Evidence-Based Clinical Practice Guideline: Inhaled Nitric Oxide for Neonates With Acute Hypoxic Respiratory Failure

Robert M DiBlasi RRT-NPS FAARC, Timothy R Myers RRT-NPS, and Dean R Hess PhD RRT FAARC

Inhaled nitric oxide (INO) is a colorless, odorless gas that is also a potent pulmonary vasodilator. When given via the inhaled route it is a selective pulmonary vasodilator. INO is approved by the United States Food and Drug Administration (FDA) for the treatment of term and near-term neonates with hypoxemic respiratory failure associated with clinical or echocardiographic evidence of pulmonary arterial hypertension. A systematic review of the literature was conducted with the intention of making recommendations related to the clinical use of INO for its FDA-approved indication. Specifically, we wrote these evidence-based clinical practice guidelines to address the following questions: (1) What is the evidence for labeled use? (2) What are the specific indications for INO for neonates with acute hypoxemic respiratory failure? (3) Does the use of INO impact oxygenation, mortality, or utilization of extracorporeal membrane oxygenation (ECMO)? (4) Does INO affect long-term outcomes? (5) Is INO cost-effective therapy? (6) How is the appropriate dosing regimen and dose response to INO established? (7) How is the dose of INO titrated and weaned? (8) Which INO delivery system should be used? (9) How should INO be implemented with different respiratory support devices? (10) What adverse effects of INO should be monitored, and at what frequency? (11) What physiologic parameters should be monitored during INO? (12) Is scavenging of gases necessary to protect the caregivers? Using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) scoring system, 22 recommendations are developed for the use of INO in newborns. *Key words: inhaled nitric oxide; mechanical ventilation; neonate; persistent pulmonary hypertension of the newborn; hypoxemia.* [Respir Care 2010;55(12): 1717–1745. © 2010 Daedalus Enterprises]

Introduction

Inhaled nitric oxide (INO) is a colorless, odorless gas that is also a potent pulmonary vasodilator. When given via inhalation, NO rapidly diffuses across the alveolar-capillary membrane and is bound to hemoglobin, and thus has little effect on the systemic circulation.[1,2] This results

Robert M DiBlasi RRT-NPS FAARC is affiliated with the Respiratory Care Department, Seattle Children's Hospital and Center for Developmental Therapeutics, Seattle Children's Research Institute, Seattle, Washington. Timothy R Myers RRT-NPS is affiliated with Women's and Children's Respiratory and Procedural Services, and the Pediatric Heart Center, Rainbow Babies and Children's Hospital, and with the Department of Pediatrics, Case Western Reserve University; Cleveland, Ohio. Dean R Hess PhD RRT FAARC is affiliated with Respiratory Care Services, Massachusetts General Hospital, and with the Department of Anesthesia, Harvard Medical School, Boston, Massachusetts.

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Correspondence: Robert M DiBlasi RRT-NPS FAARC, Respiratory Care Department, Seattle Children's Hospital and Center for Developmental Therapeutics, Seattle Children's Research Institute, 1900 Ninth Avenue, Seattle WA 98101. E-mail: robert.diblasi@seattlechildrens.org.

in limiting the effect of INO to the lungs, making it a selective pulmonary vasodilator. There are several physiologic effects that make INO an appealing therapy for infants with pulmonary hypertension. INO can decrease pulmonary vascular resistance, improve ventilation-perfusion inequalities, and reduce right-to-left intra-cardiac shunting of blood through the foramen ovale and ductus arteriosus,[3] all of which can contribute to improved arterial oxygenation and hemodynamic stability.

Neonatal hypoxic respiratory failure may be caused by persistent pulmonary hypertension of the newborn (PPHN) and other diseases that contribute to pulmonary arterial hypertension. These diseases include respiratory distress syndrome, meconium aspiration syndrome, pneumonia, sepsis, congenital diaphragmatic hernia, and some congenital cardiac anomalies. In the early 1990s, several case studies and case series reported the use of INO for the treatment of PPHN. This was followed by several multicenter randomized controlled double-blinded studies of INO for PPHN. On December 23, 1999, the United States Food and Drug Administration (FDA) approved the use of INO for the treatment of term and near-term (> 34 wk) neonates with hypoxic respiratory failure associated with pulmonary hypertension.

The only FDA-approved formulation of INO is INOmax, marketed by Ikaria, Clinton, New Jersey. The trade name for INOmax and the specific labeled indication is

> INOmax, in conjunction with ventilatory support and other appropriate agents, is indicated for the treatment of term and near-term (> 34 wk) neonates with hypoxic respiratory failure associated with clinical or echocardiographic evidence of pulmonary hypertension, where it improves oxygenation and reduces the need for extracorporeal membrane oxygenation.

On September 23, 2005, the Therapeutic Products Directorate of Health Canada issued a Notice of Compliance for INOmax, NO for inhalation, in essence approving Ikaria to market NO for infants ≥ 34 weeks in Canada.

INO is commonly used as a front-line therapy in neonates with hypoxic respiratory failure associated with pulmonary hypertension. However, many practical questions remain related to its appropriate clinical use for its labeled indication. The cost of the drug has been a concern since its release. Its cost has a substantial impact on the operating costs of many hospitals. It appears that much of the increase in the use of the drug has been for indications that are off-label. The use of INO is increasingly used with premature infants, pediatric patients, and adults with hypoxemic respiratory failure. However, for the purpose of this evidence-based review and clinical practice guideline, we will focus only on the evidence related to the FDA labeled indications in neonates with hypoxic respiratory failure associated with pulmonary hypertension.

Accordingly, a systematic review of the literature was conducted with the intention of making recommendations related to the clinical use of INO for its FDA-approved indication. Specifically, we wrote these evidence-based clinical practice guidelines to address the following questions:

1. What is the evidence for labeled use?
2. What are the specific indications for INO for neonates with acute hypoxemic respiratory failure?
3. Does the use of INO impact oxygenation, mortality, or utilization of extracorporeal membrane oxygenation (ECMO)?
4. Does INO affect long-term outcomes?
5. Is INO cost-effective?
6. How is the appropriate dosing regimen and dose response to INO established?
7. How is the dose of INO titrated and weaned?
8. Which INO delivery systems should be used?
9. How should INO be implemented with different respiratory support devices?
10. What adverse effects of INO should be monitored, and at what frequency?
11. What physiologic parameters should be monitored during INO?
12. Is scavenging of gases necessary to protect the caregivers?

Methods

To identify the evidence addressing these questions, a PubMed (MEDLINE) search was conducted using the following search terms:

"Inhaled nitric oxide" with limits of English language, human studies, all child (0–18 y)

"Nitric oxide and neonate" with limits of English language, human studies, all child (0–18 y)

"Nitric oxide therapy" with limits of English language, human studies, all child (0–18 y)

"Nitric oxide administration" with limits of English language, human studies, all ages

"Nitric oxide delivery" with limits of English language, human studies, all ages

"Nitric oxide and monitoring" with limits of English language, human studies, all ages

The search timeframe included published papers indexed between January 1, 1990, and December 31, 2009. References and abstracts were retrieved into reference-management software (EndNote, ISI, Berkeley, California) for further analysis.

By inspection of their titles, references having no possible relevance to the study questions were eliminated. For the titles that remained, the abstracts were reviewed and assessed for relevance, and additional references were elim-

inated as appropriate. This process was conducted independently by 3 individuals, after which their reference lists were merged to provide the reference base for further analysis. Throughout the process of developing these guidelines, the authors surveyed cross-references to identify additional references to be added to the reference base for analysis. Results of the searches and inclusion and exclusion criteria resulted in the inclusion of 131 relevant articles (Fig. 1).

Data were extracted from the selected references using a standardized critique form. To validate this form and to establish the reliability of the review process, several references were initially evaluated by members of the committee during a face-to-face meeting. All references were then independently examined by at least two of the authors. The critiques were compared and differences were resolved using an iterative process.

Recommendations were based on a modification of the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) scoring system.[4] The strength of the recommendation is given a level of 1 when the benefits clearly outweigh the risks and burdens (or vice versa) for nearly all patients. A level of 2 is weaker and given when risks and benefits are more closely balanced or are more uncertain. The quality of the evidence is given a grade of A, B, C, or D for high, moderate, low, and very low, respectively.

The draft document was peer-reviewed by experts on the subject of INO therapy in newborns. Each of the reviewer's comments was carefully assessed and the document was further revised as appropriate.

What Is the Evidence for the Labeled Indication?

The most comprehensive systematic review and meta-analysis of the use INO therapy in term or near-term infants comes from the Cochrane Collaboration.[5] Only randomized trials were included in that review, resulting in 12 studies that were analyzed. The overall quality of the studies was variable. The highest quality studies were fully blinded, adequately powered, multi-center randomized controlled trials with external data-monitoring groups that examined clinically important outcomes.[6,7] Some studies were of intermediate quality, because they had variable degrees of blinding and examined primarily oxygenation outcome.[8-10] A third group of studies were single (or few) center studies that were unblinded, had very small sample sizes, and/or investigated short-term oxygenation responses.[11-15] Following this systematic review, the results of one additional prospective randomized controlled and unblinded multi-center trial was reported.[16]

What Are the Specific Indications for INO for Infants With Acute Hypoxemic Respiratory Failure?

This is a practical question facing the clinician at the bedside caring for a newborn with acute hypoxemic respiratory failure. It can be addressed by careful examination of the evidence from randomized controlled trials (Table 1)[7-22] and observational studies (Table 2).[23-45] The randomized controlled trials enrolled term or near-term newborns born at $\geq$ 34 weeks gestation. Although the criteria for post-partum age differed among those studied, patients were generally $<$ 5 days old and were treated for a maximum of 14 days.

All studies included some criteria for the severity of lung function and the degree of shunt. Although the oxygenation criteria differed to some extent among the studies, most were consistent with $P_{aO_2} < 100$ mm Hg on F_{IO_2}

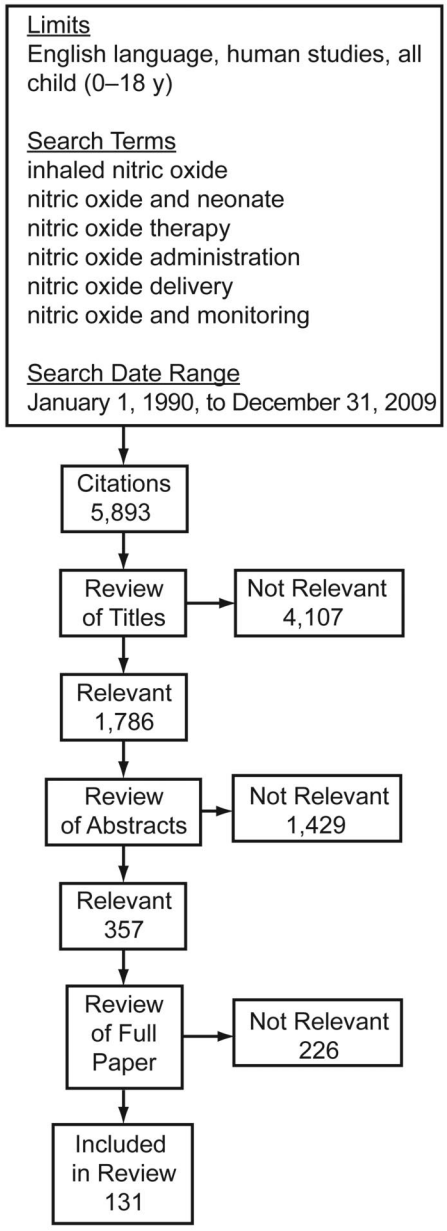

Fig. 1. Literature review process.

Table 1. Criteria for Initiating INO, From Randomized Controlled Trials

First Author	Study Design	Subjects	P_{aO_2}	Oxygenation Index	Exclusions
Barefield[14] 1996	Single-center RCT	8 control 9 INO Echo evidence of PPHN	P_{aO_2} < 100 mm Hg on F_{IO_2} 1.0	Not stated	< 35 wk, weight ≤ 2 kg, major congenital anomaly, congenital diaphragmatic hernia, profound asphyxia, substantial bleeding
NINOS[7] 1997	Multi-center RCT	121 control 114 INO	Not stated	≥ 25 2 at least 15 min apart	< 34 wk gestation, > 14 d of life, CHD
NINOS[17] 1997	Multi-center RCT	28 control 25 INO All with CDH	Not stated	≥ 25 2 at least 15 min apart	< 34 wk gestation, > 14 d of life
Roberts[8] 1997	Multi-center RCT	28 control 30 INO Echo evidence of PPHN	≤ 55 mm Hg on F_{IO_2} 1.0 on 2 consecutive determinations 30 min apart	Not stated	< 37 wk gestation, previous ECMO or high-frequency ventilation, CDH, suspected lung hypoplasia, CHD, uncorrected hypotension, polycythemia, pneumothorax, lethal chromosomal abnormality
Kinsella[18] 1997	Multi-center RCT	107 INO 98 HFOV Echo evidence of PPHN	P_{aO_2} < 80 mm Hg on F_{IO_2} 1.0	Not stated	Neonates < 34 wk gestation, urgent need for ECMO, lethal congenital anomaly
Day[11] 1997	Single-center RCT	11 control 39 INO Echo evidence of PPHN	Not stated	≥ 25	Congenital heart disease
Wessel[12] 1997	Single-center RCT	23 control 26 INO Echo evidence of PPHN	P_{aO_2} < 100 mm Hg on F_{IO_2} 1.0	Not stated	< 34 wk, congenital heart disease, congenital diaphragmatic hernia
Davidson[10] 1998	Multi-center RCT	41 control 114 INO Echo evidence of PPHN	P_{aO_2} 40–100 mm Hg on F_{IO_2} 1.0, mean airway pressure ≥ 10 cm H_2O	Not stated	< 37 wk gestation, > 72 h of life, lung hypoplasia syndromes, congenital heart disease, > grade 2 intracranial hemorrhage, uncorrected polycythemia, mean systemic arterial pressure < 35 mm Hg, lethal syndrome, chromosomal abnormality, use of intravenous vasodilators after entry criteria were met at study site, uncontrollable coagulopathy
Cornfield[13] 1999	Multi-center RCT	23 control 15 INO Echo evidence of PPHN	P_{aO_2} < 100 mm Hg on 2 blood gases 60 min apart	≥ 25 on 2 separate blood gases 60 min apart	Neonates ≤ 34 wk gestation, infants > 7 d old, congenital anomaly, intraventricular hemorrhage of grade 3 or 4, emergency need for ECMO, CHD
Franco-Belgian INO Trial Group[19] 1999	Multi-center RCT	52 control 55 INO	Not stated	15–40	Lethal congenital anomaly, CHD, CDH, pulmonary hypoplasia; refractory septic shock; abnormal neurological status due to severe birth asphyxia or grade 3 or 4 intracranial hemorrhage
Clark[6] 2000	Multi-center RCT	122 control 126 INO Echo evidence of PPHN	Not stated	> 25	< 34 wk gestation, > 4 d of life, urgent need for ECMO, refractory hypotension (mean arterial pressure < 35 mm Hg), profound hypoxemia (P_{aO_2} < 30 mm Hg), lethal congenital anomaly, substantial bleeding diathesis, active seizures, and history of severe asphyxia
Christou[15] 2000	Single-center RCT	20 control 21 INO Echo evidence of PPHN	P_{aO_2} < 100 mm Hg on F_{IO_2} 1.0	Not stated	Major congenital anomaly; gestational age ≤ 34 wk
Finer[20] 2001	Single-center RCT of 2 INO doses	15 at 1–2 ppm 21 at 10–20 ppm	P_{aO_2} < 100 mm Hg on 2 blood gases taken at least 30 min apart within a 2-h period	≥ 10	> 34 wk gestation, > 30 d old, CDH, CHD, intraventricular hemorrhage grade 2 or worse, platelets < 100,000, decision made not to provide full medical treatment
Sadiq[21] 2003	Multi-center RCT	42 Control 43 INO Echo evidence of PPHN	$P_{(A\text{-}a)O_2}$ 500–600 mm Hg on 2 consecutive blood gases at least 1 h apart on F_{IO_2} 1.0	Not stated	≤ 2 kg, lethal malformation, no surfactant
Konduri[22] 2004	Multi-center RCT	149 control 150 INO Echo evidence of PPHN	Not stated	15–24 on F_{IO_2} ≥ 0.80 on any 2 arterial blood gases at least 15 min and ≤ 12 h apart	< 34 wk gestation, > 14 d old, life-threatening congenital malformations, CHD other than patent ductus arteriosus or patent foramen ovale, CDH, previous INO therapy, high-frequency jet ventilation

INO = inhaled nitric oxide
RCT = randomized controlled trial
CHD = congenital heart disease
PPHN = persistent pulmonary hypertension of the newborn
ECMO = extracorporeal membrane oxygenation
HFV = high-frequency ventilation
HFOV = high-frequency oscillatory ventilation
$P_{(A\text{-}a)O_2}$ = alveolar-arterial oxygen difference
CDH = congenital diaphragmatic hernia

Table 2. Criteria for Initiating INO, From Observational Studies

First Author	Study Design	Subjects	P_{aO_2}/Oxygenation	Oxygenation Index	Exclusions
Roberts[23] 1992	Prospective case series	6 Clinical evidence of PPHN	Not stated	Not stated	None stated
Kinsella[24] 1992	Prospective case series	9 Echo evidence of PPHN	$P_{aO_2} < 40$ mm Hg	> 40	None stated
Kinsella[25] 1993	Prospective case series	9 Echo evidence of PPHN	$P_{aO_2} < 40$ mm Hg	> 40	Gestational age ≤ 34 wk
Kinsella[26] 1994	Prospective case series	15 PPHN	ECMO criteria	ECMO criteria	None stated
Finer[27] 1994	Prospective case series	23 Echo evidence of PPHN	F_{IO_2} 1.0	≥ 20 after surfactant	< 35 wk gestation, lethal malformations, structural cardiac disease, IVH
Buhrer[28] 1995	Prospective case series	10 Hypoxemic respiratory failure	$F_{IO_2} > 0.8$ for ≥ 16 h, or > 0.9 for ≥ 8 h P_{aO_2} not stated	Not reported	< 14 d old, birth weight < 1,500 g, CHD, IVH, excessive hyperbilirubinemia, systemic hypotension, severe bilateral lung hypoplasia
Turbow[29] 1995	Prospective case series	13 Echo evidence of PPHN	$P_{(A\text{-}a)O_2} > 610$ mm Hg	> 35–40	Gestational age < 36 wk
Muller[30] 1996	Prospective case series	10 PPHN	$P_{aO_2} < 40$ mm Hg for > 2 h or < 50 mm Hg > 4 h	> 40	< 35 wk gestational age, CHD, IVH, family history of red blood cell disease
Stranak[31] 1996	Retrospective case series	15 Echo evidence of PPHN	$P_{(A\text{-}a)O_2} > 550$ mm Hg on F_{IO_2} 1.0	> 25	< 35 wk gestation, severe CDH, severe IVH, irreversible lung injury, lethal chromosomal abnormalities, prolonged metabolic acidosis, severe circulatory failure, prolonged bleeding time or coagulopathy, treated with surfactant < 4 h prior to INO
Demirakça[32] 1996	Prospective case series	17 Echo evidence of PPHN	Not stated	> 20	< 34 wk gestational age
Goldman[33] 1996	Prospective case series	25 Echo evidence of PPHN	Not stated	> 25	Irreversible cardiopulmonary disease
Lönnqvist[34] 1997	Prospective cases series	26 Echo evidence of PPHN	Not stated	25–40	> 7 d old, irreversible disease, severe uncorrected cardiac malformation, systemic hypotension, vasodilator < 1 h prior to inclusion, IVH, untreated pneumothorax, surfactant therapy < 6 h prior to inclusion
Hoffman[35] 1997	Retrospective case series	50 Echo evidence of PPHN	$P_{(A\text{-}a)O_2} > 600$ mm Hg	> 40	Gestational age ≤ 35 wk, lethal chromosomal abnormality, IVH
Laubscher[36] 1997	Prospective multi-center case series	30 Rescue therapy	$F_{IO_2} > 0.5$ P_{aO_2} not stated	Not stated	Bleeding tendency or low platelet count, IVH
Biban[37] 1998	Prospective case series	20 Echo evidence of PPHN	F_{IO_2} 1.0	> 25	Gestational age < 34 wk, structural heart defect
Mok[38] 1999	Retrospective case series	32 PPHN	Not stated	Not stated	< 36 wk gestation, with CHD
Lönnqvist[39] 1999	Retrospective case series	20 Echo evidence of PPHN	Not stated	Not stated	INO used as a last resort before ECMO
Kossel[40] 2000	Prospective case series	34	Not stated	> 40	Gestational age ≤ 34 wk, CHD, IVH, mechanical ventilation > 14 d
Tworetzky[41] 2001	Prospective case series	7 Echo evidence of PPHN	$P_{aO_2} < 75$ mm Hg	Not stated	Not stated
Gupta[42] 2002	Retrospective case series	241 Echo evidence of PPHN	$P_{aO_2} < 40$ mm Hg O_2 saturation < 80%	Not stated	Not stated
Hwang[43] 2004	Retrospective case series	51 PPHN	Echo or clinical evidence of PPHN	Not stated	Not stated
Guthrie[44] 2004	Retrospective multi-center case series (Duke Neonatal Nitric Oxide Registry)	476	Not stated	Not stated	Congenital anomaly
Fakioglu[45] 2005	Prospective case series	34	$P_{(A\text{-}a)O_2} > 500$ mm Hg for > 4 h	> 20	Congenital diaphragmatic hernia or congenital heart disease

INO = inhaled nitric oxide
PPHN = persistent pulmonary hypertension of the newborn
ECMO = extracorporeal membrane oxygenation
IVH = intraventricular hemorrhage
CHD = congenital heart disease
$P_{(A\text{-}a)O_2}$ = alveolar-arterial oxygen difference

1.0 and an oxygenation index (OI) > 25. Echocardiographic evidence of PPHN was used in some studies, but not all.

INO does not benefit newborns with congenital diaphragmatic hernia, and its use is not indicated in those patients.[7] In addition, there are concerns that outcomes may be worse in infants with congenital diaphragmatic hernia who received INO, compared to controls. Data are available from 2 studies related to the use of INO with congenital diaphragmatic hernia.[7,17] The incidence of death or requiring ECMO was 40/46 in controls and 36/38 with INO (relative risk 1.09, 95% CI 0.95–1.26). Mortality was not affected by use of INO (18/46 controls, compared with 18/38 with INO, relative risk of death 1.20, 95% CI 0.74–1.96). There were no significant differences in oxygenation outcomes between the 2 groups 30 min following study gas initiation.[7] Moreover, there was a significant increase ($P = .04$) in the requirement for ECMO in the group receiving INO (31/46 controls, compared with 32/38 with INO, relative risk 1.27, 95% CI 1.00–1.62).

The use of INO therapy has been described for the preoperative and postoperative management of hypoxic infants with pulmonary hypertension related to congenital heart disease. In the preoperative cases, pulmonary hypertension can arise from increased pulmonary blood flow and consequent remodeling of the pulmonary vascular bed. Cardiac catheterization studies have demonstrated that pulmonary vascular resistance and pulmonary arterial pressure are lower in infants with congenital heart disease treated with INO therapy (20 ppm) than with F_{IO_2} 1.0 ($P < .02$).[46]

Cardiopulmonary bypass during repair of congenital heart disease has been associated with severe lung inflammation and increases in pulmonary hypertension in the immediate postoperative period.[47] These postoperative hypertensive crises occur in approximately 7% of patients with congenital heart disease, with an associated mortality of about 29%.[48] In these infants, INO therapy administered in the postoperative period was shown to decrease pulmonary arterial pressure[49] and increase cardiac output.[50]

In a Cochrane review, Bizzarro and Gross[51] evaluated outcomes related to the use of INO therapy for the postoperative management of patients with congenital heart disease necessitating repair. Based on a low enrollment of individual studies, the authors concluded that postoperative use of INO does not result in a significant reduction in mortality and the number of pulmonary hypertensive crises, nor does its use appear to significantly alter hemodynamics or result in any improvement in other clinically relevant outcomes such as arterial oxygenation. This analysis consisted of 4 randomized controlled trials in patients who ranged in age from 1 day to 20 years of age. However, it is unclear how many of the infants included in these studies met the FDA label claim. Thus, there are insufficient data to support the routine use of INO therapy in postoperative management of hypoxic term or near-term infants with congenital heart disease.

Although it has not been studied, strong physiologic rationale supports the contraindication of using INO in newborns with congenital heart disease dependent on right-to-left shunt. Although also not studied, strong ethical rationale supports the contraindication of using INO in newborns with lethal congenital anomalies and congestive heart failure.

Does the Use of INO Impact Oxygenation, Mortality, or ECMO Utilization?

A major question surrounding the use of INO therapy is whether it alters the clinical course of critically ill, hypoxemic infants who have not responded to conventional methods of respiratory support. As mentioned previously, a comprehensive Cochrane review and meta-analysis, summarized by Finer and Barrington,[5] was designed to determine whether INO therapy in the term or near-term hypoxemic infant improves oxygenation and reduces mortality and ECMO utilization.

The 2 indices of oxygenation typically reported in the literature related to INO are the OI and P_{aO_2}. OI is calculated as:

$$OI = [(F_{IO_2} \times \bar{P}_{aw})/P_{aO_2}] \times 100$$

where $\bar{P}_{aw}$ is mean airway pressure. OI at 30–60 min after initiation of INO was reported in 6 studies.[7-9,11,12,15] All but one trial[15] reported a significant improvement in OI following INO therapy. The meta-analysis by Finer and Barrington,[5] showed that OI within 30–60 min of starting INO is significantly lower (weighted mean difference −9.59, 95% CI 12.50 to −6.68). P_{aO_2} 30–60 min after treatment was evaluated in 6 studies.[7-9,11,12,15] All studies except one[15] reported a significant benefit of INO. The meta-analysis[5] shows that P_{aO_2} 30–60 min after treatment was significantly higher in the INO group (weighted mean difference 45.5 mm Hg, 95% CI 34.7–56.3).

Death or requirement for ECMO was reported in 8 trials. In 6 studies,[7-9,11,13,16] crossover use of INO in controls who did not respond to initial treatment was not allowed, while in the remaining 2 studies[10,15] crossover use of INO in controls was permitted. Analysis[7-9] of the 6 studies[6,8,10,12,15,17] that did not allow crossover use of INO in controls found a statistically significant reduction in the combined outcome of death and requirement for ECMO (relative risk 0.65, 95% CI 0.55–0.76, risk difference −0.20, 95% CI −0.27 to −0.13) (Fig. 2). None of the studies that reported mortality found a significant effect on this outcome alone (relative risk 0.91, 95% CI 0.60–1.37) (Fig. 3). Requirement for ECMO was reported in 8 studies, and the meta-

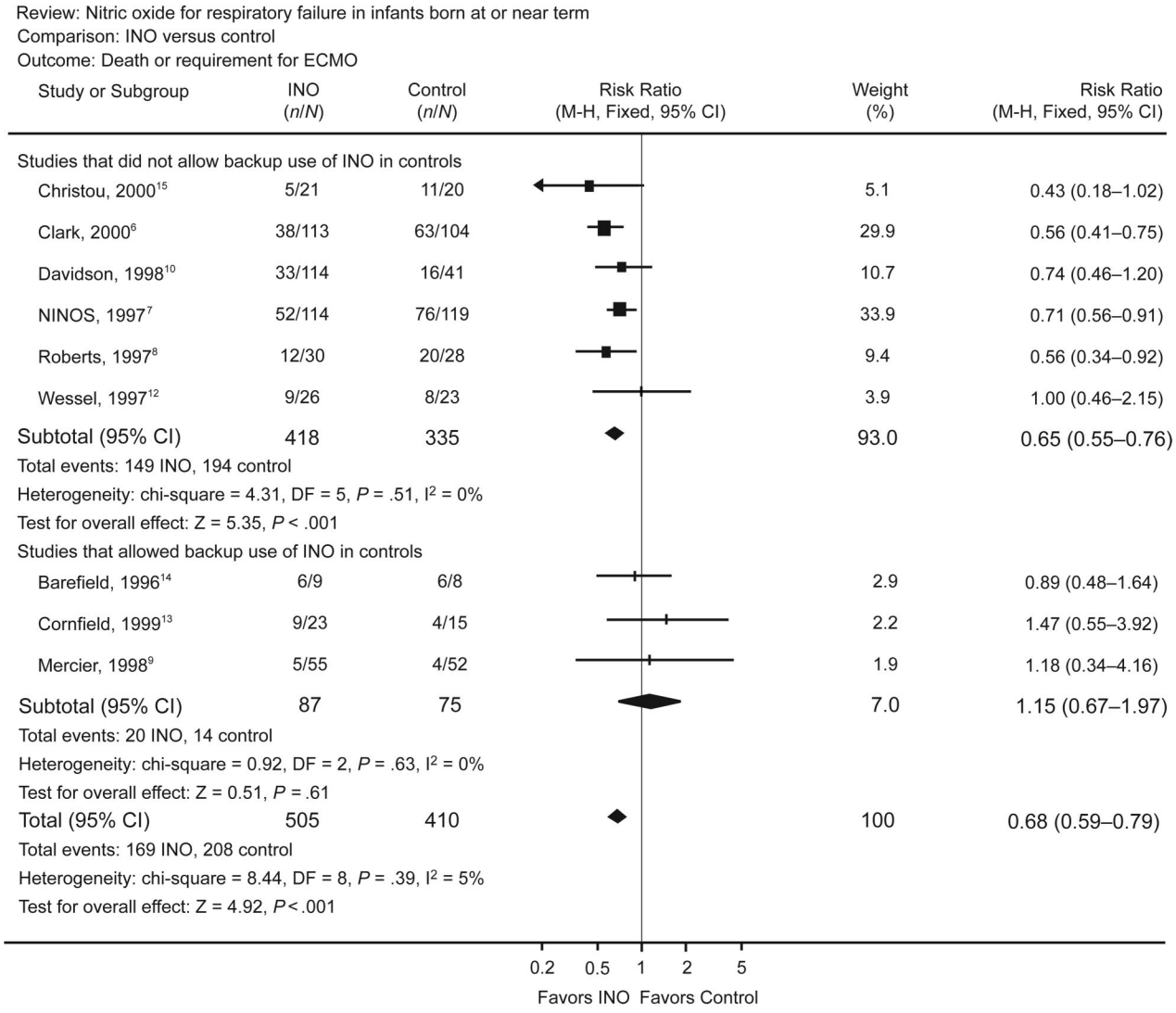

Fig. 2. Analysis of studies of inhaled nitric oxide (INO) that used the outcomes of survival or requirement for extracorporeal membrane oxygenation (ECMO) with and without backup use of INO in controls. M-H = Mantel-Haenszel risk ratio. NINOS = Neonatal Inhaled Nitric Oxide Study Group. (Adapted from Reference 5, with permission.)

analysis showed a significant reduction in requirement for ECMO (relative risk 0.63, 95% CI 0.54–0.75, risk difference −0.19, 95% CI −0.26 to −0.12). The number-needed-to-treat with INO to prevent one infant from requiring ECMO is 5.3 (95% CI 3.8–8.3) (Fig. 4).

The majority of infants described in the Cochrane meta-analysis by Finer and Barrington[5] were described as being extremely ill when INO therapy was initiated. A number of studies explored whether outcomes are better when INO therapy is instituted earlier in the disease course.

Konduri et al[22] reported that INO improves oxygenation but does not reduce the combined incidence of ECMO/mortality when initiated at an OI of 15–25, compared with initiation at OI ≥ 25, suggesting no benefit in terms of outcome with initiation of INO earlier in the disease process. The Franco-Belgian Collaborative NO trial group[19] evaluated outcomes in mechanically ventilated pre-term (< 33 wk) and near-term infants (≥ 33 wk) treated with early (OI 12.5–30) and later (OI 15–40) INO therapy at 10 ppm. In the near-term infants, low-dose INO therapy instituted early in the course of respiratory failure significantly improved oxygenation, and shortened the duration of mechanical ventilation and stay in the intensive care unit.

González et al[16] evaluated whether early treatment with INO therapy in newborns with moderate respiratory failure improves oxygenation and attenuates the development of severe hypoxemic respiratory failure. Mechanically ventilated infants were randomized to receive INO therapy as: (1) an early method of therapy (with OI between 10 and

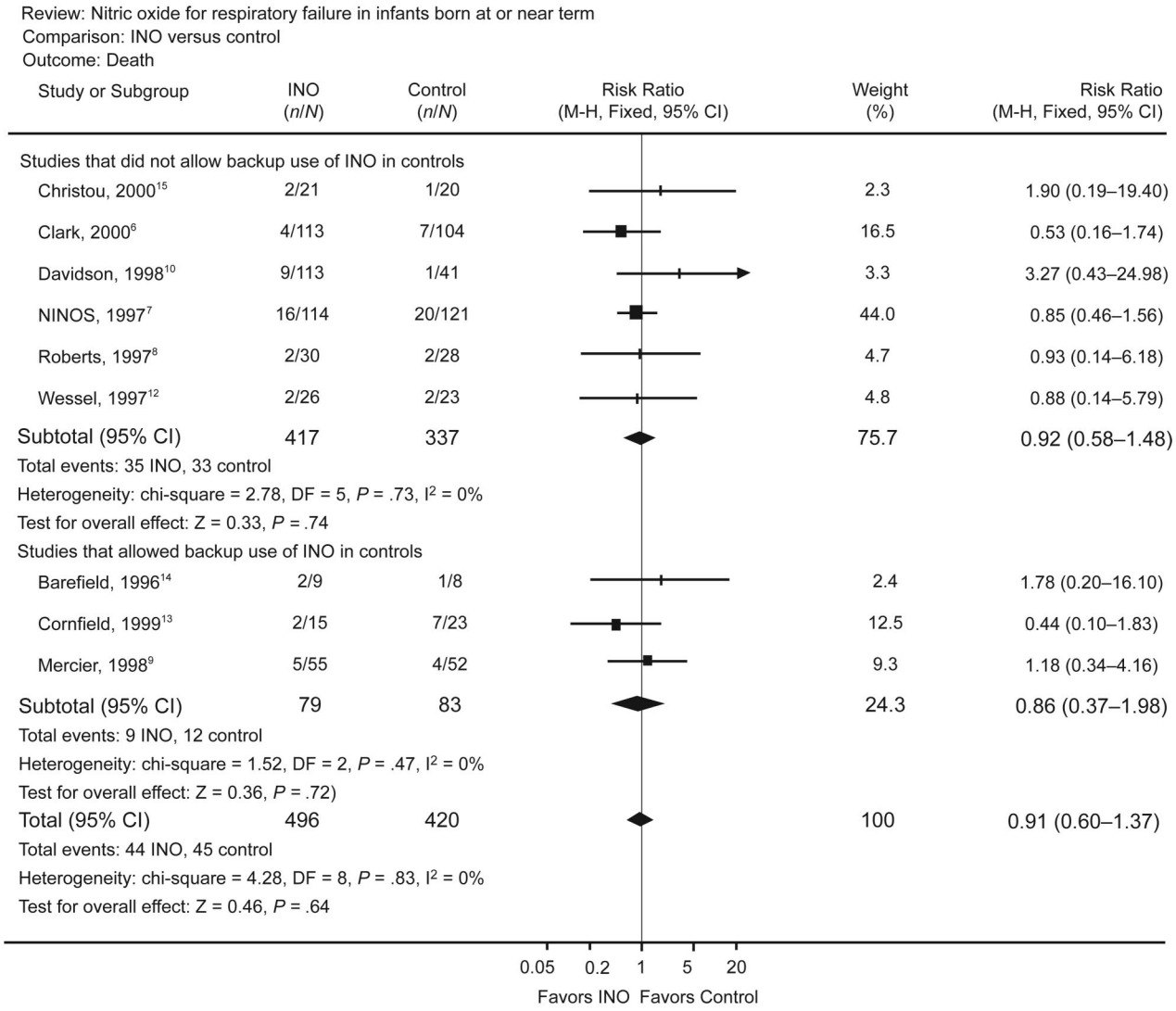

Fig. 3. Analysis of studies of inhaled nitric oxide (INO) that used the outcome of survival with and without backup use of INO in controls. M-H = Mantel-Haenszel risk ratio. NINOS = Neonatal Inhaled Nitric Oxide Study Group. (Adapted from Reference 5, with permission.)

30), or (2) when infants, being managed with F_{IO_2} 1.0 had OI > 40. In the early-INO group ($n = 28$), mean OI decreased significantly at 4 hours ($P < .05$) and remained lower over 48 hours. In the control group ($n = 28$), OI increased and remained significantly higher over the subsequent 48 hours ($P < .001$) following administration of INO. The median requirement for oxygen therapy was significantly less in the early INO group than in the control group ($P < .003$). The findings of that study suggest that there may be some clinical benefit to initiating INO therapy earlier in the disease process.

Does INO Therapy Affect Long-Term Outcomes?

Long-term outcomes were evaluated in 8 studies of different designs and methodological validity (Table 3).[52-59] For survivors of the 1997 Neonatal Inhaled Nitric Oxide Study Group (NINOS) study,[8] there was no significant difference in the occurrence of neurodevelopmental sequelae between the INO and control infants.[57] There were no differences in the occurrence of hearing impairment or in infant development scoring systems. The occurrence of seizures was less in the INO infants (4/85 INO infants, compared with 13/87 controls, $P = .046$). There were no differences in requirement for later hospital readmission, use of home medications, apnea monitors, home oxygen, use of gastrostomy tubes, or requirement for speech therapy. Survivors with congenital diaphragmatic hernia had comparable neurodevelopmental outcomes at follow-up.

Rosenberg et al[52] conducted a prospective observational longitudinal medical and neurodevelopmental follow-up of 51 infants treated as neonates for PPHN with INO. The

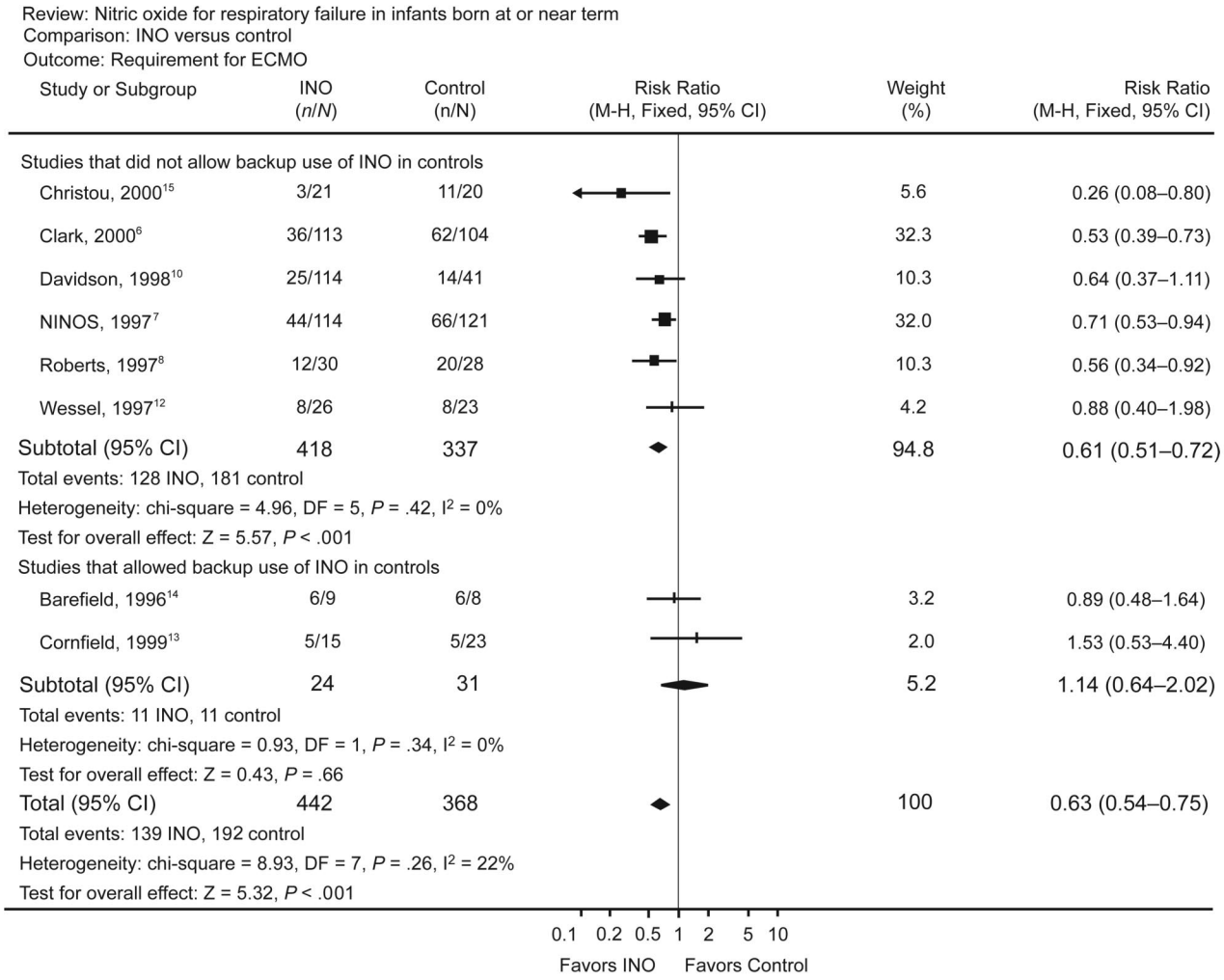

Fig. 4. Analysis of studies of inhaled nitric oxide (INO) that used the outcome of requirement for extracorporeal membrane oxygenation (ECMO) with and without backup use of INO in controls. M-H = Mantel-Haenszel risk ratio. NINOS = Neonatal Inhaled Nitric Oxide Study Group. (Adapted from Reference 5, with permission.)

Table 3. Studies of Long-Term Outcomes in Patients Who Received INO at Birth

First Author	Year	Study Design	Subjects
Rosenberg[52]	1997	Observational cohort	51
Dobyns[53]	1999	Observational cohort	22
Lipkin[54]	2002	Multi-center RCT	155 (41 control, 114 INO)
Clark[55]	2003	Multi-center RCT	201 (total control and INO)
Ichiba[56]	2003	Observational cohort	18
NINOS[57]	2000	Multi-center RCT	173 (88 control, 85 INO)
Ellington[58]	2001	Multi-center RCT	60 (25 control, 35 INO)
Konduri[59]	2007	Multi-center RCT	199 (149 control, 150 INO)

INO = inhaled nitric oxide
RCT = randomized controlled trial

original number of treated infants was 87, of whom 62 survived, 51 were seen at 1 year of age, and 33 completed a 2-year evaluation. The 1-year and 2-year follow-up of the INO infants found 11.8% (1-year) and 12.1% (2-year) rates of severe neurodevelopmental disability. Rosenberg et al concluded that medical and neurodevelopmental outcomes were similar to those reported in non-treated PPHN neonatal patients.

Dobyns et al[53] investigated whether the use of INO for severe PPHN causes impaired lung function during infancy. It was a prospective study of lung function in 22 infants who received ($n = 15$) or did not receive ($n = 7$) INO, and were compared to healthy control infants ($n = 18$). Passive respiratory mechanics and functional residual capacity were measured. No differences were found in lung function between treatment groups and healthy control infants of the same age. Dobyns et al concluded that INO for

the treatment of severe PPHN does not alter lung function during early infancy.

Lipkin et al[54] evaluated the medical and neurodevelopmental outcomes of children with moderately severe PPHN treated with or without INO. This was a follow-up at 1 year of patients enrolled in the Davidson et al study.[10] From an initial enrollment of 155 subjects, there was follow-up for 133 of the 144 children who survived. No significant differences between the placebo and INO groups were seen for any long-term outcomes. Re-hospitalization occurred in 22%, and growth did not differ. The composite neurodevelopment and audiologic outcome showed impairment in 46% of the infants. There were major neurologic abnormalities in 13%, cognitive delays in 30%, and hearing loss in 19% of the infants. Adverse outcomes were the same in INO and control groups.

Clark et al[55] reported the 1-year follow-up of patients enrolled in their randomized controlled trial of INO.[7] There was no difference in 1-year mortality between infants who received INO and controls. There were no inter-group differences in the numbers of patients who required medications for pulmonary disease or supplemental oxygen. The number of neonates reported to have an abnormal neurological examination or developmental delay was also similar in both groups. Clark et al concluded that use of low-dose INO reduces the use of ECMO without increasing the incidence of adverse outcomes at 1 year of age.

Ellington et al[58] assessed 60 of 83 survivors of a randomized controlled trial of INO.[13] No differences were found in pulmonary, neurologic, cognitive, behavioral, or neurosensory outcomes; hospital readmission rates; or parental ratings of child's health. The overall neurologic handicap rate was 15%, and the rate of hearing deficit was 7%. The rate of important behavioral problems was 26%. Levels of satisfaction expressed were high for each group. No differences in parental ratings were found between groups. The authors concluded that no adverse health or neurodevelopmental outcomes were observed among infants treated with INO therapy. Enrollment in either arm of this randomized controlled trial did not seem to affect parental satisfaction with the hospital care that their child received.

Ichiba et al[56] described the outcomes at 3 years in 18 term and near-term infants treated with INO. None of the infants had substantial sensorial hearing loss at 3 years. A third of the infants had reactive airways disease at 18 months, but 3 infants showed spontaneous resolution by 3 years. One infant was diagnosed with mild neurodevelopmental disability.

Konduri et al[59] performed a neurodevelopmental follow-up in survivors at 18–24 months, who were supported with early INO (OI 15–25) or a standard approach (OI $\geq$ 25).[19] There were no differences in neurodevelopmental impairment or hearing loss between the 2 groups.

Is INO Therapy Cost-Effective?

A concern related to the use of INO is its expense. The cost-effectiveness of this therapy has been explored in several studies. Lönnqvist et al[39] reported that the cost of INO compares favorably to ECMO. However, that analysis is dated and does not apply to the current costs of INO. Truog et al[60] calculated the charges for INO therapy and for ECMO for each patient, and concluded that INO can reduce costs by avoiding ECMO. Neither of those studies used sophisticated cost-effective analysis strategies.

Jacobs et al[61] conducted a cost-effectiveness analysis based on 123 subjects enrolled in the Canadian arm of 2 parallel randomized controlled trials of INO for hypoxemic respiratory failure. It was conducted from the perspective of the provider and included cost until hospital discharge. Costs were estimated from the resources used at a single center. For babies without congenital diaphragmatic hernia, Jacobs et al found that patients receiving INO therapy had mean costs of $2,404 United States dollars more than patients receiving placebo, but that difference was not statistically significant. ($P = .25$). There was no statistically significant difference in reported mortality. In a follow-up study,[62] Jacobs et al incorporated 18–24-month follow-up cost and outcome data on the 96 babies without congenital diaphragmatic hernia, 68 of whom completed follow-up (20 died). There were no statistically significant differences in costs between treated and non-treated infants reported.

Lorch et al[63] created a decision model using outcomes data from 6 published randomized controlled trials of INO in hypoxemic newborns and from a cohort of 123 babies with PPHN treated at a single hospital over an 11-year period. Costs were estimated from the resources used by the single-center cohort. They conducted their analysis from the United States societal perspective. In the study, INO increased the cost of care by $1,141 per infant, with a cost-effectiveness of $33,234 per life saved and $19,022 per Quality-Adjusted Life Year (QALY) gained (with cost analysis from intervention to 1 year post-discharge). Extending the time for cost analysis to lifetime improved the ratio to $976 per QALY.

Angus et al[64] used a decision model to assess the cost-effectiveness of INO, using the outcome data from the 2 largest randomized controlled trials. Several sources were used to convert resources to costs, including an analysis of the detailed hospital bills of 260 babies referred to 1 of 4 ECMO centers for possible ECMO treatment. Their analysis was conducted from the United States societal perspective. They reported that if INO is used only in ECMO centers it is both more effective and cheaper than placebo (cost savings of $1,880 per case, 95% CI $7,420 cheaper to $3,550 more expensive). The cost savings was predominantly due to decreased need for ECMO in the INO group.

The cost-effectiveness was $62,666 saved per QALY. The relatively small sample sizes of the 2 trials on which the analyses are based led to considerable uncertainty around the point estimates of cost-effectiveness. It should be noted that these cost-effectiveness studies were based on the assumption of on-label use, and the time horizon was restricted to the first year of life, conservatively assuming that all costs and effects of INO have disappeared at 1 year.

How Is the Appropriate Dosing Regimen and Dose Response to INO Established?

Starting doses of 5–20 ppm were used in randomized controlled trials (Table 4) and observational trials (Table 5) of INO in newborns. Evidence is lacking for benefit of doses > 20 ppm. In the NINOS study,[8] infants with severe hypoxemia were randomized to receive an F_{IO_2} of 1.0 (placebo control gas) or INO (experimental gas). For infants who did not respond to 20 ppm INO or placebo, similar proportions of the INO group and the control group had at least partial responses to 80 ppm INO or placebo as well. However, infants who had complete responses at 20 ppm did not have a similar response when INO was increased to 80 ppm. In the Davidson et al study[10] there were no dose-dependent differences between the 5, 20, and 80 ppm and its ability to produce a sustained improvement in oxygenation. In that study, methemoglobinemia (defined as > 7%) occurred only in the 80 ppm group. In a study by Cornfield et al,[13] INO at 2 ppm did not acutely improve oxygenation or prevent clinical deterioration, but did attenuate the rate of clinical deterioration. Infants who received 20 ppm had an acute improvement in oxygenation only if they were not previously treated with 2 ppm. Cornfield et al concluded that initial treatment with a subtherapeutic dose of INO may diminish the clinical response to 20 ppm. Finer et al[20] reported that INO at doses as low as 1–2 ppm was as efficacious as 10 or 20 ppm. An initial dose of 1–2 ppm did not differ significantly from an initial dose of 10–20 ppm in terms of improving P_{aO_2}, OI, or response rate. The length of time that infants required INO did not differ by the initial dose, but more infants in the low-dose group required dose escalation, compared with the high-starting-dose group. The authors of the Cochrane Review[5] concluded that, on the basis of the evidence presently available, it appears reasonable to use INO with an initial concentration of 20 ppm for term and near-term infants with hypoxic respiratory failure who do not have a diaphragmatic hernia.

For the studies that evaluated the initial response to INO therapy, oxygenation criteria were evaluated. In those studies, INO therapy was typically discontinued if a response could not be demonstrated. Due to the rapid onset of action of INO, a response, if present, can be seen quickly (within 1 hour). Evidence is lacking for benefit of continuing INO therapy in patients who do not demonstrate a response in terms of improved oxygenation. Due to the costs associated with INO therapy, its continued use when an improvement in oxygenation has not been demonstrated cannot be supported by the available evidence.

It is possible that non-response to INO is related to a lack of adequate ventilation and/or lung recruitment (eg, the gas does not reach all portions of the lung). Thus, when INO is initiated, the clinician should ensure (as much as possible) that the lungs are adequately inflated and that sufficient mean airway pressure is being applied to maintain end-expiratory lung volume.[65,66]

How Is the Dose of INO Titrated and Weaned?

An issue of practical importance is rebound hypoxemia and pulmonary hypertension when INO is discontinued.[67-71] In a retrospective review, Sokol et al[72] reported a 30 mm Hg decline in P_{aO_2} when INO was discontinued from a dose of 1 ppm. Secondary analysis of a multi-center prospective randomized double-blind study,[11] reported that decreases in the P_{aO_2} were observed only at the final step of withdrawal (ie, when the INO was discontinued). The weaning process began when respiratory status appreciably improved (OI < 10). A reduction in INO to 1 ppm before discontinuation of the drug minimized the decrease in P_{aO_2} when INO was discontinued. By assessing the decrease in P_{aO_2}, when INO was discontinued from a dose of 1 ppm, they suggested that a rebound decrease in P_{aO_2} could be prevented with a 20% increase in F_{IO_2}. In a retrospective study, Carriedo and Rhine[73] reported that withdrawing INO in non-responders did not result in rebound when NO exposure was limited to 30 min; this supports prompt discontinuation of INO following a short trial in non-responders. Aly et al[67] also reported that rebound hypoxemia can be ameliorated by an increase in F_{IO_2} before discontinuation of INO. Case studies and case series have reported benefit from use of phosphodiesterase inhibitors to attenuate rebound hypoxemia when INO is discontinued.[74-79]

Which INO Delivery System Should Be Used?

Prior to the late 1990s, the majority of mechanically ventilated infants receiving INO therapy were supported using time-cycled, pressure-limited, continuous-flow ventilators. Customized INO gas delivery systems consisting of separate NO and N_2 gas cylinders, gas blenders, flow meters, stand-alone NO/NO_2 gas monitors, and improvised scavenging systems were commonly implemented. NO was continuously titrated into the inspiratory limb of the ventilator, using a flow meter, and the mean delivered INO concentration was estimated using a theoretical calculation, or was measured using a combined NO/NO_2 analyz-

Table 4. INO Dose and Response Criteria, From Randomized Controlled Trials

First Author	Starting Dose (ppm)	Response Criteria	Approach to Non-responders	INO Dosing Titration	INO Discontinuation Criteria	Comments
Barefield[14] 1996	20–80	P_{aO_2} > 80 mm Hg for > 1 h	If P_{aO_2} < 40 mm Hg, INO initiated at 40 ppm or increased by 40 ppm. If P_{aO_2} 40–99 mm Hg, INO initiated at 20 ppm or increased by 20 ppm. If P_{aO_2} ≥ 100 mm Hg, INO maintained at that dose.	If P_{aO_2} > 150 mm Hg, INO reduced by 5 ppm until 20 ppm; F_{IO_2} then reduced until < 0.7, then INO reduced by 5-ppm decrements to 5 ppm.	Reduced from 5 ppm to zero ppm by decrements of 1–2 ppm	—
NINOS[7] 1997	20	Increase in P_{aO_2} after 30 min of INO Complete response: > 20 mm Hg Partial response: 10–20 mm Hg No response: < 10 mm Hg	INO discontinued if no response at 20 ppm or 80 ppm	With complete response, continued at 20 ppm. With less than complete response, 80 ppm. With partial response, continued at the lowest INO dose that produced at least a partial response.	Algorithms for weaning INO, escalating INO dose after clinical deterioration, and restarting INO after unsuccessful weaning not reported. INO could continue for a cumulative maximum of 14 d.	No clear benefit from increasing INO from 20 ppm to 80 ppm
Roberts[8] 1997	80	INO considered successful if P_{aO_2} > 55 mm Hg or oxygenation index < 40	INO immediately discontinued in patients with no initial response	Reduced by 10 ppm after 20 min and twice a day, if P_{aO_2} > 55 mm Hg. If P_{aO_2} decreased by 15% or to < 55 mm Hg within 10 min after the change, then INO raised to the previously acceptable level.	INO reduced after 20-min study period and twice a day thereafter. If P_{aO_2} > 55 mm Hg, INO decreased by 10 ppm. If P_{aO_2} decreased by 15% or to ≤ 55 mm Hg 10 min after change, INO returned to previous level. Otherwise, INO decreased to zero ppm or maximum of 40 ppm.	Half the infants needed < 2 d of INO. Longest INO treatment 8.5 d Median INO dose rapidly decreased to ≤ 20 ppm by 2 d
Day[11] 1997	20	Not evaluated	INO continued until F_{IO_2} < 0.5 or patient received ECMO	Not described	Not described	—
Wessel[12] 1997	80	Not evaluated	—	Weaning per preset protocol that lowered the dose from 80 ppm to 40 ppm after 1 h. If tolerated, that dose was continued up to 12 h and dose reductions to 5 ppm were attempted each day.	INO discontinued when dose could be reduced to 5 ppm for at least 12 h while P_{aO_2} > 60 mm Hg and F_{IO_2} ≤ 0.5.	—
Kinsella[18] 1997	20	P_{aO_2} ≥ 60 mm Hg on F_{IO_2} 1.0 for 2 h	Non-responders treated with INO and HFOV. No patient in whom 20 ppm INO failed had a sustained response to 40 ppm.	20 ppm for 4 h and then decreased to 6 ppm. If P_{aO_2} ≥ 60 mm Hg was not sustained with 20 ppm, a trial of 40 ppm was allowed.	At 24 h, INO discontinued. If adequate oxygenation not sustained after discontinuing INO, INO restarted for another 24 h. Treatment continued until INO withdrawal was not associated with a decrease in oxygenation.	With severe lung disease, response to HFOV plus INO was better than to HFOV alone or INO with conventional ventilation. Without substantial lung disease, both INO and HFOV plus INO were more effective than HFOV alone

(continued)

Table 4. INO Dose and Response Criteria, From Randomized Controlled Trials (continued)

First Author	Starting Dose (ppm)	Response Criteria	Approach to Non-responders	INO Dosing Titration	INO Discontinuation Criteria	Comments
Davidson[10] 1998	5, 20, or 80	INO success: improved $P_{aO_2} \geq 60$ mm Hg on $F_{IO_2} < 0.6$ and mean airway pressure < 10 cm H_2O INO failure: $P_{aO_2} < 40$ mm Hg for 30 min	NA	Sequential 20% INO decrements at a minimum of 30 min and a maximum of 4 h	Discontinued when 20% of initial dose was reached.	—
Cornfield[13] 1999	2	Oxygenation index < 35 for 1 h after INO	Non-responders to 2 ppm received 20 ppm	Not described	Not described	Sub-therapeutic INO dose may adversely affect clinical response to a therapeutic INO dose
Franco-Belgian INO Trial Group[19] 1999	10	Oxygenation index at 2 h	Unclear. Therapy decisions left to primary-care physician	Decreased to 5 ppm and slowly tapered	Not described	—
Clark[6] 2000	20	Not evaluated	NA	Decreased to 5 ppm at 4 h if stable, $P_{aO_2} \geq 60$ mm Hg, and pH ≤ 7.55; otherwise, evaluated every 4 h for INO decrease. During the first 24 h, INO could be returned to 20 ppm if $P_{aO_2} \leq 60$ mm Hg and F_{IO_2} was 1.0. After 24 h, INO 5 ppm.	INO continued at 5 ppm until $F_{IO_2} < 0.7$, the neonate had been treated for 96 h, or the neonate was 7 d old, whichever came first.	—
Christou[15] 2000	40	Not evaluated	Not evaluated	Decreased to 20 ppm after 1 h. If oxygenation did not deteriorate, the lowest acceptable INO dose was determined daily.	Not described	—
Finer[20] 2001	1–2 or 10–20 (randomly determined)	$> 20\%$ increase in P_{aO_2} and $> 20\%$ decrease in oxygenation index	Doubling of INO within the protocol dose range (low-dose group 1, 2, 4, and 8 ppm; high-dose group 10, 20, 40, and 80 ppm). If a low-dose-group patient at 8 ppm did not have a full response after 1 h, tried 20 ppm and increased per the high-dose protocol. INO discontinued in non-responders.	Attempt every 12 h to decrease INO by 50%	Discontinuation was performed from doses of 0.5–1 ppm	—

(continued)

Table 4. INO Dose and Response Criteria, From Randomized Controlled Trials (continued)

First Author	Starting Dose (ppm)	Response Criteria	Approach to Non-responders	INO Dosing Titration	INO Discontinuation Criteria	Comments
Sadiq[21] 2003	10–80	> 20% improvement in $P_{(A\text{-}a)O_2}$ or oxygenation index	INO discontinued in non-responders	Started at 10 ppm, followed by increases of 10–20 ppm every 30 min until no further P_{aO_2} increase or until 80 ppm was reached.	Weaning of INO allowed only when minimal ventilator settings and F_{IO_2} 0.3–0.5 achieved, or if methemoglobin > 5%.	—
Konduri[22] 2004	5	≥ 20 mm Hg increase in P_{aO_2}	All were continued on INO, regardless of initial response, until they weaned off	Started at 5 ppm; 20 ppm if < 20 mm Hg P_{aO_2} increase on 5 ppm. Kept at 20 ppm if ≥ 10 mm Hg P_{aO_2} increase. If < 10 mm Hg P_{aO_2} increase at 20 ppm, returned to 5 ppm	Weaning at 12-h intervals, per the protocol's algorithm. INO dose weaned to 0.5 ppm before discontinuing.	—

INO = inhaled nitric oxide
HFOV = high-frequency oscillatory ventilation
NA = not applicable
$P_{(A\text{-}a)O_2}$ = alveolar-arterial oxygen difference

Table 5. INO Dose and Response Criteria, From Observational Studies

First Author	Starting Dose (ppm)	Response Criteria	Approach to Non-responders	Dosing Titration	Discontinuation Criteria	Comments
Roberts[23] 1992	80	Improved post-ductal S_{pO_2}	NA	NA	Short-term study. INO discontinued in all subjects after 30 min	—
Kinsella[24] 1992	10–20	P_{aO_2}	INO sequentially administered at 10 and 20 ppm	ND	INO discontinued after 4 h or 24 h, per study protocol	—
Kinsella [25] 1993	20	P_{aO_2}, $P_{(A\text{-}a)O_2}$, oxygenation index	All infants received INO for 24 h	After 4 h at 20 ppm, INO decreased to 6 ppm for 20 h	INO discontinued at 24 h. Restarted for 12–24 h if oxygenation could not be maintained	—
Kinsella[26] 1994	20	P_{aO_2}, $P_{(A\text{-}a)O_2}$, oxygenation index	All infants received INO for 24 h	20 ppm for 4 h, then dose decreased to 6 ppm for the following 20 h	INO discontinued at 24 h. If adequate oxygenation (arterial/alveolar oxygen ratio < 0.10) not sustained, INO restarted for another 24 h	—
Finer[27] 1994	5, 10, 20, 30, 40, 60, or 80	Increase of 10 mm Hg in P_{aO_2} or 10% in O_2 saturation	Dose-response study. Doses administered in random order	Responders received lowest dose that generated a response for 24 h. Then dose decreased 5 ppm every 15 min. If P_{aO_2} decreased 10 mm Hg, INO increased to previous dose	INO discontinued if oxygenation index < 10	No $P_{(A\text{-}a)O_2}$ difference between any of the doses
Buhrer[28] 1995	8	P_{aO_2} increase $\geq$ 10 mm Hg	Doubled at 10-min intervals (up to 80 ppm) until positive response observed	Dose doubled or halved to achieve sustained P_{aO_2} improvement	Discontinued when INO ceased to improve P_{aO_2} or when $P_{aO_2} > 50$ mm Hg could be achieved on $F_{IO_2} \leq 0.5$ without INO	—
Turbow[29] 1995	20	Decrease of 20% in $P_{(A\text{-}a)O_2}$ or 40% in oxygenation index	Infants treated with ECMO	Decreased to 6 ppm at 4–12 h	Not stated	—
Muller[30] 1996	20	P_{aO_2} increase of 10 mm Hg	Dose increased in 10-ppm increments, up to 80 ppm	INO discontinued in non-responders	INO withdrawal tested every 12 h	—
Stranak[31] 1996	20	P_{aO_2}, $P_{(A\text{-}a)O_2}$, oxygenation index	Not stated	20 ppm for 6 h, decreased to 15 ppm, then to 3 ppm, as quickly as possible	INO weaned when $F_{IO_2} < 0.6$, unless interruption caused deterioration of cardiopulmonary stability. Temporary F_{IO_2} increase to maintain P_{aO_2} after INO weaning	—
Demirakça[32] 1996	20	P_{aO_2}	Dose titration with 1, 5, 10, 20, 40, and 80 ppm INO; 15 min for each step	After dose-response testing, used the dose that achieved the best P_{aO_2}	Daily INO discontinuation attempt with PEEP $\leq$ 6 cm H_2O and $F_{IO_2} \leq 0.8$. INO discontinued if P_{aO_2} remained stable after INO withdrawal and required F_{IO_2} increase $< 20\%$	Effective dose was 20 ppm

(continued)

Table 5. INO Dose and Response Criteria, From Observational Studies (continued)

First Author	Starting Dose (ppm)	Response Criteria	Approach to Non-responders	Dosing Titration	Discontinuation Criteria	Comments
Goldman[33] 1996	20	> 20% improvement in P_{aO_2}	INO trial at 70 ppm	INO reduced by 1–2 ppm every 15–30 min while keeping ventilator settings unchanged. The lowest INO dose needed to keep the post-ductal O_2 saturation between 88% and 95% was determined.	When INO was discontinued, a 0.1 F_{IO_2} increase was allowed to maintain O_2 saturation > 88%. If required F_{IO_2} increase was > 0.1, low-dose INO (< 5 ppm) was used.	—
Lönnqvist[34] 1997	3	≥ 25% decrease in oxygenation index	Stepwise INO increase: 10 min at 3, 10, 30, 60, and 100 ppm	Dose-response study	Not stated	INO doses < 30 ppm were sufficient to decrease the oxygenation index by ≥ 25% in the vast majority of responding patients
Hoffman[35] 1997	25	25% increase in either P_{aO_2} or O_2 saturation, or 25% decrease in oxygenation index, $P_{(A\text{-}a)O_2}$, or virtual shunt	Dose increased by 10 ppm (up to 50 ppm) every 30 min until beneficial response achieved. If no beneficial response within 2 h, INO discontinued	INO decreased by 5 ppm every 30 min to the lowest dose that maintained the beneficial response, or until 1 ppm was reached	Daily INO discontinuation attempt. INO not restarted if there was a < 25% change in P_{aO_2}, oxygen saturation, oxygenation index, $P_{(A\text{-}a)O_2}$, or virtual shunt after INO discontinued	—
Laubscher[36] 1997	10	20% decrease in oxygenation index	If no response to 10 ppm, trials of 20 and 40 ppm. INO discontinued in non-responders	Not stated	Not stated	—
Biban[37] 1998	10	P_{aO_2} or $P_{(A\text{-}a)O_2}$	INO increased by steps of 10 ppm, up to maximum 40 ppm	Not stated	Not stated	—
Kossel[40] 2000	10	P_{aO_2}	INO increased from 10 ppm to 80 ppm, in 10-ppm steps	Not stated	Not stated	—
Tworetzky[41] 2001	5, 20, or 40, randomly applied	P_{aO_2} and pulmonary-to-systemic arterial pressure ratio	Not stated	Not stated	Not stated	Initial INO dose of 20 ppm optimum
Gupta[42] 2002	25	O_2 saturation increase to > 80% (preferably > 90%)	ECMO	When F_{IO_2} < 0.6 and infant stable, attempted INO weaning in 5-ppm decrements every 2–4 h, as tolerated, down to 5 ppm	Once stable on INO of 5 ppm, INO discontinued while keeping F_{IO_2} constant. If O_2 saturation dropped 10% or to < 85%, this was considered weaning failure and INO was restarted at 5 ppm. After the infant recovered, F_{IO_2} was increased by 0.4 and a second INO weaning attempt was made.	—

(continued)

Table 5. INO Dose and Response Criteria, From Observational Studies (continued)

First Author	Starting Dose (ppm)	Response Criteria	Approach to Non-responders	Dosing Titration	Discontinuation Criteria	Comments
Hwang[43] 2004	5–10	Pre/post-ductal oxygen saturation difference	Not stated	INO decrement of 5 ppm attempted every 4–9 h	INO decreased from 5 ppm to off. INO restarted if S_{pO_2} decreased by 10% or to < 85%	—
Guthrie[44] 2004	Low dose: < 18 Mid-dose: 18–22 High dose: > 22	P_{aO_2}/F_{IO_2}	Not stated	Not stated	Not stated	Low-dose INO (< 18 ppm) appears to be as efficacious as high-dose INO (> 22 ppm)
Fakioglu[45] 2005	80	≥ 20% increase in oxygenation index or $P_{(A\text{-}a)O_2}$ after 1 h of INO	—	1 h after starting INO, dose reduced to 40 ppm and maintained for at least 12 h. INO then reduced to 20, 10, and 5 ppm, at 15-min intervals. Patient received lowest dose that kept P_{aO_2} > 60 mm Hg or oxygen saturation > 90%	Weaned from INO at 5 ppm if $F_{IO_2} \leq 0.6$. Weaning via 1-ppm INO decrements over several hours. If patient failed to maintain acceptable oxygenation, INO was resumed.	—

INO = inhaled nitric oxide
$P_{(A\text{-}a)O_2}$ = alveolar-arterial oxygen difference
ECMO = extracorporeal membrane oxygenation
NA = not applicable
ND = no data

er.[80,81] In order to maintain consistent INO delivery to the patient, the clinician was required to manually adjust the INO gas flow, using a flow meter, following changes in ventilator settings or with changes in the patient's inspiratory flow and minute ventilation requirements.[82] Adequate gas mixing and a relatively stable INO level could be obtained when continuous-flow INO delivery systems were used in earlier-generation infant ventilators.[83] Clinicians applied continuous-flow INO delivery systems to newer-generation microprocessor ventilators that provided phasic (or intermittent) gas flow profiles during the respiratory cycle, which results in greater fluctuations and underestimation of INO gas delivery to the patient.[84-86] Moreover, continuous INO gas delivered to the circuit during exhalation had the potential for accumulation of a large and potentially toxic bolus of NO/NO_2 gas to be delivered to the patient with the onset of the next ventilator breath.[81,86,87] In addition to the wide variability of delivered INO, continuous-flow INO delivery systems have also been identified with patient-safety issues during mechanical ventilation, including tidal volume augmentation, ventilator trigger compromise, and ventilator failure.[88] Based on these factors, systems that use a constant flow titration of INO gas may not provide an accurate and reliable INO level, may pose major patient-safety issues, and are not be recommended to deliver INO therapy.

Following FDA approval in 1996, the first universal INO delivery system with an integrated gas injector module, hot-film flow sensor, fast-response gas monitoring/alarm system, and back-up delivery system was designed for use with most forms of mechanical ventilation.[89] This INO delivery system measures flow within the ventilator system, using a hot-film anemometer, and injects NO into the inspiratory limb, using mass flow controls, at a rate that is proportional to the measured ventilator flow to deliver the desired INO level (aka proportional-flow system).[90] Compared with earlier-generation INO delivery systems (constant flow titration method), proportional-flow INO delivery systems have been shown to provide more consistent and accurate delivery of INO gas concentration[89,90] without having to independently adjust the NO flow following changes in the ventilator settings.[91]

According to the FDA, INO therapy should only be administered using an approved delivery system.[92] This system is composed of a gas injector module that is capable of maintaining a constant INO concentration during the inspiratory flow, regardless of variation in flow rate within the respiratory cycle. The delivery system should also minimize the amount of time that INO is mixed with oxygen, to avoid potentially toxic gases from forming. In addition, this system should include the following components: (1) INO gas analyzer with high/low alarms, (2) NO_2 gas analyzer with high alarms, and (3) oxygen analyzer with high/low alarms. Continuous monitoring of gas levels and alarms can warn the clinician of changes in the delivered INO and F_{IO_2} concentrations, accumulation of NO_2, and disruption in the gas supply (ie, catastrophic emptying of gas cylinders and unintended disconnections). Cylinder gauges that monitor the gas pressure are also helpful in determining the level of gas supply. Back-up gas cylinders and a manifold system that provides uninterrupted gas supply to the patient are useful in providing seamless delivery of INO therapy when exchanging gas cylinders. In the event that the INO system becomes inoperable, a secondary or back-up INO delivery system (ie, manual ventilation) should also be included to minimize disruption of gas delivery and potential patient decompensation. These systems should also have a back-up battery in the event of a power failure.

Current INO delivery systems use a single aluminum gas or drug canister with pharmaceutical grade NO (800 ppm) mixed with N_2 as the inert gas (INOmax). The cylinder contains 1,936 L of NO/N_2 at 2,000 PSI and weighs 44 lbs when full. The gas is also certified to contain less than 5 ppm of nitrogen dioxide (NO_2). All INO drug mixtures must be handled and stored in compliance with federal, state, and local regulations.

Currently there are 3 FDA-approved commercially available delivery devices for the administration of INO. They are the INOvent (Datex-Ohmeda), INOmax DS (Ikaria), and AeroNOx (International Biomedical). The INOvent is the most widely used system, and is most commonly employed with conventional and high-frequency ventilators. This device is being phased out as a delivery system by the gas manufacturer and replaced with the INOmax DS. The AeroNOx system can also be used with mechanical ventilators, but is only capable of stable INO delivery during periods of constant flow. This device is most frequently used for INO therapy during patient transport. A brief description of the operational principles of these devices is listed in Table 6. Each has a safety feature that shuts down delivery when the monitoring system measures an NO concentration of $\geq$ 100 ppm.

How Should INO Be Implemented With Different Respiratory Support Techniques?

INO delivery devices are typically used with conventional, anesthesia, transport, manual, high-frequency oscillatory, and high-frequency jet ventilators. Due to the improved understanding of the role of ventilators in the initiation of lung injury[93-95] and potential for increasing pulmonary vascular resistance,[96] INO therapy is also applied noninvasively in spontaneously breathing infants, using nasal cannula, infant oxyhoods, and nasal CPAP systems. It should be noted that there may be subtle differences in system configuration when using different INO delivery systems in conjunction with the multitude of available

Table 6. Device-Specific Details on INO Delivery Systems

	INOvent, Datex-Ohmeda	INOmax DS, Ikaria	AeroNOx, International Biomedical
Delivery	Delivers NO into the inspiratory limb. Provides a user-set, constant INO concentration throughout the inspiration. Specifically designed injector enables tracking of ventilator waveforms and delivery of a synchronized and proportional INO dose.	Delivers NO into the inspiratory limb. Provides a user-set, constant INO concentration throughout the inspiration. Specifically designed injector enables tracking of ventilator waveforms and delivery of a synchronized and proportional INO dose.	Valve controls NO flow out of the device and into the patient circuit. NO flow measured by a mass flow meter.
Monitoring	Continuous online monitoring of NO, NO_2, and O_2 via electrochemical cells	Continuous online monitoring of NO, NO_2, and O_2 via electrochemical cells	Continuous online monitoring of NO, NO_2, and O_2 via electrochemical cells.
Sampling rate	230 mL/min from the inspiratory limb	230 mL/min from the inspiratory limb	150 mL/min from the inspiratory limb of the circuit
Alarms	NO, NO_2, O_2	NO, NO_2, O_2	NO, NO_2, O_2
Backup delivery	Backup delivery fixed at 20 ppm at 15 L/min	INOBlender 0–80 ppm at 5–14 L/min, or fixed at 250 mL/min bleed	AeroNOx Bagger fixed at 250 mL/min = 20 ppm at 10 L/min
Battery	Bedside up to 30-min. Transport head up to 3 h fully charged	Up to 6 h fully charged	Up to 6 h fully charged

INO = inhaled nitric oxide

respiratory support modalities. Connections to various delivery systems are unique to each device. There are few studies that have been designed to test safety and efficacy of each respiratory support device during INO therapy. Where evidence-based recommendations on device safety and efficacy are lacking, the clinician should always refer to the specific manufacturer recommendations prior to implementing INO therapy with any form of respiratory support.

Mechanical Ventilation

During mechanical ventilation, the stability of delivered INO gas concentration may be affected by the respiratory rate, inspiratory-expiratory ratio, minute volume, inspiratory time, flow rate, mode, peak inspiratory pressure, and PEEP. The location of the gas injector module in the inspiratory limb of the ventilator circuit is a critical factor in establishing the appropriate dose of INO. Corrugated patient tubing has been shown to provide better mixing of INO than smooth-bore tubing, without an increase in NO_2 accumulation.[85] Although the vast majority of the research has been done using continuous-flow INO delivery systems, the same principles of gas mixing and monitoring apply to proportional-flow systems during mechanical ventilation. Gas injection placed into the inspiratory limb close to the patient may not allow enough time for NO and ventilator system gas flow mixing to occur within the circuit, resulting in an inconsistent level of INO delivery.[81] It has been suggested that the INO gas injector module be placed where circuit gas flow fluctuations are minimal, to maintain the appropriate delivered NO concentration throughout the entire respiratory cycle. Placing the injector module between the ventilator gas output and the dry side of the humidifier allows more time for gas mixing to occur, and, thus, a more stable level of INO can be provided to the patient.[97]

INO delivery systems sample gas from the inspiratory limb of the ventilator system to analyze INO, NO_2, and F_{IO_2} concentrations. This is most commonly achieved by placing the sampling port in the inspiratory limb of the respiratory support device, downstream from the site of injection, no greater than 15 cm before the patient connection/interface. Additionally, the continuous gas sampling by the INO monitoring system may affect triggering, tidal volume delivery, and PEEP stability during mechanical ventilation. However, since these systems also add gas to the inspiratory limb of the ventilator, these changes are minimal. Regardless, it is necessary to continuously monitor the ventilation system for disparities between the set and measured ventilation parameters before and after implementation of INO therapy, and with changes in the INO settings. Of equal importance, it is also necessary to adjust the ventilator accordingly, to obtain the desired minute ventilation and mean airway pressure during INO therapy.

Manual ventilation is frequently administered in combination with INO delivery, using self-inflating and flow-inflating resuscitator bags.[98] Most INO delivery systems incorporate manual resuscitators as the back-up form of ventilation, and should be used during an electric or injector module failure. Clinicians will also use these systems during periodic disconnection from mechanical ven-

tilation and during patient transport. These systems are used only on an intermittent basis, and, thus, the reservoirs and tubing of manual resuscitators may allow NO to mix with oxygen to form NO_2. It has been suggested that using the smallest manual resuscitator possible to adequately deliver the desired tidal volume and the highest rated gas flow that is practical should reduce these effects. Further, once the flow has been turned on, the bag should be squeezed 4–6 times to empty residual gas in the bag prior to using the system to ventilate the patient.[89]

Anesthesia Ventilators

INO therapy is used during and following the surgical repair of certain congenital cardiac lesions or during cardiac catheterization in infants with pulmonary hypertension. Therefore, it is frequently necessary to safely administer INO therapy in conjunction with inhaled anesthetic gases using an anesthesia ventilator. The issues surrounding the use of INO delivery systems with anesthesia ventilators have been described using adult test lung models.[99] However, the safety and efficacy of this practice are yet to be determined in infants.

During administration of anesthetic gas a partial rebreathing or circle system is used. This system allows the patient to breathe a combination of fresh and exhaled gas, following CO_2 elimination with an absorbing apparatus, to conserve the amount of anesthesia used. The presence of an anesthesia bag in the circuit can promote gas mixing but also potentially allows the formation of NO_2. When the INO injector module is placed within the inspiratory limb of the ventilator, flow is measured and INO gas is titrated accordingly. However, since the monitor is also measuring exhaled breath INO content, the measured INO level in the circuit will increase over time.

Ceccarelli et al[99] evaluated the use of a proportional INO delivery device during anesthesia ventilation, using an adult test lung model. They found that, as long as the fresh gas supply was set higher than the patient's minute ventilation requirement, the delivered INO level was approximately within 10% of the set INO level. However, when the fresh gas supply fell below the patient's minute ventilation, the INO delivery system measured a higher delivered INO level than what was set. One limitation of that in vitro study was that Ceccarelli et al did not evaluate INO delivery using ventilator settings commonly used with neonates. As such, these adult data would be very difficult to extrapolate to neonatal ventilation. In many cases, clinicians resort to using conventional mechanical ventilators in the operating room for administration of INO therapy to neonates.

High-Frequency Ventilation

Because INO therapy may produce a more favorable response when using a ventilatory approach that optimizes alveolar recruitment,[100] it is frequently administered during high-frequency oscillatory ventilation (HFOV) and high-frequency jet ventilation (HFJV). In a study by Coates et al,[101] hypoxic infants with pulmonary hypertension who required INO had similar short-term outcomes, regardless of whether INO therapy was delivered via HFOV or HFJV.

Fujino et al[102] evaluated simulated INO delivery during HFOV, using both continuous-flow and proportional-flow INO delivery systems. The 3100a HFOV (CareFusion, Yorba Linda, California) was configured using settings commonly used to support neonates, and at a multitude of INO settings. The major finding of the study was that INO therapy was more consistent using the proportional-flow INO delivery system. In addition, placing the INO injector before the humidifier (where pressure fluctuations are minimal) resulted in appropriate mixing of INO within the circuit, and, thus, a more stable delivered INO level. These findings also suggest that analyzed NO and NO_2 levels could be accurately monitored by placing the gas sampling line in the inspiratory circuit, either close to the patient Y-piece or midway through the circuit. The active exhalation during HFOV can cause flow to travel back and forth through the injector, which may result in delivery of INO twice that of the desired (or set) level. Therefore, it has been suggested that a one-way valve be placed between the injector and dry side of the humidifier, to prevent retrograde flow back into the injector.

Two studies[103,104] have evaluated INO delivery during HFJV using the Life Pulse HFJV (Bunnell, Salt Lake City, Utah). Of note, the HFJV is used in conjunction with a conventional mechanical ventilator. Mortimer et al[103] conducted a bench study where INO was injected into the patient circuit of the conventional ventilator only. They concluded that INO delivery during HFJV is reliable using certain ventilator settings, but that this practice is unreliable and should be avoided due to poor entrainment of INO from the conventional ventilator circuit during tandem jet breaths.

Platt et al[104] injected INO directly into the HFJV circuit using a proportional-flow INO delivery system during simulated neonatal ventilation. The effects of air entrainment from the conventional ventilator circuit and mixing of NO injected through the endotracheal tube adapter were evaluated by measuring NO proximal as well as distal to the endotracheal tube. INO therapy was evaluated during HFJV used in conjunction with the conventional ventilator set on CPAP and intermittent positive-pressure ventilation. The concentration of INO measured proximal to the endotracheal tube was appreciably different from the level set on the INO delivery system because of the relatively low flow

rate of gas through the HFJV circuit at the injection site, which was well below the minimum flow rate specified for this INO delivery system. This was more evident when using an INO level > 20 ppm and could be remedied by adjusting the set INO level to obtain the desired level based on the proximal INO measurement. Fluctuations of INO concentration, caused by entrainment of NO-free intermittent-mandatory-ventilation breaths (5 breaths/min) from the conventional ventilator circuit, were generally < 10% of the set concentrations. The effects of air entrainment from the ventilator circuit appeared negligible when INO therapy was administered in the therapeutic range of 10–20 ppm, where distally measured NO levels were < 0.5 ppm from the set value. Measured NO_2 was ≤ 1.3 ppm for all ventilator settings and NO concentrations. Based on these findings, administering INO therapy appears to be safe and effective as long as it is injected through the HFJV circuit.

Nasal Continuous Positive Airway Pressure

INO therapy has been used in combination with nasal continuous positive airway pressure (CPAP) systems to support spontaneously breathing infants with hypoxic lung disease. Lindwall et al[105,106] reported that INO can be delivered safely and effectively using continuous-flow-titration INO delivery devices with the Infant Flow Nasal CPAP system (CareFusion, Yorba Linda, California). Trevisanuto et al evaluated the feasibility of INO therapy using a neonatal CPAP helmet in a bench study,[107] followed by a case report[108] describing the successful application in the long-term treatment of an infant with pulmonary hypertension. INO therapy appeared feasible with that system and was found to be an effective treatment option in one patient. However, those systems were studied using only a continuous-flow INO titration system.

There are currently no studies that have been designed to evaluate the safety and efficacy of applying an approved proportional-flow INO delivery device during nasal or helmet CPAP. Additional studies are required to properly assess the consistency of NO delivery, rate of NO_2 production, and the potential effects of sampling on the delivered CPAP level to the patient.

Oxygen Administration Devices

Ivy et al[109] were the first to describe the application of INO therapy using an oxygen hood and nasal cannula to support a spontaneously breathing infant with PPHN. The infant was supported with INO of 6–23 ppm. Methemoglobin was measured twice daily and remained < 5% throughout the treatment period. Kinsella et al[110] evaluated whether the prolonged treatment with noninvasive INO therapy delivered through a nasal cannula would sustain pulmonary vasodilation in neonatal patients at risk for developing PPHN following extubation from mechanical ventilation. Infants were supported initially using an oxygen hood, and eventually weaned to a nasal cannula. A proportional-flow INO delivery system was used in conjunction with the nasal cannula, set at 1 L/min, using a blended gas source, to obtain INO concentrations of 5–10 ppm. Additionally, NO was measured using an NO analyzer sampling port placed into the nasopharynx. Nasopharyngeal NO concentrations were 5.4 ± 0.5 ppm and 2.4 ± 0.4 ppm with INO measured proximally in the delivery device at INO set at 10 and 5 ppm, respectively. In this series of patients, 10 of 47 (21%) newborn infants with protracted PPHN were treated successfully using INO therapy administered via nasal cannula following discontinuation of mechanical ventilation.[110]

Ambalavanan et al[111] evaluated INO therapy with a proportional-flow delivery system applied to infants with PPHN, using an infant hood. In this pilot study, 8 newborns were randomized to receive INO therapy delivered through an infant hood or oxygen delivered through a nasal cannula. Two of the infants who received INO therapy via oxygen hood had a P_{aO_2} > 100 mm Hg, whereas oxygenation was unchanged in the patients receiving oxygen via nasal cannula.

What Adverse Effects of INO Should Be Monitored?

Continuous monitoring of INO, NO_2, and O_2 is recommended during the delivery of INO. As mentioned previously, this is achieved by sampling gas from the inspiratory limb of the respiratory support device downstream from the site of injection, no greater than 15 cm before the patient connection/interface. The available approved INO delivery devices use electro-chemical cells to measure the concentrations of INO, NO_2, and O_2. NO and NO_2 are measured in ppm and O_2 is measured in percentage. Alarm packages include high and low NO and O_2, and high NO_2 alarm settings.

Nitric Oxide

Inhaled NO in sufficient concentrations is considered an environmental pollutant, and when inhaled at extremely high doses (5,000–20,000 ppm) can have direct toxic effects on the lung.[112] NO is a free oxygen radical that can react with molecules to form toxic chemical compounds in the lung, including peroxynitrite formation, which damages DNA, induces lipid peroxidation, and reacts with proteins.[113] INO-mediated lung injury results primarily from inactivation of surfactant protein A[114] and decreased surfactant production.[115,116] Prolonged INO exposure is also associated with a transient increase in markers of oxidative lung injury, but this finding does not appear to

predict the development of chronic lung disease in term or near-term newborns with hypoxic respiratory failure.[117] Additionally, hypoxic newborn infants treated with INO (≤ 20 ppm) do not appear to be at any greater risk of developing pulmonary toxicity than are infants not treated with INO therapy.[118]

Despite the claims that INO therapy, used within the therapeutic range, does not increase the risk for infants developing INO-mediated toxicity and consequent lung injury, clinicians should monitor INO continuously and wean patients aggressively from INO therapy if they are not responding, to eliminate any unnecessary exposures. Additionally, alarm limits should be set to warn clinicians about potential increases in INO concentration. Currently, there are no recommended guidelines for setting NO alarms during INO therapy.

F_{IO_2}

The delivered F_{IO_2} can be reduced as a result of dilution with INO therapy. For example, in INO delivery devices that inject INO distal to the ventilator gas outlet, at an INO dose of 20 ppm (with a gas source of 800 ppm), the F_{IO_2} will be reduced by approximately 2.5%. Therefore, it makes it difficult to near impossible to obtain an F_{IO_2} of 1.0 during INO therapy.[89] The F_{IO_2} measured by the INO delivery system downstream from the point of NO injection should be used, whereas the F_{IO_2} monitored at the ventilator is measured prior to any gas mixing in the system.

Nitrogen Dioxide

Nitrogen dioxide (NO_2) is a toxic byproduct that forms when NO and O_2 gases are allowed to mix. This chemical reaction can take place in the gas delivery system or ventilator, the airway interface, and the lungs. In animal studies, inhaled NO_2 at approximately 2 ppm affected alveolar development and surfactant production, altered the epithelial lining of the terminal bronchioles, and induced loss of cilia.[119,120] In human studies, inhaled NO_2 at approximately 2 ppm affected alveolar permeability[121] and increased airway responsiveness.[122]

NO_2 accumulation is more likely to form when using high F_{IO_2} in combination with a high INO concentration.[123] Location of the INO injection site and the type of mechanical ventilator used are 2 important considerations that may result in gas mixing differences and NO_2 production.[124] For instance, ventilators that apply low bias flow or no bias flow during exhalation may allow more contact time for gases to chemically react and allow greater NO_2 production than do earlier-generation ventilators that apply a constant flow rate during the respiratory cycle. However, these effects have not been evaluated extensively using proportional-flow INO delivery systems.

There are a number of strategies that can help to avoid excessive NO_2 delivery to patients during INO therapy. Accumulation of NO_2 can form in the manifolds and tubing of the INO delivery system, and, thus, proper purging (as recommended by the system manufacturer) of these systems is vital prior to instituting INO therapy. Further, systems that have been stagnant for some time period may have NO_2 accumulation (eg, self-inflating manual resuscitator) that would benefit from being purged prior to being used in a patient.

Sampling close to the patient ensures an accurate NO_2 measurement because INO and O_2 react very rapidly to form NO_2. Sampling is done on the inspiratory limb to ensure that the exhaled NO and NO_2 are not measured. Although this has not been studied, the gas sampling is most commonly performed from the inspiratory limb of the respiratory support device downstream from the site of injection, no greater than 15 cm before the patient connection/interface. There are no established clinical guidelines for setting upper alarm limits on the INO delivery device for patients receiving INO therapy. Based on the limited available experimental data in humans and animals, it appears reasonable to set the upper NO_2 alarm limit at approximately 2 ppm, to prevent toxic gas exposure to the lungs.

In one study, the NO_2 level was found to be less than 0.5 ppm whether the neonates were treated with placebo, 5 ppm INO, or 20 ppm INO over the first 48 hours. The 80 ppm group had a mean peak NO_2 of 2.6 ppm.[11] In the majority of the randomized controlled trials evaluating INO in the therapeutic range, the reported levels have all been well below 2 ppm, and in infants receiving > 20 ppm, INO therapy was not discontinued but rather reduced due to increased methemoglobin (Table 7).

Methemoglobinemia

Methemoglobinemia is a complication that results when INO binds with heme groups within the hemoglobin. The greatest risk factor for methemoglobin formation is associated with the use of high INO doses. Methemoglobin can reduce the capacity of the hemoglobin molecule to bind with O_2, and consequently reduces systemic O_2 delivery. In the majority of clinical trials, the maximum methemoglobin level was reached approximately 8 hours after initiation of inhalation. In one study, 13 of 37 (35%) of neonates treated with INO 80 ppm had methemoglobin exceeding 7%; whereas, lower methemoglobin levels were virtually nonexistent at lower INO doses.[11,15] In some situations the methemoglobin level may peak as late as 40 hours following the initiation of INO therapy. Following discontinuation or reduction of INO, the methemoglobin level typically returns to baseline over a period of hours. Based on these data, severe methemoglobinemia is

Table 7. Complications of INO, From Randomized Controlled Trials

First Author	Initial INO Dose Reported (ppm)	Methemoglobin Monitoring Protocol	Measured Methemoglobin Levels	NO_2 Monitoring Protocol	Measured NO_2 Levels	Bleeding Complications
Barefield[14] 1996	20–80	MetHb measured before INO and every 4–8 h on INO	Mean MetHb 3.1% in all infants. All MetHb measurements < 7%	Not measured	Not measured	One infant in the INO group died from ICH during ECMO
Day[11] 1997	20	MetHb measured before INO and 30–60 min following INO treatment	MetHb 1.5 ± 0.1% during conventional ventilation; 2.4 ± 0.3% (2 patients > 4%) during high-frequency jet ventilation	NO_2 monitored continuously	Not measured	One infant developed ICH
Wessel[12] 1997	5–80	MetHb measured 15 min and 24 h following INO treatment	Median peak MetHb 1.7%	NO_2 monitored continuously	Peak $NO_2 \leq 1$ ppm in 19 of 26 patients. No patient had confirmed $NO_2 > 5$ ppm	Tendency for lower ICH in the INO group
NINOS[17] 1997		MetHb measured at 1, 3, 6, and 12 h after initiation, and subsequently at 12 h	No infants required discontinuation of INO related to MetHb	NO_2 monitored continuously and recorded every 2 h	No infants required INO discontinuation due to NO_2	No differences in bleeding disorders or neurologic sequelae
NINOS[7] 1997	20–80	MetHb measured at 1, 3, 6, and 12 h after INO, until 24 h after discontinuation. INO weaned by 50% if MetHb 5–10%. INO discontinued if MetHb > 10%	No infants required discontinuation of INO related to MetHb	NO_2 monitored continuously. INO discontinued if $NO_2 > 7$ ppm. INO decreased by 50% if NO_2 5–7 ppm	No infants required INO discontinuation due to NO_2	One INO infant and 2 control infants developed ICH
Roberts[8] 1997	20–80	MetHb measured at 1, 3, 6, and 12 h after INO, until 24 h after discontinuation. INO weaned by 50% if MetHb 5–10%. INO discontinued if MetHb > 10%	No infants required discontinuation of INO related to MetHb	NO_2 monitored continuously	No infants required INO discontinuation due to NO_2	No differences in severity or incidence of ICH between study groups
Kinsella[18] 1997	6–20	MetHb measured at baseline, 30 min, 1, 2, 4, 12, and 24 h, and every 24 h for duration of INO	MetHb range 1.0–4.7% over 24 h	Not measured	Not measured	Not measured
Davidson[10] 1998	5–80	MetHb measured by an unmasked investigator, but not reported	Not reported	NO_2 measured continuously by an unmasked investigator, but not reported	Not reported	Not measured
Cornfield[13] 1999	2	MetHb measured every 6 h on the first day and at least twice daily for duration of study	MetHb range 0.9–1.3% over a 24 h period	NO_2 monitored continuously	Not measured	Not measured
Franco-Belgian INO Trial Group[19] 1999	10	Not measured	Not measured	Not measured	Not measured	INO not associated with higher incidence of ICH
Christou[15] 2000	20–40	MetHb measured daily	All MetHb measurements < 5%	NO_2 monitored continuously	No abnormal NO_2 levels	Not measured
Clark[6] 2000	5–20	MetHb measured before INO and at 4, 24, and 96 h during INO. Reduced INO by 50% if MetHb > 4% and discontinued INO if MetHb remained high.	Only 2 patients had MetHb > 4%	NO_2 monitored continuously. INO reduced by 50% if $NO_2 > 5$ ppm, and discontinued if NO_2 remained high	No patients had $NO_2 > 5$ ppm	INO not associated with higher incidence of ICH
Finer[20] 2001	1–80	MetHb measured before INO and at 6 h, and every 8 h thereafter. Reduced INO by 50% if MetHb > 5%. Discontinued INO if MetHb remained > 8%	Mean peak MetHb 2.19 ± 1.66% in high-INO-dose group, and 1.36 ± 1.13 in low-dose group. INO not weaned or discontinued in any infant due to elevated MetHb	NO_2 monitored continuously. INO reduced by 50% if $NO_2 > 3.5$ ppm, and discontinued if NO_2 remained high	No infants required INO discontinuation due to NO_2	No infants had ICH
Sadiq[21] 2003	10–80	No measurement frequency mentioned. INO weaned if MetHb > 5%	Mean MetHb 1.45 ± 0.95% in all patients treated. MetHb did not exceed > 5% in any patient	NO_2 monitored continuously	Not measured	Not measured
Konduri[22] 2004	5–20	No measurement frequency mentioned. INO weaned if MetHb > 5%. INO discontinued if MetHb > 10%.	INO not weaned or discontinued in any infant due to elevated MetHb	NO_2 monitored continuously. INO weaned if NO_2 3–5 ppm, and discontinued if > 5 ppm	No infants required INO discontinuation due to NO_2	One INO infant and 2 control infants had severe ICH
González[16] 2010	20	MetHb measured before INO and every 24 h while on INO	No reported MetHb increase in the infants treated with INO	NO_2 monitored continuously	No elevated NO_2 in the infants treated with INO	No higher incidence of bleeding or coagulation disorder in either INO group

INO = inhaled nitric oxide
MetHb = methemoglobin
ICH = intracranial hemorrhage
ECMO = extracorporeal membrane oxygenation

not a major cause for concern if INO is delivered at the suggested starting dose of ≤ 20 ppm (see Table 7). Patient serum methemoglobin should be monitored approximately 8 hours and 24 hours after initiation of therapy, and daily thereafter. As a general clinical rule, it has also been suggested that INO should be weaned or discontinued if the methemoglobin level rises above 5%.

Bleeding Disorders

INO therapy has been shown to inhibit platelet aggregation, adhesion, and agglutination.[125] A major concern is that there may be an increased risk of intracranial hemorrhage in newborn infants. In a small group of infants with hypoxic lung disease, the bleeding time on INO (40 ppm for 30 min) was prolonged significantly, when compared with the bleeding time performed 24 hours after the INO therapy was discontinued ($P < .05$); however, no infants had any clinical evidence of bleeding before or after the study was conducted.[126] In all of the randomized controlled trials in infants, the use of INO has not been reported to increase the occurrence of intracranial hemorrhage or any other bleeding-related disorders (see Table 7). Thus, the clinical risks of coagulopathy during INO therapy appear to be negligible. In addition, other laboratory tests may be included in the regular panel for patients at risk for bleeding, including platelets, clotting time, hematocrit, and hemoglobin. However, there are no clinical recommendations suggesting that these tests are necessary for all infants receiving INO therapy. In addition, these findings compare well with the evidence that INO does not result in any long-term neurodevelopmental sequelae in treated infants.

What Physiologic Parameters Should Be Monitored During INO Therapy?

In addition to the gas monitoring capabilities built into INO delivery systems, as well as clinician monitoring for toxic effects in patients, there are certain unique physiologic monitoring requirements for patients receiving INO. Patients on INO are nearly always in a critical care or transport environment and thus are typically monitored with the customary cardio-respiratory monitoring systems. Hemodynamic monitoring may be useful to detect cardiovascular rebound effects when weaning INO. Echocardiograph is a useful, but expensive, method used to assess the degree of pulmonary hypertension and response to INO therapy. Pulmonary hypertension has been estimated in infants via echocardiogram as the presence of either tricuspid regurgitation; and/or as bidirectional or right-to-left shunting at the ductus arteriosus or foramen ovale; and/or as systolic pulmonary artery pressure ≥ two thirds of the systemic systolic blood pressure.[18]

Monitoring pre-ductal and post-ductal oxygen saturations may provide a useful noninvasive strategy for determining the effectiveness of INO. A disparity between the pre-ductal and post-ductal saturation measurements > 5% can indicate increases in right-to-left shunting due to increased pulmonary vascular resistance. In patients with severe pulmonary hypertension, a large disparity between pre-ductal and post-ductal saturations (approximately 30%) may be initially seen. However, post-ductal oxygen saturation begins to approach pre-ductal oxygen saturation in patients who are responding to INO. Pulse oximetry presents some unique challenges in this population because of the possibility of elevated methemoglobin, which can cause pulse oximeters to read falsely low or high S_{pO_2}.

Is Scavenging of Gases Necessary to Protect the Caregiver During INO Therapy?

Early INO systems advocated scavenging (ie, contained collection and elimination of exhaled and unused gas) to reduce the risk of NO and NO_2 exposure to healthcare providers and patients in adjacent work areas. This was accomplished by exhausting gases through anesthesia filters or large canisters attached to the hospital vacuum system. The exposure limit set by the Occupational Safety and Health Administration (OSHA) for INO is 25 ppm as a time-weighted average throughout an 8-hour work shift.[127] The exposure limit for NO_2 is 5 ppm,[128] which is a ceiling limit, not to be exceeded at any time during the work shift. Studies done in intensive-care and transport settings have demonstrated that the NO and NO_2 levels in the area immediately adjacent to the patient receiving INO were well below the OSHA safe exposure levels without gas scavenging.

Philips et al[129] evaluated employee and area exposure during simulated conventional, manual, and high-frequency ventilation in an intensive-care room, and during initial set-up (ie, purging) and disassembly of the INO delivery system. Based on their observations, personal exposures were found to be infrequent, of short duration, and well below the established regulatory limits. They concluded that the NO and NO_2 were quickly diluted by mixing with room air and by providing adequate air exchange in the room (approximately 6 cycles per hour), so personal exposure is thus limited.

Lindwall et al[106] evaluated caregiver exposure during simulated INO therapy using nasal CPAP administration within an Isolette and during catastrophic release of an INOmax cylinder. They found that short-term exposures were brief and well below the recommended workplace exposure limits.

The standard application of INO therapy and catastrophic release of NO during transport raise concerns for exposing healthcare providers and non-ventilated patients to dan-

gerously high levels of environmental NO and NO_2 while confined to close spaces (fixed wing, helicopters, and ambulance cabins). Portable scavenging systems have been previously described in these settings.[130] Kinsella et al[131] evaluated the potential environmental risks for exposing caregivers to NO/NO_2 during INO therapy combined with mechanical ventilation and following simulated catastrophic release of an INO gas cylinder (D-type cylinder). These experiments were conducted within the patient care cabins of a helicopter, fixed wing, and ground transport ambulance. During INO therapy with mechanical ventilation, the measured NO and NO_2 levels (< 0.1 ppm) were well below the recommended healthcare giver exposure limits. Adequacy of air exchange within ambulances and aircraft appears to render environmental toxicity unlikely and the use of scavenging systems unnecessary during transport. However, important measures should be taken to provide adequate air exchange is cycling through the travel compartment at all times.

Recommendations

1. A trial of INO is recommended in newborns ($\geq$ 34 wk gestation, $<$ 14 d of age) with $P_{aO_2} < 100$ mm Hg on F_{IO_2} 1.0 and/or an oxygenation index (OI) $>$ 25 (Grade 1A).

2. It is recommended that INO therapy be instituted early in the disease course, which potentially reduces the length of mechanical ventilation, oxygen requirement, and stay within the intensive care unit (Grade 1A).

3. It is recommended that INO should not be used routinely in newborns with congenital diaphragmatic hernia (Grade 1A).

4. It is suggested that INO therapy should not be used routinely in newborns with cardiac anomalies dependent on right-to-left shunts, congestive heart failure, and those with lethal congenital anomalies (Grade 2C).

5. It is suggested that there are insufficient data to support the routine use of INO therapy in postoperative management of hypoxic term or near-term infants with congenital heart disease (grade 2C).

6. The recommended starting dose for INO is 20 ppm (Grade 1A).

7. It is recommended that response to a short trial (30–60 min) of INO should be judged by an improvement in P_{aO_2} or oxygenation index (OI); if there is no response, INO should be discontinued (Grade 1A).

8. For the newborn with parenchymal lung disease, it is recommended that optimal alveolar recruitment be established prior to initiation of INO therapy (Grade 1A).

9. For newborns with a response to INO therapy, it is recommended that the dose should be weaned to the lowest dose that maintains that response (Grade 1A).

10. It is recommended that INO should not be discontinued until there is an appreciable clinical improvement; that the INO dose should be weaned to 1 ppm before an attempt is made to discontinue; and that the F_{IO_2} should be increased prior to discontinuation of INO therapy (Grade 1A).

11. It is recommended that FDA-approved INO delivery systems should be used to assure consistent and safe gas delivery during therapy (Grade 1C).

12. During conventional mechanical ventilation, it is suggested that the INO gas injector module should be placed on the dry side of the humidifier (Grade 2C).

13. During conventional ventilation, it is suggested that the sampling port be placed in the inspiratory limb of the ventilator, downstream from the site of injection, no greater than 15 cm proximal the patient connection/interface (Grade 2C).

14. It is suggested that the F_{IO_2} be measured downstream from the injection of INO into the circuit (Grade 2C).

15. It is suggested that the patient/ventilator system be continuously monitored for changes in ventilation parameters, with adjustments to maintain desired settings during INO therapy (Grade 2C).

16. It is suggested that the lowest effective doses of INO and O_2 be used, to avoid excessive exposure to NO, NO_2, and methemoglobinemia (Grade 2C).

17. It is suggested that the INO delivery system be properly purged before use to minimize inadvertent exposure to NO_2 (Grade 2C).

18. It is suggested that the high NO_2 alarm be set at 2 ppm on the delivery system to prevent toxic gas exposure to the lungs (Grade 2C).

19. It is suggested that methemoglobin be monitored approximately 8 hours and 24 hours after therapy initiation and daily thereafter.

20. It is suggested that the INO dose be weaned or discontinued if methemoglobin rises above 5% (Grade 2C).

21. It is suggested that continuous pulse oximetry and hemodynamic monitoring be used to assess patient response to INO therapy (Grade 2C).

22. It is suggested that scavenging of exhaled and unused gases during INO therapy is *not* necessary (Grade 2C).

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