase survival and/or reduce the occurrence or severity of bronchopulmonary dysplasia among premature infants who receive respiratory support?

A body of evidence is strongest when results are consistent across trials despite heterogeneity in study design and populations. Therefore, the Panel chose to address this question by including all of the trials that enrolled premature infants ≤ 34 weeks gestation irrespective of the timing, dosing regimen, duration of inhaled nitric oxide (iNO) therapy, or subcategorization of the subjects.

None of the individual trials included in the systematic reviews showed a statistically significant effect of iNO on survival in this population. Meta-analysis by the Johns Hopkins University Evidence-based Practice Center (JHU EPC) of 11 randomized controlled trials (RCTs) revealed that treatment with iNO did not increase survival. The individual patient data (IPD) approach used in the MAPPiNO study of pooled data from 11 RCTs demonstrated no statistically significant effect of iNO on death at any time, death by 36 weeks postmenstrual age (PMA), or death before discharge. Given that the mortality of premature infants is highest during the first week after birth, age at the time of study enrollment is likely to be a particularly important factor in analyzing the effect of iNO on survival. However, inclusion or exclusion of the one trial with enrollment exclusively after 1 week did not affect the results of the meta-analysis. Thus overall, in premature infants ≤ 34 weeks gestation requiring respiratory support, current evidence shows that treatment with iNO in the neonatal period does not increase survival.

Bronchopulmonary dysplasia (BPD) is defined in the Introduction. The evolution of BPD over decades has been reflected in numerous and various definitions, usually based on the persistence of respiratory symptoms, pulmonary radiographic appearance, and the persistent need for treatments at a specified age (e.g., requiring supplemental oxygen at 28 days of age, requiring supplemental oxygen at 36 weeks PMA).

Interpretation of results from RCTs was complicated by different studies calculating BPD rates using survivors versus the total group as the denominator, and by the competing risks of death and BPD. In other words, an infant who dies in the first weeks of life is not at risk for developing BPD, which is usually based on criteria at 28 days. Since most of the trials and the JHU EPC

systematic review included analyses of BPD alone, however, the Panel also examined that evidence. None of the individual trials included in the systematic reviews showed statistically significant differences in BPD at 36 weeks PMA in those who received iNO compared with controls. The JHU EPC meta-analysis (8 RCTs) of BPD among surviving infants at 36 weeks PMA found no statistically significant differences in rates of BPD between iNO and control groups. The approach utilized in the MAPPiNO IPD meta-analysis did not report on BPD as a sole outcome variable. Thus, among premature infants who required respiratory support and were surviving at 36 weeks PMA, current evidence does not support the hypothesis that treatment with iNO in the neonatal period reduces the occurrence of BPD.

The composite outcome of “death or BPD at 36 weeks PMA” was reported, although not always as a primary outcome, in 11 iNO RCTs. Two individual trials found statistically significant reductions in the composite outcome of death or BPD in the iNO treated group. The JHU EPC meta-analysis of 11 RCTs showed a small, statistically significant reduction in the composite variable death or BPD at 36 weeks PMA. Exclusion of the one trial with enrollment after 1 week of age did not change the results of the meta-analysis. The MAPPiNO IPD meta-analysis of pooled data from 10 trials showed a similarly small effect size for BPD or death as the JHU EPC analysis, but did not achieve statistical significance. The small effect on this composite outcome should be interpreted cautiously.

The JHU EPC systematic review of the effect of iNO on the severity of BPD in the RCTs was compromised by the wide variation in BPD definitions and other study parameters. The JHU analysis concluded that insufficient data are available to perform a meta-analysis for any measure of severity due to the lack of uniformity in definitions and study measures used. There is insufficient evidence to support the hypothesis that treatment with iNO in the neonatal period reduces the severity of BPD. Two individual trials reported a statistically significant favorable effect of iNO on pulmonary outcomes reflecting severity of BPD; rates of hospitalization and respiratory support at 40 and 44 weeks PMA; and a statistically significant reduction in the average duration of supplemental oxygen. Although these trials raise intriguing questions, the effects of iNO on the severity of BPD have not been adequately studied in subpopulations, a subject addressed in the Panel’s response to Question 4.

The available evidence therefore is insufficient to recommend the routine use of iNO in clinical care of premature infants <34 weeks gestation requiring respiratory support.

2. Are there short-term risks of inhaled nitric oxide therapy among premature infants who receive respiratory support?

Premature infants are at risk for short-term complications, including patent ductus arteriosus (PDA), late-onset (>7 days) sepsis, necrotizing enterocolitis (NEC), retinopathy of prematurity (ROP), pulmonary complications (e.g., air leak, pulmonary hemorrhage), and brain injury (e.g., intraventricular hemorrhage [IVH], intraparenchymal hemorrhage [IPH], and periventricular leukomalacia [PVL]). Although these are morbidities seen in premature infants which might be exacerbated by iNO, there may be other important indicators to evaluate short-term risks. However, iNO may lead to accumulation of methemoglobin, formed by the reaction of nitric oxide with hemoglobin.

The JHU EPC analyses showed no evidence for an increased risk of PDA, late-onset sepsis, NEC, ROP, pulmonary complications, or toxic levels of methemoglobin. The MAPPiNO IPD meta-analysis also showed no statistically significant difference in the incidence of air leak, pulmonary hemorrhage, or severe ROP.

The JHU EPC systematic evidence review showed no overall difference between iNO-treated and control infants with respect to IVH, IPH, or PVL.

The updated Cochrane meta-analysis showed no statistically significant effects on brain injury, either severe IVH or the combined outcomes of severe IVH or PVL with early routine administration of iNO. Early rescue administration of iNO was associated with a nonsignificant trend toward increased severe IVH.

The MAPPiNO IPD meta-analysis showed a nonsignificant trend toward increased severe neurological events (e.g., IVH, IPH, cystic PVL) with iNO treatment.

In summary, there is no evidence that treatment with iNO either increases or decreases the risk of several short-term complications of prematurity, including PDA, late-onset sepsis, severe ROP, and pulmonary complications (e.g., air leaks, pulmonary hemorrhage). The risks for these complications are greatest for the infants born earliest (at 22 to 27 weeks gestation), and the iNO trials have not reported on these risks stratified by either birth weight or gestational age with the exception of studies described in the Panel's response to Question 4. Future research should attempt to fill this gap.

In these trials, administration of iNO at doses up to 20 ppm did not produce levels of methemoglobin that would be considered toxic in term infants or adults.

Considering all trials together, there is no convincing evidence to support the hypothesis that iNO administration increases or decreases the risk of PVL or IVH in premature infants ≤ 34 weeks gestation. These studies varied in design, and only three had baseline head sonograms before treatment with iNO. When head ultrasound studies were obtained, the timing of these studies and the categorization of brain injury were not uniform.

3. Are there effects of inhaled nitric oxide therapy on long-term pulmonary and/or neurodevelopmental outcomes among premature infants who receive respiratory support?

Long-Term Pulmonary Outcomes

The Johns Hopkins University Evidence-based Practice Center (JHU EPC) reported two randomized controlled trials (RCTs) examining long-term pulmonary outcomes. One large study demonstrated a statistically significant decrease in use of lung-related medications and fewer parental reports of respiratory symptoms at 12 months in children receiving inhaled nitric oxide (iNO) compared with controls; a smaller study found no statistically significant difference in reported use of lung medications or reports of symptoms at 12 months. Neither study found a

statistically significant difference in rates of hospitalization for lung problems or wheezing at 12 months. The lack of a difference in hospitalization or wheezing casts doubt on the clinical importance of a difference in medication use between those who received iNO and the controls.

When the results of the two 12-month pulmonary follow-up studies were combined in a meta-analysis by the JHU EPC, the statistically significant decrease in the reported use of pulmonary medications in children who received iNO remained, because the smaller study did not have an influence on the overall results.

No studies of long-term pulmonary outcome have included available measurements of pulmonary function, gas exchange, or radiologic appearance. An important deficit of these studies was a failure to account for common confounders following discharge from the neonatal intensive care unit known to have substantial effects on the use of pulmonary medications.

The Panel concludes, as did the JHU EPC, that there is evidence in one trial of an advantage in long-term pulmonary outcome for the use of iNO, but that this evidence is not strong enough to justify the widespread use of iNO to prevent long-term pulmonary disease.

Long-Term Neurodevelopmental Outcomes

None of the trials examining long-term neurodevelopmental outcomes in children have convincingly demonstrated a long-term neurodevelopmental effect of iNO. Individually, none of the trials found a statistically significant difference in the incidence of motor delay between those who had received iNO and controls. Few individual trials and none of the meta-analyses revealed a statistically significant association between neonatal iNO treatment and any neurodevelopmental outcome up to 5 years of age. For cerebral palsy, the two trials that did show associations conflicted in the direction of association. There is insufficient evidence to determine whether there is an effect of iNO on motor impairment or if it differs by the birth weight of the treated infants. There also were no significant differences between the iNO and control groups in the proportion of children with visual or hearing impairment.

Studies of long-term neurodevelopment in preterm infants ≤ 34 weeks gestation treated with iNO have been hampered by variation in measures used to assess neurodevelopmental status and the ages at which outcomes are measured, and by the lack of physiologic, radiologic, functional, or quality-of-life measures used as outcomes. Most studies of long-term effects typically have used overly broad measures of development in the absence of physiologic or anatomic examinations; many also have used the measure at too young an age. While 18 to 24 months is appropriate for detecting cerebral palsy, testing at school age is more appropriate for diagnosing intellectual disability. Newer methods of assessment, including correlated neuroimaging and standardized behavioral testing, should be included in any future assessments of the long-term neurodevelopmental consequences of iNO.

Long-term studies of pulmonary and neurodevelopmental health following premature birth are logistically challenging and expensive. Funding agencies should support the expense of long-term follow-up, and investigators should provide comprehensive plans for retention of subjects over the life of the trial.

4. Does the effect of inhaled nitric oxide therapy on bronchopulmonary dysplasia and/or death or neurodevelopmental impairment vary across subpopulations of premature infants?

In response to this question, the Panel elected to review common clinical variables that may interact with inhaled nitric oxide (iNO) treatment apart from timing or duration of treatment, which is covered in the Panel response to Question 5. Analysis of subpopulations is limited by the fact that few trials have identified subgroups, subgrouping results in small sample sizes in each subcategory, and trials are often not powered to detect subgroup differences. In addition, when trials did define subgroups, definitions varied across trials and were usually post hoc.

Based on the Johns Hopkins University Evidence-based Practice Center (JHU EPC) systematic review, there is insufficient evidence to evaluate whether factors such as sex, gestational age, ethnic group/race, and socioeconomic status were associated with increased benefit or risk from iNO therapy. There is no information regarding effects of growth restriction, antenatal steroid use, multiple gestation, chorioamnionitis, or other antenatal factors.

The JHU EPC systematic review reveals insufficient evidence of decreased incidence of death or bronchopulmonary dysplasia (BPD) particular to any subgroup of premature infants treated with iNO. Five studies (representing three independent clinical trials) reported outcomes by birth weight. Two of the three trials demonstrated a significant reduction in the composite outcome of death or BPD when iNO was administered to premature infants $\geq 1,000$ grams, but not in those $< 1,000$ grams.

This review raises a concern for safety of iNO in premature infants $< 1,000$ grams. Three studies of infants of this birth weight treated within 48 hours of delivery reported an increased risk of death, severe intraventricular hemorrhage (IVH) and periventricular leukomalacia (PVL), neurodevelopmental impairment, BPD, and/or oxygen dependence at 1 year of age. However, in another large study that initiated iNO at 7 days of life, no such safety concerns were noted in this birth-weight category.

Based on the JHU EPC systematic review of published studies, there is insufficient evidence of improvement in neurodevelopmental outcomes in any subgroup of premature infants treated with iNO.

Published trials have shown insufficient evidence of benefit to premature infants with pulmonary hypoplasia or hypertension, likely due to small numbers of such patients and severity of illness. Additional studies in this population will be difficult to accomplish. Therefore, clinical use in this population should be left to clinical discretion.

Based on published data, the Panel recommends special caution in studies of early rescue use of iNO in premature infants < 34 weeks gestation weighing $< 1,000$ grams.

5. Does the effect of inhaled nitric oxide therapy on bronchopulmonary dysplasia and/or death or neurodevelopmental impairment vary by timing of initiation, mode of delivery, dose and duration, or concurrent therapies?

As previously stated in the Introduction, in the trials published to date, three distinct subgroups have been identified by a Cochrane meta-analysis, by timing of initiation, clinical phase, or severity of illness: (1) early (<3 days) routine initiation in preterm infants receiving respiratory support (“early routine”), (2) early (<3 days) initiation in ventilated infants by oxygenation criteria (“early rescue”), and (3) later (>3 days) initiation in infants at high risk of developing bronchopulmonary dysplasia (BPD), as defined by persistent need for respiratory support (“later rescue”). There is a clinical and biological rationale for this subdivision of trials. This meta-analysis within the first two subgroups reveals no significant reduction in death, BPD, or the composite outcome of death or BPD in the iNO study groups. However, the later rescue group is predominantly represented by one, large multicenter trial. In this trial, the treatment protocol, designed to test a novel hypothesis, was unique not only in the timing of initiation, but also in dosing and duration. This trial revealed an overall reduction in the composite outcome of death or BPD and a post hoc finding of greater efficacy when treatment was initiated during the second postnatal week, as compared with the third postnatal week. The method of treatment allocation and statistical analysis of multiples enrolled in the trial made it difficult to integrate this trial’s findings in a conventional meta-analysis. Nevertheless, different statistical approaches to the analysis of multiples did not substantially change the estimate of the effect of iNO.

The effect of mode of ventilation (conventional versus high frequency) on efficacy and safety of iNO was evaluated in two trials, in one by prospective randomization and in the other by post hoc analysis. No studies have directly compared delivery by continuous positive airway pressure (CPAP) or nasal cannula versus endotracheal positive pressure ventilation. There is insufficient evidence to determine whether mode of ventilation impacts outcome from iNO treatment.

None of the trials published to date randomized subjects by dose or treatment duration of iNO. Despite this limitation, these trials can be subdivided into three broad dosage groups: 5 parts per million (ppm), 10 ppm, and 20 ppm. In a dose-stratified meta-analysis by the Johns Hopkins University Evidence-based Practice Center (JHU EPC), which combined all three treatment initiation subgroups, iNO therapy in the group that received a maximum dose of 10 ppm was associated with a statistically significant reduction in the risk of BPD, but not death, or the composite outcome of death or BPD. These results do not form a basis for deciding that one dosing regimen was superior, because they were based on post hoc comparisons and there was too much variability among the study designs within each dose group. A more focused examination of dosing and treatment duration within clinically meaningful subgroups is needed.

Little is known about the effect of concurrent therapies on the efficacy and safety of iNO. Only one trial directly addressed the effect of iNO with a concurrent therapy, glucocorticoids. Further research is needed to determine the effect of concurrent therapies—such as antenatal and postnatal glucocorticoids, surfactant, vitamin A, indomethacin, and caffeine—on the efficacy and safety of iNO.

There is no evidence to suggest that variations in these treatment regimen factors (e.g., dose, timing, mode of administration) are harmful in terms of BPD, death, or neurodevelopmental outcome. The design of future trials comparing treatment regimens should include a longer duration of follow-up to ensure long-term safety.

There is insufficient evidence to conclude that the efficacy of iNO therapy with respect to BPD and/or death, or neurodevelopmental impairment, varies by timing of initiation, mode of delivery, dose and duration of therapy, or concurrent therapies. A major limitation is that only one trial reporting these outcomes has randomized infants by treatment subgroups. Regimens vary considerably among the published studies, such that only broad categorizations of timing or dosing are appropriate for meta-analysis. Although the evidence suggests that some treatment regimens may provide greater benefit, further randomized controlled trials (RCTs) designed to address these specific hypotheses must be undertaken. Among the treatment regimen factors examined in RCTs, timing of initiation, dosing, and treatment duration currently show the most promise for further research.

6. What are the future research directions needed to better understand the risks, benefits, and alternatives to nitric oxide therapy for premature infants who receive respiratory support?

1. Understanding risks, benefits, and alternatives to inhaled nitric oxide (iNO) therapy for premature infants requires investigation of iNO's mechanisms of action through additional basic research in developmentally relevant experimental models. In particular, future animal and model system studies should focus on understanding the respective roles of dosing, delivery, and timing of therapy and of accompanying ventilation strategies, oxygen management, and concurrent therapies that optimize the benefits of iNO and reduce the risk of adverse short- or long-term effects. A clearer understanding of the pharmacology and toxicology of iNO in premature infants is needed to identify better markers of its toxicity and short-term risks. In addition, studies that focus on increasing tissue-specific production of endogenous nitric oxide should be considered.
2. Future trials for evaluation of safety and efficacy of iNO for premature infants should be informed by prior trials as well as by future studies in premature animals or other model systems. These trials and preclinical studies should examine both short- and long-term pulmonary and neurodevelopmental outcomes and investigate effect-modifying factors (e.g., pharmacokinetic, genetic, racial/ethnic, and disease risk factors).
3. Future randomized trials should be designed to assess variations in the timing, dose, and duration of treatment, to include a placebo control, to ensure a sample size sufficient to detect a significant interaction between gestational age category and treatment arm, and to consider an appropriate developmental window for efficacy and safety. The positive results of one multicenter trial, which was characterized by later timing, higher dose, and longer duration of treatment, require confirmation. Future trials should attempt to quantify the individual effects of each of these treatment-

- related variables (timing, dose, and duration), ideally by randomizing them separately.
4. Future trials should assess the long-term effects of iNO treatment. Important safety and efficacy questions require that study subjects be followed to a minimum of school age with standardized assessments of behavior, cognitive ability, neuroanatomy, and neurophysiology.
 5. Design of future efficacy and safety trials of iNO for premature infants should include interdisciplinary teams of experts in high-risk obstetrics, neonatology, pediatric pulmonology, pediatric neurology, neurodevelopmental follow-up, neonatal pharmacology, lung development, brain development, nitric oxide physiology, biostatistics, and clinical trial design, as well as ethicists, nurses, respiratory therapists, and families.
 6. Given the large differences in outcomes of death and bronchopulmonary dysplasia (BPD) among neonatal intensive care units, new strategies should be considered which improve outcomes by reducing neonatal intensive care unit-specific variations in care.
 7. In addition to the Panel's iNO research recommendations, future research should pursue promising strategies other than iNO.
 8. Delay between treatment use and assessment of important outcomes creates a barrier to rapid progress in testing potentially effective treatments. Biomarker, neuroimaging, pulmonary function testing, pulmonary imaging, and other techniques with potentially better predictive accuracy should be developed and tested.

Conclusions

1. Taken as a whole, the available evidence does not support use of inhaled nitric oxide (iNO) in early routine, early rescue, or later rescue regimens in the care of premature infants <34 weeks gestation who require respiratory support.
2. There are rare clinical situations, including pulmonary hypertension or hypoplasia, that have been inadequately studied in which iNO may have benefit in infants <34 weeks gestation. In such situations, clinicians should communicate with families regarding the current evidence on its risks and benefits as well as remaining uncertainties.
3. Basic research and animal studies have contributed to important understandings of iNO benefits on lung development and function in infants at high risk of BPD. These promising results have only partly been realized in clinical trials of iNO treatment in premature infants. Future research should seek to understand this gap.

4. Predefined subgroup and post hoc analyses of previous trials showing potential benefit of iNO have generated hypotheses for future research for clinical trials. Prior strategies shown to be ineffective are discouraged unless new evidence emerges. The positive results of one multicenter trial, which was characterized by later timing, higher dose, and longer duration of treatment, require confirmation. Future trials should attempt to quantify the individual effects of each of these treatment-related variables (timing, dose, and duration), ideally by randomizing them separately.
5. Based on assessment of currently available data, hospitals, clinicians, and the pharmaceutical industry should avoid marketing iNO for premature infants <34 weeks gestation.

Consensus Development Panel

Panel Chairperson: F. Sessions Cole, M.D.

Panel and Conference Chairperson
Park J. White, M.D. Professor of Pediatrics
Assistant Vice Chancellor for Children's Health
Vice Chairperson
Department of Pediatrics
Director
Division of Newborn Medicine
Washington University School of Medicine
Chief Medical Officer
St. Louis Children's Hospital
St. Louis, Missouri

Claudia Alleyne, M.D.

Medical Director
Neonatal Intensive Care Unit
Kaiser Permanente Anaheim Medical Center
Anaheim, California

John D.E. Barks, M.D.

Professor
Department of Pediatrics and
Communicable Diseases
University of Michigan Medical School
Director
Division of Neonatal-Perinatal Medicine
C.S. Mott Children's Hospital
University of Michigan Health System
Ann Arbor, Michigan

Robert J. Boyle, M.D., FAAP

Professor of Pediatrics
Associate Faculty
Center for Biomedical Ethics
Department of Pediatrics
Division of Neonatology
University of Virginia Medical Center
Charlottesville, Virginia

John L. Carroll, M.D., FAAP

Professor
Department of Pediatrics
College of Medicine
University of Arkansas for Medical Sciences
Section Chief, Pediatric Pulmonary Division
Arkansas Children's Hospital
Little Rock, Arkansas

Deborah Dokken, M.P.A.

Family Health Care Advocate
Consultant in Family-Centered Care
Chevy Chase, Maryland

William H. Edwards, M.D.

Professor and Vice Chair of Pediatrics
Neonatology Section Chief
Medical Director CHaD Nurseries
Children's Hospital at Dartmouth
Co-Director, Vermont Oxford Network
Lebanon, New Hampshire

Michael Georgieff, M.D.

Martin Lenz Harrison Professor of
Pediatrics and Child Psychology
Director
Division of Neonatology
Director
Center for Neurobehavioral Development
University of Minnesota School of
Medicine, Twin Cities
Minneapolis, Minnesota

Katherine Gregory, Ph.D., R.N.
Assistant Professor of Nursing
William F. Connell School of Nursing
Boston College
Nurse Scientist
Brigham and Women's Hospital
Chestnut Hill, Massachusetts

Michael V. Johnston, M.D.
Chief Medical Officer and Executive
Vice President
Blum/Moser Professor for Pediatric
Neurology
Kennedy Krieger Institute
Professor of Neurology, Pediatrics, and
Physical Medicine and Rehabilitation
Johns Hopkins University
School of Medicine
Baltimore, Maryland

Michael Kramer, M.D.
Scientific Director
Institute of Human Development, Child and
Youth Health
Canadian Institutes of Health Research
James McGill Professor
Departments of Pediatrics and of
Epidemiology, Biostatistics and
Occupational Health
McGill University Faculty of Medicine
Montreal Children's Hospital
Montréal, Québec
CANADA

Christine Mitchell, M.S., M.T.S., R.N.
Associate Director
Clinical Ethics
Division of Medical Ethics
Harvard Medical School
Director
Office of Ethics
Children's Hospital Boston
Boston, Massachusetts

Josef Neu, M.D.
Professor of Pediatrics
Director
Neonatology Fellowship Training Program
Division of Neonatology
Department of Pediatrics
College of Medicine
University of Florida, Gainesville
Gainesville, Florida

DeWayne M. Pursley, M.D., M.P.H.
Chair
Section on Perinatal Pediatrics
American Academy of Pediatrics
Assistant Professor of Pediatrics
Harvard Medical School
Chief
Department of Neonatology
Beth Israel Deaconess Medical Center
Boston, Massachusetts

Walter Robinson, M.D., M.P.H.
Senior Research Scientist
Center for Applied Ethics
Education Development Center, Inc.
Associate Professor of Pediatrics
Department of Pediatrics
Division of Pediatric Allergy, Immunology,
and Pulmonary Medicine
Center for Biomedical Ethics and Society
Vanderbilt University School of Medicine
Nashville, Tennessee

David H. Rowitch, M.D., Ph.D.
Professor of Pediatrics and
Neurological Surgery Investigator
Howard Hughes Medical Institute
Chief of Neonatology
University of California, San Francisco
San Francisco, California

Speakers

Steven H. Abman, M.D.

Professor
Department of Pediatrics
Director
Pediatric Heart Lung Center
Director
Ventilator Care Program
Co-Director
Pediatric Pulmonary Hypertension Program
University of Colorado School of Medicine
Children's Hospital
Aurora, Colorado

Marilee C. Allen, M.D.

Professor of Pediatrics
Johns Hopkins School of Medicine
Division of Neonatology
Johns Hopkins Children's Center
Neurodevelopmental Disabilities
Co-Director of Neonatal Intensive Care Unit
Development Clinic
Kennedy Krieger Institute
Baltimore, Maryland

Roberta A. Ballard, M.D.

Professor of Pediatrics
Division of Neonatology
Department of Pediatrics
University of California, San Francisco
Emeritus Professor of Pediatrics
University of Pennsylvania
San Francisco, California

Keith J. Barrington, M.D., M.B.Ch.B.

Professor of Pediatrics
University of Montreal
Chief of Neonatology
University Hospital Center, Sainte-Justine
Montréal, Québec
CANADA

Elizabeth A. Cristofalo, M.D., M.P.H.

Assistant Professor of Pediatrics
Neonatal-Perinatal Medicine
Johns Hopkins Children's Center
Johns Hopkins Hospital
Baltimore, Maryland

Maureen M. Gilmore, M.D.

Assistant Professor
Neonatal-Perinatal Medicine
Johns Hopkins Children's Center
Johns Hopkins Hospital
Division of Neonatology
Johns Hopkins Bayview Medical Center
Baltimore, Maryland

Alan E. Guttmacher, M.D.

Director
Eunice Kennedy Shriver National Institute
of Child Health and Human Development
National Institutes of Health
Bethesda, Maryland

Susan R. Hintz, M.D., M.S. Epi

Associate Professor of Pediatrics
Division of Neonatal Medicine and
Developmental Medicine
Stanford University School of Medicine
Director
Center for Comprehensive Fetal Health
Lucile Packard Children's Hospital
Palo Alto, California

Kathleen A. Kennedy, M.D., M.P.H.

Richard W. Mithoff Professor of Pediatrics
Director
Division of Neonatal-Perinatal Medicine
Director
M.S. in Clinical Research Degree Program
University of Texas-Houston Medical
School
Houston, Texas

John P. Kinsella, M.D.

Professor of Pediatrics
Section of Neonatology
Medical Director
Newborn/Young Child Transport Service
Director of Clinical Research
Pediatric Heart Lung Center
Children's Hospital
University of Colorado, Denver
Aurora, Colorado

Jean-Christophe Mercier, M.D., M.Sci.

Professor of Pediatrics
University of Paris 7 Denis Diderot
Chief
Department of Pediatric Emergency Care
Hôpital Robert-Debré
Paris
FRANCE

Barbara K. Schmidt, M.D., M.Sc.

Kristine Sandberg Knisely Chair
in Neonatology
Department of Pediatrics
University of Pennsylvania School
of Medicine
Children's Hospital of Philadelphia
Philadelphia, Pennsylvania

Michael D. Schreiber, M.D.

Professor and Executive Vice Chairperson
Department of Pediatrics
University of Chicago
Chicago, Illinois

Philip W. Shaul, M.D.

Professor of Pediatrics
Director
Division of Pulmonary and Vascular
Biology
Lowe Foundation Professor of Pediatric
Critical Care Research
Department of Pediatrics
University of Texas Southwestern Medical
Center at Dallas
Dallas, Texas

Roger F. Soll, M.D.

President
Vermont Oxford Network
Wallace Professor of Neonatology
Department of Pediatrics
University of Vermont College of Medicine
Burlington, Vermont

Robin H. Steinhorn, M.D.

Raymond and Hazel Speck Berry
Professor of Pediatrics
Vice Chairperson, Pediatrics
Chief
Division of Neonatology
Children's Memorial Hospital
Feinberg School of Medicine of
Northwestern University
Chicago, Illinois

Robert S. Tepper, M.D., Ph.D.

Mary Agnes Kennedy and Kathryn Kennedy
Weinberger Professor
Pediatric Pulmonology and Critical
Care Section
Department of Pediatrics
Herman B. Wells Center for
Pediatric Research
Indiana University School of Medicine
James Whitcomb Riley Hospital for
Children
Indianapolis, Indiana

Krisa P. Van Meurs, M.D.

Professor of Pediatrics, Neonatology
Associate Chief, Clinical Programs
Division of Neonatal and
Development Medicine
Associate Chairperson, Clinical Research
Department of Pediatrics
Stanford University School of Medicine
Lucile Packard Children's Hospital
Palo Alto, California

Michele C. Walsh, M.D., M.S.
Professor of Pediatrics
Case Western Reserve University
Medical Director
Neonatal Intensive Care Unit
Co-Chief
Division of Neonatology
Rainbow Babies & Children's Hospital
University Hospitals Case Medical Center
Cleveland, Ohio

Planning Committee:

Planning Chairperson: Rosemary D. Higgins, M.D.

Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
Center for Developmental and Perinatal Medicine
Eunice Kennedy Shriver National Institute of Child
Health and Human Development
National Institutes of Health
Bethesda, Maryland

Lisa Ahramjian, M.S.

Communications Specialist
Office of Medical Applications of Research
Office of the Director
National Institutes of Health
Bethesda, Maryland

Jennifer Miller Crowell, M.D.

Acting Director
Office of Medical Applications of Research
Office of the Director
National Institutes of Health
Bethesda, Maryland

Carol J. Blaisdell, M.D.

Medical Officer
Lung Developmental Biology and
Pediatric Pulmonary Diseases
Division of Lung Diseases
National Heart, Lung, and Blood Institute
National Institutes of Health
Bethesda, Maryland

Anthony G. Durmowicz, M.D.

Medical Officer
Division of Pulmonary and Allergy Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Silver Spring, Maryland

Stephanie Chang, M.D., M.P.H.

Medical Officer
Evidence-Based Practice Centers Program
Center for Outcomes and Evidence
Agency for Healthcare Research and Quality
Rockville, Maryland

Alan H. Jobe, M.D., Ph.D.

Professor of Pediatrics
Division of Pulmonary
Biology/Neonatology
Cincinnati Children's Hospital Medical
Center
Cincinnati, Ohio

F. Sessions Cole, M.D.

Panel and Conference Chairperson
Park J. White, M.D. Professor of Pediatrics
Assistant Vice Chancellor for Children's
Health
Vice Chairman, Department of Pediatrics
Director, Division of Newborn Medicine
Washington University School of Medicine
Chief Medical Officer
St. Louis Children's Hospital Division of
Newborn Medicine
St. Louis, Missouri

Barnett S. Kramer, M.D., M.P.H.

Associate Director for Disease Prevention
Office of Disease Prevention
Office of the Director
National Institutes of Health
Bethesda, Maryland

Kelli K. Marciel, M.A.

Communications Director
Office of Medical Applications of Research
Office of the Director
National Institutes of Health
Bethesda, Maryland

Planning Committee members provided their input at a meeting held August 19–21, 2009.
The information provided here was accurate at the time of that meeting.

Lawrence M. Noguee, M.D.
Professor
Department of Pediatrics
Johns Hopkins University School of
Medicine
Baltimore, Maryland

Tonse N.K. Raju, M.D., D.C.H.
Medical Officer
Pregnancy and Perinatology Branch
Eunice Kennedy Shriver National Institute
of Child Health and Human Development
National Institutes of Health
Bethesda, Maryland

Barbara K. Schmidt, M.D., M.Sc.
Director of Clinical Research
Division of Neonatology
Department of Pediatrics
Children's Hospital of Philadelphia
Philadelphia, Pennsylvania

Philip W. Shaul, M.D.
Professor of Pediatrics
Department of Pediatrics
University of Texas
Southwestern Medical Center
Dallas, Texas

Barbara Stonestreet, M.D.
Professor
Department of Pediatrics
The Warren Alpert Medical School
Brown University
Women and Infants' Hospital of Rhode
Island
Providence, Rhode Island

Robin H. Steinhorn, M.D.
Chief
Division of Neonatology
Children's Memorial Hospital
Chicago, Illinois

Linda J. Van Marter, M.D., M.P.H.
Associate Professor of Pediatrics
Newborn Medicine
Harvard Medical School
Children's Hospital Boston
Boston, Massachusetts

Planning Committee members provided their input at a meeting held August 19–21, 2009.
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Conference Sponsors

***Eunice Kennedy Shriver* National Institute
of Child Health and Human
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Acting Director

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Thomas R. Frieden, M.D., M.P.H.
Director