Clinical UM Guideline

Subject:	Inhaled Nitric Oxide		
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Description

This document addresses the use of inhaled nitric oxide (INO or iNO). INO has been proposed as a technique to improve oxygenation in critically ill individuals with hypoxic respiratory failure, both to reduce mortality and, in neonates, to reduce the need for extracorporeal membrane oxygenation (ECMO). Hypoxic respiratory failure may result from respiratory distress syndrome (RDS), persistent primary pulmonary hypertension, pulmonary hypoplasia, congenital diaphragmatic hernia (CDH), meconium aspiration, pneumonia, or sepsis.

Clinical Indications

Medically Necessary:

I. Inhaled nitric oxide is considered **medically necessary** as a component of the treatment of hypoxic respiratory failure (see definition) in neonates when the following criteria are met:
   A. The neonate was born at 34 or more weeks of gestation; **and**
   B. Conventional therapies have failed; **and**
   C. Neonate does not have a congenital diaphragmatic hernia.

II. Inhaled nitric oxide is considered **medically necessary** as a method of assessing (not treating) pulmonary vasoreactivity in individuals with pulmonary hypertension.

Not Medically Necessary:

Inhaled nitric oxide is considered **not medically necessary** when the criteria above are not met and for all other indications, including, but not limited to:
   A. Treatment of hypoxic respiratory failure in premature neonates born at less than 34 weeks gestational;
   B. Treatment of acute respiratory distress syndrome in adults;
   C. Pre-operative, operative, and post-operative management of congenital heart disease.

Coding

The following codes for treatments and procedures applicable to this guideline are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider

reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

When services may be Medically Necessary when criteria are met:

ICD-10 Procedure	
3E0F7SD	Introduction of nitric oxide gas into respiratory tract, via natural or artificial opening

ICD-10 Diagnosis	
I27.0	Primary pulmonary hypertension
I27.20-I27.29	Other secondary pulmonary hypertension
I27.83	Eisenmenger's syndrome
I27.9	Pulmonary heart disease, unspecified
P07.30	Preterm newborn, unspecified weeks of gestation
P07.37-P07.39	Preterm newborn, gestation age 34/35/36 completed weeks
P22.0-P22.9	Respiratory distress of newborn
P24.01	Meconium aspiration with respiratory symptoms
P24.11	Neonatal aspiration of (clear) amniotic fluid and mucus with respiratory symptoms
P24.81	Other neonatal aspiration with respiratory symptoms
P24.9	Neonatal aspiration, unspecified
P28.0	Primary atelectasis of newborn
P28.5	Respiratory failure of newborn
P28.9	Respiratory condition of newborn, unspecified
P29.30	Pulmonary hypertension of newborn

When services are Not Medically Necessary:
For the procedure and diagnosis codes listed above when criteria are not met, for all other diagnoses not listed; or for situations designated in the Clinical Indications section as not medically necessary.

Discussion/General Information

INO is a selective pulmonary vasodilator without significant effects on the systemic circulation. INO therapy can improve oxygenation and ventilation, reduce the need for extracorporeal membrane oxygenation (ECMO), and lower the incident of chronic lung disease and death among term and near-term infants with respiratory failure. In 1999, the U.S. Food and Drug Administration (FDA) approved INOmax® (nitric oxide for inhalation) (INO Therapeutics, Hazelwood, MO) for use, in conjunction with ventilatory support and other appropriate agents, in the treatment of term and near-term (greater than 34 weeks) neonates with hypoxic respiratory failure associated with clinical or echocardiographic evidence of pulmonary hypertension. INO improves oxygenation and reduces the need for ECMO. INOmax is contraindicated in neonates known to be dependent on right-to-left shunting of blood.

Respiratory failure is commonly seen in the term, near-term (born at 34 or more weeks of gestation), and preterm (less than 34 weeks of gestation) infants admitted to neonatal intensive care units with many possible causes, including meconium aspiration syndrome, sepsis, pulmonary hypoplasia, primary pulmonary hypertension of the newborn, and surfactant deficiency. Management of infants with respiratory failure is largely supportive and includes administration of oxygen, mechanical ventilation, neuromuscular blockade, steroids, exogenous surfactant and INO therapy. Acute respiratory distress syndrome (ARDS), a type of respiratory failure in pre-term infants, is commonly the result of surfactant deficiency and less often due to pulmonary hypertension with shunting, thus treatment of ARDS varies for term/near-term and preterm neonates.

Conventional therapies

Management of pulmonary hypertension typically includes treatment of underlying diseases such as RDS and neonatal infections, promoting optimal lung recruitment, and assuring adequate ventilation and oxygenation to minimize hypoxemic pulmonary vasoconstriction. Optimizing cardiac output is essential to support systemic and pulmonary blood flow. Pulmonary vasodilation with iNO is helpful for term and near-term infants with pulmonary hypertension (PH) that persists after achieving optimal lung recruitment. Both hyperinflation and atelectasis are associated with increased pulmonary vascular resistance (PVR). The goal of ventilation should be to keep the lungs optimally inflated, maintain arterial carbon dioxide tension ($PaCO_2$) in the 35 to 50 mm Hg range, arterial oxygen tension (PaO_2) < 50 mm Hg, oxygen saturation targets between 90% and 97%, and blood pH between 7.3 and 7.4 (Mani, 2024).

Term and Near-Term Neonates

INO therapy has been shown to improve oxygenation and ventilation, reduce the need for ECMO, and lower the incidence of chronic lung disease and death among term/near-term infants with respiratory failure (Clark, 2000; Neonatal Inhaled Nitric Oxide Study Group, 1997b).

A 2017 Cochrane Review by Barrington and colleagues evaluated the use of INO for respiratory failure in infants born at or near term gestation. The authors included 17 studies, which compared INO therapy to standard therapy without INO, 10 of which were determined to be of moderate to high quality. INO appeared to result in improved outcomes for term and near-term hypoxemic infants. Oxygenation was improved in approximately 50% of infants receiving INO. Infants with CDH had slightly worse outcomes with INO. The authors concluded, “INO is effective at an initial concentration of 20 ppm for term and near-term infants with hypoxic respiratory failure who do not have a diaphragmatic hernia.”

The American Academy of Pediatrics (AAP) (Kuman, 2014) clinical report regarding the use of inhaled nitric oxide in preterm infants includes the following summary statements:

- The results of randomized controlled trials, traditional meta-analyses, and an individualized patient data meta-analysis study indicate that neither rescue nor routine use of iNO improves

survival in preterm infants with respiratory failure (Evidence quality, A; Grade of recommendation, strong).

- The preponderance of evidence does not support treating preterm infants who have respiratory failure with iNO for the purpose of preventing/ameliorating BPD, severe intraventricular hemorrhage, or other neonatal morbidities (Evidence quality, A; Grade of recommendation, strong).
- The incidence of cerebral palsy, neurodevelopmental impairment, or cognitive impairment in preterm infants treated with iNO is similar to that of control infants (Evidence quality, A).
- The results of 1 multicenter, randomized controlled trial suggest that treatment with a high dose of iNO (20 ppm) beginning in the second postnatal week may provide a small reduction in the rate of BPD. However, these results need to be confirmed by other trials.
- An individual-patient data meta-analysis that included 96% of preterm infants enrolled in all published iNO trials found no statistically significant differences in iNO effect according to any of the patient-level characteristics, including gestational age, race, oxygenation index, postnatal age at enrollment, evidence of pulmonary hypertension, and mode of ventilation.
- There are limited data and inconsistent results regarding the effects of iNO treatment on pulmonary outcomes of preterm infants in early childhood.

Congenital Diaphragmatic Hernia (CDH)

CDH is caused by a defect in the diaphragm that leads to protrusion of abdominal contents into the thorax and interferes with normal lung development (Chandrasekharan, 2017; Gien, 2016). In severe cases, CDH is associated with lung hypoplasia and immaturity, persistent pulmonary hypertension of the newborn (PPHN) and cardiac dysfunction. Secondary to pulmonary hypertension, there is shunting of blood from right to left. An early randomized controlled trial (RCT) of infants 34 weeks gestation or more with CDH did not find any significant improvement in survival or oxygenation (Nitric Oxide Study Group, 1997a). INO is not FDA approved for the treatment of PPHN caused by CDH and is also contraindicated in neonates known to be dependent on right-to-left shunting of blood (INOmax PI, 2015). However, the use of INO for the treatment of CDH appears to be continuing.

Malowitz and colleagues (2014) examined mortality and medical interventions (including INO) for neonates born with CDH. Infants 34 weeks gestation or more with CDH from 29 neonatal intensive care units (NICUs) born between 1999 and 2012 were identified. Only NICUs with an average of two or more CDH cases per year were included. Mortality and the proportion of infants exposed to medical interventions, during four periods of time (1999–2001, 2002–2004, 2005–2007, and 2008–2012) were examined. A total of 760 infants with CDH were identified. Use of INO increased from 20% of infants to 50%, sildenafil use increased from 0 to 14%, and milrinone use increased from 0 to 22% ($p<0.001$) from 1999-2001 to 2008-2012. Overall mortality (28%) did not significantly change over time as compared to the earliest time period. The authors reported that “despite the evidence for harm and lack of evidence for efficacy, INO use has significantly increased.” Additionally, they indicated that the safety and efficacy of interventions (including INO) in infants with CDH requires randomized clinical trials or prospective cohort studies of comparative effectiveness with careful data collection.

Putnam and colleagues (2016) performed a review of the Congenital Diaphragmatic Hernia Study Group (CDHSG) registry from January 1, 2007 to December 31, 2014. A total of 3367 newborns with CDH from 70 centers were entered into the registry. Sixty-eight centers (97.1%) used INO during the study. A positive association between INO use and mortality per center was reported. Treatment with INO was associated with a 15% higher absolute mortality rate after taking into account multiple "patient and operative characteristics." The authors concluded that "current data are lacking to support the widespread use of INO in this patient population because more recent data have found that its use may be associated with worse outcomes."

The American Association for Respiratory Care (AARC) (2010) published an evidence-based clinical practice guideline for INO in neonates with acute hypoxic respiratory failure. The AARC recommendations included that "INO should not be used routinely in newborns with congenital diaphragmatic hernia."

The American Pediatric Surgical Association (APSA) Outcomes and Evidence Based Practice (OEBP) committee (Puligandla, 2015) issued recommendations for CDH care. Evidence for the use of INO in neonates with CDH was obtained from three RCTs (Clark, 2000; Kinsella, 1997, NINOS Study Group, 1997a) and a Cochrane review (Finer, 2006). The quality of evidence was limited due to the age of available studies (over 10 years old) and by modest sample sizes. The committee concluded that based on level 2 evidence "iNO cannot be recommended to routinely treat pulmonary hypertension in CDH patients (grade C recommendation)." A grade C recommendation was defined as Level 4 studies (case series) or extrapolation from Level 2 (cohort studies low quality RCTs, outcomes research) or 3 (case control studies). The authors further noted that certain practice patterns continue, such as the use of INO, despite evidence showing no benefit.

In 2024, Noh published the results of a multicenter cohort study using data from the Congenital Diaphragmatic Hernia Study Group to assess the impact of early INO use in the first 3 days of life prior to the use of extracorporeal life support (ECLS). Of the 1777 participants in the study, 863 (48.6%) received early INO. The authors reported that participants receiving INO had lower birth weight, larger defect sizes, more severe pulmonary hypertension, and abnormal ventricular size and function. After controlling for these factors, early INO use was associated with increased mortality (Odds Ratio [OR], 2.06, p=0.03) and increased ECLS use (OR 3.44, p<0.001). They concluded that INO in the first 3 days of life prior to ECLS was not associated with a reduction in mortality or ECLS and the widespread use of INO in this population requires reconsideration.

Premature Neonates

Studies involving the use of INO for premature neonates (less than 34 weeks of gestation) are currently inconclusive and use of this treatment remains controversial for premature infants with severe respiratory failure. In a double-blind, randomized, placebo controlled, single-center trial, Schreiber and colleagues (2003) examined the effect of INO during the first week of life on the incidence of chronic lung disease and death in premature infants (n=207) requiring mechanical ventilation and surfactant-replacement therapy (mean gestational age, 27.2 ± 2.7 weeks). Compared to the control group, the treatment group experienced a lower incidence of death or chronic lung disease (48.6% vs. 63.7%). In a post hoc analysis, the authors concluded those infants with mild to moderate respiratory distress were most likely to benefit. While these results were promising, an accompanying editorial

pointed out that the significant difference between the two groups was in part related to the unexpectedly high rate of unfavorable outcomes (death or chronic lung disease) in the control group (Martin, 2003). The author also noted an uncertainty about the overall safety of INO in premature infants, in addition to uncertainty about optimal dosage, timing, and duration of therapy.

Mestan and colleagues (2005) conducted a prospective, longitudinal follow-up study of premature infants who had received INO or placebo to investigate neurodevelopmental outcomes at 2 years of age. The study included 138 children (82% of survivors who had participated in the Schreiber 2003 study). Neurologic examination, neurodevelopmental assessment and anthropometric measurements were made by examiners who were unaware of the children's original treatment assignment. In the group given INO, 17 of 70 children (24%) had abnormal neurodevelopmental outcomes, defined as either disability (cerebral palsy, bilateral blindness, or bilateral hearing loss) or delay (no disability, but one score of less than 70 on the Bayley Scales of Infant Development II), as compared with 31 of 68 children (46%) in the placebo group (relative risk [0.53; 95% confidence interval [CI], 0.33 to 0.87; p=0.01).

Van Meurs and colleagues (2005) conducted a randomized controlled trial (n=420) on neonates less than 34 weeks gestation, with a birth weight of 401 to 1500 grams, and with severe respiratory failure, to determine if INO treatment would reduce the incidence of bronchopulmonary dysplasia (BPD) or death. The rate of death or BPD was 80% in the INO group, as compared with 82% in the placebo group (Relative Risk [RR], 0.97; 95% CI, 0.86 to 1.06; p=0.52), and the rate of BPD was 60% versus 68% (RR, 0.90; 95% CI, 0.75 to 1.08; p=0.26). There were no significant differences in the rates of severe intracranial hemorrhage or periventricular leukomalacia. Post hoc analyses suggest rates of death and BPD are reduced for infants with a birth weight greater than 1000 grams, whereas infants weighing 1000 grams or less who are treated with INO have higher mortality and increased rates of severe intracranial hemorrhage. The authors concluded use of INO in critically ill premature infants weighing less than 1500 grams does not decrease the rates of death or BPD and suggested further trials are required to determine whether INO benefits infants with a birth weight of 1000 grams or more.

According to a review by Kinsella (2006a), trials of INO in premature newborns have resulted in conflicting outcomes. The authors reported that results of ongoing trials will help clarify the potential risks and benefits of INO therapy in this population. A multicenter, randomized trial (Kinsella, 2006b) investigated the safety and efficacy of early inhaled, low dose INO therapy in a multicenter, randomized trial. This study involved 793 newborns who were 34 weeks or less gestational age and had respiratory failure requiring mechanical ventilation. Random assignments were made of either INO (5 parts per million [ppm]) or placebo gas for 21 days or until extubation with stratification according to birth weight. The authors concluded that among premature newborns with respiratory failure, low-dose INO did not reduce the overall incidence of bronchopulmonary dysplasia, except among those with a birth weight of at least 1000 grams, but it did reduce the overall risk of brain injury. Long-term follow-up studies of these infants are ongoing to determine later outcomes of early INO therapy.

Ballard and colleagues (2006), in a randomized, stratified, double-blind, placebo-controlled trial of INO, studied infants with a gestational age of 26 weeks and a birth weight of 1250 grams or less who required ventilation between 7 and 21 days of age. A total of 294 infants received INO and 288 received a placebo. The survival rate without BPD at 36 weeks postmenstrual age was 43.9% in the group receiving INO and 36.8% in the group

receiving a placebo. The authors concluded that prolonged INO therapy initiated between 7 and 21 days of age in preterm infants receiving mechanical ventilation improved survival without BPD and without short-term adverse effects. However, the authors further noted that definitive recommendations regarding the use of INO among infants at high risk for BPD await further long-term neurodevelopmental follow-up in completed trials.

Hintz and colleagues (2007) studied neurodevelopmental outcomes at 18-22 months in 420 premature infants less than 34 weeks of gestation, weighing less than 1500 grams with severe respiratory failure. These infants were previously enrolled in the National Institute of Child Health and Human Development Preemie iNO trial which was a multicenter, randomized, placebo controlled study of INO. Study findings did not reveal reduced death or improved neurodevelopmental outcomes in the infants exposed to INO. The authors concluded that until more information is obtained, routine use of INO among premature infants should be restricted to research settings.

A randomized study by Van Meurs and colleagues (2007) examined INO use in 29 infants greater than 1500 grams but less than 34 weeks gestation with severe respiratory failure. The sample size limited definitive conclusions, but suggested that INO does not affect the rate of BPD and death.

Di Fiore and colleagues (2007) assessed the effect of INO on resistance and compliance in ventilated preterm infants with evolving BPD. A total of 71 ventilated preterm infants were enrolled in a randomized, double-blinded, placebo controlled multicenter study; 37 infants received placebo gas and 34 infants received INO. Results indicated there was no effect of INO on expiratory resistance or compliance at 1 hour, 1 week, or 2 weeks of study gas administration. Study limitations included limited sample size and a number of infants lost to follow-up due to extubation and other factors.

Huddy and colleagues (2008) reported results of a multicenter RCT (INNOVO trial) which studied neonatal ventilation with INO versus ventilatory support without INO for severe respiratory failure in preterm infants. A total of108 infants (55 INO arm and 53 controls) from 15 neonatal units were recruited and followed up to age 4 or 5 years. By 1 year of age, 59% had died and 84% of the survivors had signs of impairment or disability. Children were assessed at age 4 to 5 years by examination, interview, cognitive, and behavioral assessments. The outcomes were divided into seven domains and were described as normal, impaired or disabled (mild, moderate or severe) by the degree of functional loss. Thirty-eight of the 43 survivors had follow-up assessments. In the INO group 62% (34/55) had died or were severely disabled as compared to 70% (37/53) in the no INO group (RR, 0.89; 95% CI, 0.67 to 1.16). Only 8 children of the original 108 recruited to the trial were classified as normal across all of the domains at 4 to 5 years of age.

Mercier and colleagues (2010) studied 800 preterm infants with a gestational age between 24 and 28 weeks plus 6 days with a weight of at least 500 grams, requiring surfactant or continuous positive airway pressure for RDS within 24 hours of birth. The infants were randomly assigned in a one-to-one ratio to either a placebo (nitrogen gas) or INO for a minimum of 7 days and a maximum of 21 days in a double-blind European multicenter study. The authors concluded:

> INO at 5 ppm, started within the first 24 hours after birth and continued for a median of three weeks, does not improve survival without BPD in very preterm neonates with mild to moderate RDS. Our negative results should alter practice by helping to eliminate the use of INO in preterm infants developing bronchopulmonary dysplasia.

Askie and colleagues (2011) performed a meta-analysis of data from RCTs evaluating the efficacy of INO in preterm infants (less than 37 weeks' gestation). Included were data from 12 trials with a total of 3298 infants. The primary endpoints of the analysis were death or severe neurological events during the trial and chronic lung disease (defined as receipt of supplemental oxygen at 36 weeks' postmenstrual age). Overall, death or chronic lung disease occurred in 59% of infants treated with INO and 61% of control infants. The difference between groups was not statistically significant (RR 0.96; 95% CI, 0.92 to 1.01; p=0.11). Severe neurologic events occurred in 25% of infants in the INO group and 23% in the control group (RR 1.12; 95% CI, 0.98 to 1.28; p=0.09). Subanalyses, (by birth weight, gestational age, race, etc.) did not find any characteristics significantly associated with a benefit from INO. The authors concluded that routine use of INO in preterm infants is not recommended.

In 2013, Durrmeyer and colleagues published 2-year outcomes of the European Union Nitric Oxide trial, an RCT of inhaled nitric oxide in premature infants. Of the 800 original premature neonates, a total of 737 were available for evaluation at this time point. The evaluable children excluded those who were lost to follow-up or did not receive treatment. A total of 244 of 363 (67%) evaluable children at 2 years in the INO group survived without severe or moderate disability compared to 270 of 374 (72%) evaluable children in the placebo group. The difference in disability rates was not statistically significant (p=0.09). There were also no statistically significant differences between groups in other outcomes such as growth, hospitalization rates, or use of respiratory medications.

Kinsella and colleagues (2014) performed a multicenter RCT designed to assess the safety and efficacy of early, noninvasive iNO therapy in premature newborns that did not require mechanical ventilation. Enrollment criteria included gestational age of 34 weeks or less, birth weight between 500 and 1250 grams, postnatal age less than 72 hours, and supplemental oxygen use per CPAP or nasal cannula. Prior to randomization, 124 newborns were stratified into three different groups by birth weight (500-749, 750-999, 1000-1250 grams) to iNO (10 ppm) or placebo gas (controls) until 30 weeks postmenstrual age. The primary outcome was a composite of death or BPD at 36 weeks postmenstrual age. Secondary outcomes included the need for and duration of mechanical ventilation, severity of BPD, and safety outcomes. No difference in the incidence of death or BPD was reported in the iNO and placebo groups (42% vs 40%, p=0.86, RR=1.06, 0.7 to 1.6). There were no differences between the treatment groups in the severity of BPD, the duration of mechanical ventilation, need for mechanical ventilation, or safety outcomes including severe intracranial hemorrhage. The authors concluded:

> Prolonged treatment with noninvasive iNO was safe but did not decrease the composite endpoint of death/BPD in newborns with birth weights of 500-1250 g treated within 72 hours after birth. Long-term follow-up studies of these infants are ongoing to determine later pulmonary and neurocognitive outcomes of early iNO therapy.

A 2017 Cochrane Review by Barrington and colleagues evaluated the use of INO for the treatment of respiratory failure in preterm infants. The authors located 17 randomized controlled trials of INO therapy in preterm infants. A total of 8 trials that provided early rescue treatment showed no significant effect of INO on mortality or bronchopulmonary dysplasia (BPD). Four studies examined the routine use of INO in preterm infants with pulmonary disease and no significant reduction in death or BPD occurred. Three trials evaluated later treatment with INO based on risk of BPD and no significant benefit was reported. The authors concluded that INO did not appear to be effective as rescue therapy or for early routine use and recommended further study for later use of INO to prevent BPD in preterm infants.

Hasan and colleagues (2017) conducted an RCT to determine if INO would decrease the incidence of BPD in premature infants. Included participants were < 30 weeks gestation, weighed < 1250 g, had a postnatal age of 5 to 14 days, and required mechanical ventilation or positive pressure respiratory support. The primary outcome was the rate of survival without BPD at 36 weeks' postmenstrual age (PMA). The researchers randomized the participants to receive either INO (n=229) or a placebo (n=222); however, several participants died or were withdrawn, leaving 208 participants in the INO group and 204 in the placebo group. The INO group received INO at 20 ppm for 24 days. At the end of the study, the survival rate was 34.9% for the INO group and 31.5% for the placebo group (OR 1.17; 95% CI, 0.79 to 1.73). The rate of severe BPD, postnatal corticosteroid use, average length of positive pressure support, oxygen therapy, and hospitalization days did not differ between the groups. In addition, neurodevelopmental assessments at 18-24 months were similar between the groups. The authors concluded that INO "appears to be safe but did not improve survival without BPD."

In 2017, Baczynski and colleagues published results from a retrospective cohort study over a 6-year follow-up period to describe short and long-term outcomes of preterm 89 neonates (born <35 weeks) with severe acute pulmonary hypertension in response to rescue INO therapy (≥ 1 hour INO exposure). Primary outcomes included survival without disability and mortality. Overall response rate (defined as fraction of inspired oxygen [FiO2] reduced by ≥ 0.20) to INO was 46%. Neonates who responded showed improved survival without disability (51% vs 15%; p<0.01), lower mortality (34% vs 71%; p<0.01) and lower disability among survivors (17% vs 50%; p=0.06). Authors conclude that, "A positive response to rescue INO in preterm infants with acute pulmonary hypertension is associated with survival benefit, which is not offset by long-term disability." Prospective study is warranted to confirm these findings.

Carey and colleagues (2018) performed a retrospective cohort study to determine if INO improves in-hospital survival for extremely premature neonates with RDS. Using 2004-2014 data from the Clinical Data Warehouse, the researchers analyzed 37,909 neonates born at 22 to 29 weeks who had RDS and required mechanical ventilation. The primary outcome was mortality (defined as death before discharge). The researchers matched 2 cohorts of 971 participants each: a cohort who received INO during the first 7 days of life and a matched cohort who had not received INO initially. A total of 348 and 325 participants died before discharge in the INO group and matched group, respectively. The researchers did not find a significant association between INO use and mortality (hazard ratio [HR] 1.08; 95% CI, 0.94 to 1.25; p=0.29). They concluded:

> Off-label prescription of iNO does not improve survival in extremely premature neonates with RDS. Neonates whose RDS is associated with PPHN have high rates of mortality and morbidity, neither of which is reduced by treatment with iNO in the first week of life. Among those without a concomitant diagnosis of PPHN, iNO therapy was associated with increased mortality.

The current AAP (reaffirmed 2010) policy statement on the use of INO in neonates with respiratory distress states:

> The limited data to date on hypoxic preterm neonates suggest that low-dose INO improves oxygenation but does not improve survival. Additional large randomized trials of INO in premature neonates are required because they may experience more toxic effects than term and near-term infants.

The Agency for Healthcare Research and Quality (AHRQ) (2010) in an evidence report on INO in preterm infants concludes that "there is currently no evidence to support the use of INO in preterm infants with respiratory failure outside the context of rigorously conducted randomized clinical trials."

In 2011, a National Institutes of Health (NIH) Consensus Development Conference Statement on INO for premature infants was published. The statement was based on the 2010 AHRQ-sponsored systematic review of the literature noted above. The NIH concluded that "taken as a whole, the available evidence does not support use of INO in early-routine, early-rescue, or later-rescue regimens in the care of premature infants of < 34 weeks' gestation who require respiratory support."

An AAP clinical report (Kumar, 2014) reviewed existing data for the use of INO in preterm infants and provided guidance regarding its use in this population. The following summary was provided:

1. The results of randomized controlled trials, traditional meta-analyses, and an individualized patient data meta-analysis study indicate that neither rescue nor routine use of iNO improves survival in preterm infants with respiratory failure (Evidence quality, A; Grade of recommendation, strong).
2. The preponderance of evidence does not support treating preterm infants who have respiratory failure with iNO for the purpose of preventing/ ameliorating BPD, severe intraventricular hemorrhage, or other neonatal morbidities (Evidence quality, A; Grade of recommendation, strong).
3. The incidence of cerebral palsy, neurodevelopmental impairment, or cognitive impairment in preterm infants treated with iNO is similar to that of control infants (Evidence quality, A).
4. The results of 1 multicenter, randomized controlled trial suggest that treatment with a high dose of iNO (20 ppm) beginning in the second postnatal week may provide a small reduction in the rate of BPD. However, these results need to be confirmed by other trials.
5. An individual-patient data meta-analysis that included 96% of preterm infants enrolled in all published iNO trials found no statistically significant differences in iNO effect according to

any of the patient-level characteristics, including gestational age, race, oxygenation index, postnatal age at enrollment, evidence of pulmonary hypertension, and mode of ventilation.

6. There are limited data and inconsistent results regarding the effects of iNO treatment on pulmonary outcomes of preterm infants in early childhood.

In 2016, Kinsella and colleagues for the Pediatric Pulmonary Hypertension Network proposed the following recommendations for the role of iNO in premature newborns:

1. iNO therapy should not be used in premature infants for the prevention of BPD [bronchopulmonary dysplasia], as multicenter studies data have failed to consistently demonstrate efficacy for this purpose.
2. iNO therapy can be beneficial for preterm infants with severe hypoxemia that is primarily due to PPHN [persistent pulmonary hypertension of the newborn] physiology rather than parenchymal lung disease, particularly if associated with prolonged rupture of membranes and oligohydramnios.
3. iNO is preferred over other pulmonary vasodilators in preterm infants based on a strong safety signal from short- and long-term follow-up of large numbers of patients from multicenter randomized clinical trials for BPD prevention, and
4. Placebo controlled trials are not feasible in the target population; therefore, alternate study designs such as the development of multicenter registries, informatics strategies, and other approaches should be used to address issues regarding the efficacy and safety of therapeutic options for preterm infants with life threatening PPHN physiology.

However, the authors encouraged additional research and concluded:

> iNO therapy has successfully improved clinical management and has lowered the need for ECMO therapy in term and near-term infants, but more studies are needed to more precisely define its role in premature neonates. Although we recommend that iNO not be routinely used for the prevention of BPD, we believe that iNO therapy may have an important role for subgroups of preterm infants with severe PH, especially in the setting of PPHN physiology associated with oligohydramnios, lung hypoplasia, and sepsis. Owing to promising case series findings, extensive safety data in preterm infants from past metaRegister of Controlled Trials and the lack of safety or efficacy data concerning other targeted PH therapies (PH-specific drugs), we believe that it is reasonable to use iNO in this subgroup of critically ill preterm infants. We encourage ongoing research for the impact of iNO and other therapies in the setting of severe PH in preterm infants

In 2020, Chandrasekharan and colleagues conducted a retrospective analysis of prospectively collected data to evaluate survival and neurodevelopmental impairment at 18 to 26 months in 1732 extremely low birth weight infants (< 1000g) born prior to 26 weeks with early hypoxemic respiratory failure. In total, 338 infants received INO. Mortality among those treated with INO was 54.1% compared with 44.4% mortality in infants not exposed; this difference was not statistically significant after adjusting for confounding variables. Authors conclude that in

infants born prior to 26 weeks' gestation with hypoxemic respiratory failure use of INO did not significantly impact mortality or neurodevelopmental impairment at 18 to 26 months.

A 2023 systematic review and meta-analysis by Zheng and colleagues evaluated the efficacy and safety of INO in preventing BPD and aiding in clinical decision-making. Included were data from 11 RCTs with 3651 preterm infants (≤ 34 weeks). After analysis of the studies, the INO groups were associated with a lower incidence of BPD than the control groups (RR = 0.91, 95% CI 0.85-0.97, P = 0.006). There were no statistically significant differences in the incidence of in-hospital mortality between the INO and control groups (RR = 1.02, 95% CI 0.89-1.16, P = 0.79). Secondary outcome measures included the incidence of intraventricular hemorrhage (IVH) (Grade 3/4) or periventricular leukomalacia (PVL), pulmonary hemorrhage (PH) and necrotizing enterocolitis (NEC). Analysis revealed no significant difference in the incidence of IVH (Grade 3/4) or PVL between the INO group and the control group (RR = 0.92, 95% CI 0.77-1.09, P = 0.34) or in PH rate (RR = 0.83, 95% CI 0.55-1.25, P = 0.37. Analysis revealed a significant difference in NEC rate between the two groups (RR = 1.33, 95% CI 1.04-1.71, P = 0.03), however those who were treated with an initial dose of 10 ppm INO showed no significant difference in incidence of NEC while those who received an initial dose of 5 ppm INO had greater rates of NEC. The analysis showed an initial dose of INO of 10 ppm given to preterm infants ≤ 34 weeks appeared to be more effective at reducing BPD than conventional treatment and INO given at an initial dose of 5 ppm had a comparable incidence of in-hospital mortality and adverse events compared to conventional treatment plus placebo. The authors conclude "More research is required to improve the in-hospital mortality and safety of INO in this setting."

Boly (2023) reported the results of a retrospective analysis of 107 infants born 22-26 weeks of gestation who received INO for hypoxic respiratory failure, defined as fraction of inspired oxygen (FiO2) of ≥ 0.5 or oxygenation index (OI) ≥ 10. All participants received INO for ≥ 12h. Response to INO treatment was determined 2h after initiation of therapy by consensus of three neonatologists, all of whom were blinded to the clinical outcomes. Positive response was defined as a FiO2 decrease of ≥0.2 or a OI decrease of ≥20%. Conversely, a negative response was defined as an FiO2 increase of ≥ 0.2 or an OI increase of ≥ 20%. If these criteria were not met, then the case was determined to be a non-responder. A total of 67 participants were deemed to be responders, 27 non-responders and 13 negative responders. In logistic regression modeling, postnatal age [OR 1.1, p=0.01),] but not gestational age [OR, 0.9 (0.7,1.3)], was associated with a positive response. No intergroup differences were reported, including markers of clinical illness severity, including respiratory severity score, OI, FiO2, pH, receipt of cardiotropic support, and inotrope score immediately prior to INO initiation. For the positive response group, 67% of participants had acute pulmonary hypertension, 9% had sepsis or systemic inflammatory response syndrome (SIRS), and 24% had lung disease (p<0.001). For the no response group, only 15% had acute pulmonary hypertension, 26% had a hemodynamically significant patent ductus arteriosus (PDA), 7% had sepsis or SIRS, and 52% had severe lung disease. For the negative response group, 33% had a hemodynamically significant PDA, 42% had sepsis or SIRS, and 25% had severe lung disease. The proportion of infants with pulmonary hypertension was highest among responders (p<0.001), while PDA was higher in both non-responder and negative responders (p=0.02), and lung parenchymal disease was higher (p=0.003) among non-responders. The primary outcome, combined outcome of death or grade 3 bronchopulmonary dysplasia (BPD) was lower in the positive response group vs. the no response and negative response groups (67% vs. 85% and 100%, respectively, p=0.01). No intergroup differences were reported with regard to the incidence of duration of invasive ventilation after INO,

necrotizing enterocolitis, intraventricular hemorrhage, periventricular leukomalacia, and age at discharge. The authors concluded that extremely premature infants have a positive response rate to INO comparable to term infants when used for PH in the transitional period. Additionally, they noted that infants with a negative response to INO had worse outcomes, necessitating the determination of the underlying physiology of hypoxemic neonatal respiratory failure prior to INO initiation.

Randomized trials of INO therapy in premature infants have yielded conflicting results in terms of its effect on the incidence of BPD, neurological events, and neurobehavioral outcomes. This may be related to differences in severity of illness in the study participants, dose of INO, and timing and duration of therapy, making it difficult to draw definitive conclusions regarding the use of INO in this population. The benefits and risks of INO need further study before its use can be recommended in the premature infant. Longer-term follow-up of study participants may help to clarify whether long-term health benefits result from INO therapy.

Assessment of Pulmonary Vasoreactivity

INO has also been studied as a diagnostic method of assessing pulmonary vasoreactivity in persons with pulmonary hypertension. A brief diagnostic trial (Atz, 1999) compared the ability of INO, oxygen (O2) and nitric oxide in oxygen (NO+O2) to identify reactive pulmonary vasculature in those with pulmonary hypertension during acute vasodilator testing at cardiac catheterization. In persons with pulmonary hypertension, decisions regarding suitability for corrective surgery, transplantation, and assessment of long-term prognosis are based on results obtained during acute pulmonary vasodilator testing. Two groups consisting of 71 participants were included for analysis in this study. In the first group, 46 participants had hemodynamic measurements in room air (RA), 100% O2, return to RA and NO (80 parts per million [ppm] in RA). In the second group, 25 additional participants were studied in RA, 100% O2 and 80 ppm NO in oxygen (NO+O2). In group one, O2 decreased PVR from 17.2 ± 2.1 $U.m^2$ to 11.1 ± 1.5 $U.m^2$ ($p<0.05$). Nitric oxide caused a comparable decrease from 17.8 ± 2.2 $U.m^2$ to 11.7 ± 1.7 $U.m^2$ ($p<0.05$). In group 2, PVR decreased from 20.1 ± 2.6 $U.m^2$ to 14.3 ± 1.9 $U.m^2$ in O2 ($p<0.05$) and further to 10.5 ± 1.7 $U.m^2$ in NO+O2 ($p<0.05$). A response of 20% or more reduction in PVR was seen in 22/25 individuals with NO+O2 compared with 16/25 in O2 alone ($p=0.01$). The authors concluded that INO and O2 produced a similar degree of selective pulmonary vasodilation, and combination testing with NO + O2 provided additional pulmonary vasodilation.

A randomized trial (Balzer, 2002) investigated whether preoperative hemodynamic evaluation with O2 and INO could identify individuals with pulmonary hypertension who may be appropriate candidates for heart transplantation or corrective cardiac surgery more accurately than an evaluation with O2 alone. The ratio of pulmonary and systemic vascular resistance (Rp:Rs) was determined at baseline while breathing 21% to 30% O2, and in 100% O2 and 100% O2 with 10 to 80 ppm NO to evaluate pulmonary vascular reactivity. A total of 78 individuals were determined to be operable. Of those, 74 had undergone surgery at the time data was collected. A total of 12 participants died or developed right heart failure secondary to pulmonary hypertension following surgery. Survivors were followed for a median duration of 26 months. Rp:Rs 0.33 and a 20% decrease in Rp:Rs from baseline had been chosen as two criteria for operability to retrospectively determine the efficacy of preoperative testing in selecting surgical candidates. In comparison to an evaluation with oxygen alone, sensitivity

(64% versus 97%) and accuracy (68% versus 90%) were increased by an evaluation with O2 and NO when Rp:Rs 0.33 was used as the criterion for surgery. Specificity was only 8% when a 20% decrease in Rp:Rs from baseline was used as the criterion for operability. The authors indicated that a preoperative hemodynamic evaluation with a combination of supplemental O2 and INO may identify a greater number of candidates for corrective surgery or transplantation than a preoperative evaluation with O2 alone.

Barst and colleagues (2010), in an industry sponsored study, investigated whether a combination of INO and O2 was more effective than 100% O2 or INO alone for acute vasodilator testing in children. An open, prospective, randomized, controlled trial was conducted at 16 centers. A total of 136 children were enrolled and 121 completed the study. Children 4 weeks to 18 years of age with pulmonary hypertension (PH) and increased pulmonary vascular resistance (PVR) underwent right heart catheterization for acute vasodilator testing. All participants were tested with each of three agents (80 ppm INO, 100% O2 and a combination of 80 ppm INO/100% O2) in three 10-minute treatment periods. Primary outcome measures were percentages of acute responders to each agent. Changes in PVR index and mean pulmonary arterial pressure compared to baseline were greater with INO/O2 compared to either O2 or INO alone ($p<0.001$). Survival at 1-year follow-up included (1) 90.9% of acute responders to the combination, compared with 77.8% of nonresponders to the combination, and (2) 85.7% of acute responders to O2 alone, compared with 80.6% of nonresponders to O2. There was no significant difference in acute responder rate with INO alone versus INO/O2; however, it was reported that the combination improved pulmonary hemodynamics acutely better than INO alone. One year survival data show similar rates between the INO/O2 and the O2 alone groups.

Krasuski and colleagues (2011) evaluated the ability of vasodilator response to predict survival in a heterogeneous group of individuals with pulmonary hypertension. A total of 214 treatment-naive participants with pulmonary hypertension were enrolled in the study between November 1998 and December 2008. Vasoreactivity was assessed during inhalation of iNO. There were 51 deaths (25.9%) over a mean follow-up period of 2.3 years. Kaplan-Meier analysis demonstrated that vasodilator responders had significantly improved survival ($p<0.01$). The authors concluded that "vasodilator responsiveness to iNO is an important method of risk stratifying PH patients, with results that apply regardless of clinical etiology."

In 2015, the American Heart Association and American Thoracic Society issued guidelines for the treatment of pediatric pulmonary hypertension. Included were the following recommendations related to INO that were graded as a Class I; Level of Evidence A (meaning that the procedure/treatment was deemed useful/effective with sufficient evidence from multiple randomized trials or meta-analyses).

- Inhaled nitric oxide (iNO) is indicated to reduce the need for extracorporeal membrane oxygenation (ECMO) support in term and near-term infants with persistent PH of the newborn (PPHN) or hypoxemic respiratory failure who have an oxygenation index that exceeds 25
- Cardiac catheterization should include acute vasoreactivity testing (AVT) unless there is a specific contraindication (Class I; Level of Evidence A). Additionally noted is that AVT may be studied with iNO (20–80 ppm), 100% oxygen, inhaled or intravenous PGI_2 analogs, or intravenous adenosine or sildenafil.

Additional lower-level recommendations included in the guidelines related to INO were:

- iNO can be beneficial for preterm infants with severe hypoxemia that is due primarily to PPHN physiology rather than parenchymal lung disease, particularly if associated with prolonged rupture of membranes and oligohydramnios (Class IIa; Level of Evidence B).
- iNO therapy can be used to improve oxygenation in infants with congenital diaphragmatic hernia (CDH) and severe PH but should be used cautiously in participants with suspected LV dysfunction(Class IIa; Level of Evidence B).
- Treatment with iNO can be effective for infants with Established bronchopulmonary dysplasia (BPD) and symptomatic PH (Class IIa; Level of Evidence C).
- In addition to conventional postoperative care, iNO and/or inhaled PGI_2 should be used as the therapy for pulmonary hypertension crises (PHCs) and failure of the right side of the heart (Class I; Level of Evidence B).

Class of recommendation and level of evidence is described in the guideline as follows:

> Class of Recommendation is an estimate of the magnitude of the treatment effect, with consideration given to risks versus benefits and the evidence and agreement that a given treatment or procedure is or is not useful or effective (Class I or II). Class III designation is applied for interventions that may cause harm to the patient. The Level of Evidence is an estimate of the certainty or precision of the treatment effect. The writing committee reviews and ranks evidence supporting each recommendation, with the weight of evidence ranked as Level of Evidence A, B, or C according to specific definitions. For conditions in which inadequate data are available, recommendations are based on expert consensus and clinical experience and are ranked as Level of Evidence C. The committee reviewed and ranked evidence supporting current recommendations with the weight of evidence ranked as Level A if the data were derived from multiple RCTs or meta-analyses. The committee ranked available evidence as Level B when data were derived from a single RCT or nonrandomized studies. Evidence was ranked as Level C when the primary source of the recommendation was consensus opinion, case studies, or standard of care.

The 2022 Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS) Guidelines for the Diagnosis and Treatment of Pulmonary Hypertension (Humber, 2022) recommended, "Inhaled nitric oxide, inhaled iloprost, or i.v. epoprostenol are recommended for performing vasoreactivity testing" (Class I, Level C) and INO at 10-20 parts per million (ppm) for 5-10 minutes is the standard of care for vasoreactivity testing.

Other Potential Uses

Sokol (2003), in a review of the published literature for the use of INO in children and adults with respiratory distress, evaluated five randomized controlled trials including 535 children and adults with acute hypoxemic

respiratory failure, and concluded INO did not demonstrate any statistically significant effect on mortality and transiently improved oxygenation. Lack of data prevented assessment of other clinically relevant endpoints.

A 2010 Cochrane review by Afshari and colleagues identified 14 randomized controlled trials which compared INO with no intervention or placebo in a total of 1303 participants consisting of both children and adults with acute hypoxemic respiratory failure (AHRF). AHRF was described as acute RDS and acute lung injury characterized by an inflammatory process of the alveolar-capillary membrane that may occur as a result of a primary lung disease or secondary to systemic disease processes. A significant but transient improvement in oxygenation was found in the first 24 hours; however, INO appeared to increase the risk of renal impairment among adults. The authors concluded that "INO cannot be recommended for patients with AHRF. INO results in a transient improvement in oxygenation but does not reduce mortality and may be harmful."

In a systematic review and meta-analysis, Adhikari and colleagues (2014) investigated whether INO reduces hospital mortality in individuals with severe acute respiratory distress syndrome (ARDS) (PaO2/FIO2 ≤ 100 mm Hg) as compared to those with mild-moderate ARDS (100 < PaO2/FIO2 ≤ 300 mm Hg). Parallel-group RCTs comparing nitric oxide with control (placebo or no gas) in mechanically ventilated adults or post-neonatal children with ARDS were independently selected. Nine trials (n=1142 participants) met inclusion criteria. Nitric oxide was not observed to reduce mortality in individuals with severe ARDS (RR, 1.01; 95% CI, 0.78 to 1.32; p=0.93; n=329, six trials) or mild-moderate ARDS (RR, 1.12; 95% CI, 0.89 to 1.42; p=0.33; n=740, seven trials). The authors concluded there was no beneficial effect of nitric oxide on mortality among individuals with ARDS, regardless of the severity of hypoxemia at randomization. They further noted that given the lack of related ongoing or recently completed randomized trials, new data addressing the effectiveness of nitric oxide in those with ARDS and severe hypoxemia will not be available for the foreseeable future.

A prospective, randomized placebo-controlled trial (Bronicki, 2015) assessed the use of INO for improved oxygenation and decreased duration of mechanical ventilation in children with ARDS. A total of 55 children from nine centers were randomized to either placebo or INO. Treatment continued until death, removal of ventilator support, or 28 days after the start of therapy. The primary study outcome was ventilator-free days at 28 days post randomization. A trend toward an improved oxygenation index (OI) in the INO group compared with the placebo group at 4 hours became significant at 12 hours. There was no difference in the OI between groups at 24 hours. Days alive and ventilator-free at 28 days was increased in the INO group, 14.2 ± 8.1 and 9.1 ± 9.5 days (INO and placebo groups, respectively, p=0.05). Overall survival at 28 days did not reach statistical significance, 92% (22 of 24) in the INO group and 72% (21 of 29) in the placebo group (p=0.07). However, the rate of extracorporeal membrane oxygenation-free survival was significantly greater in those randomized to INO 92% (22 of 24) vs 52% (15 of 29) for those receiving placebo (p<0.01). A significant study limitation was the limited number of participants enrolled. The authors concluded that a prospective, randomized controlled trial with more robust enrollment is indicated.

Additionally, there is insufficient evidence to support the use of INO for the prevention of ischemia-reperfusion injury/acute rejection following lung transplantation, the treatment of acute lung injury, postoperative hypoxemia in obese individuals with aortic dissection, mechanically ventilated adults with COVID-19, or vaso-occlusive crises in

those with sickle cell disease (Abboursheid, 2019; Dellinger, 1998; Ghadimi, 2022; Lubinsky, 2022; Lundin, 1999; Reiter Meade, 2003; Taylor, 2004; Weiner, 2003; Zheng, 2022).

A 2014 Cochrane review by Bizzaro and colleagues identified four RCTs comparing the effects of postoperative INO versus placebo or conventional management of 210 infants and children with congenital heart disease. The primary outcome of the review was mortality. No differences were observed between groups with respect to mortality (p=0.50), number of pulmonary hypertensive crises (p=0.79), change in mean pulmonary arterial pressure (p=0.16), mean arterial pressure (p=0.40), heart rate (p=1.00), changes in oxygenation, and measurement of maximum methaemoglobin level as a marker of toxicity. The authors noted the lack of data on long-term mortality, length of stay in an intensive care unit or hospital, and neurodevelopmental disability. They also had concerns about methodological quality of studies, sample size, and heterogeneity between studies. These results do not support a benefit for postoperative INO treatment for infants and children with congenital heart disease.

In 2020, another systematic review was published by Villarreal and colleagues to determine the effect of INO on hemodynamics, gas exchange, and hospitalization characteristics in children immediately following cardiopulmonary bypass surgery. A total of eight studies met inclusion criteria (six crossover studies and two RCTs; all but one study [James, 2016] was also included in the Cochrane review above). As noted above, most of the studies had low enrollment, methodologic flaws and heterogenous outcomes. Contrary to the Cochrane review, the authors of the current study concluded that administration of INO in children immediately after cardiopulmonary bypass decreased mean pulmonary artery pressure (<0.01) and decreased the arterial carbon dioxide concentration (<0.01) without significantly altering other hemodynamic parameters. The study reported a statistically shorter duration of mechanical ventilation and intensive care unit length of stay. Further study is warranted given the inconsistent conclusions upon systematic review.

In 2022, a double-blind, RCT was published by Schlapbach and colleagues which enrolled 1371 children (< 2 years of age) undergoing congenital heart surgery. The study's main objective was to determine the effect of nitric oxide (at 20 ppm) administered directly into the cardiopulmonary bypass oxygenator (n=679) compared to standard care cardiopulmonary bypass without nitric oxide (n=685); the primary endpoint was the number of ventilator-free days from the initiation of bypass until day 28 of follow-up. Secondary endpoints included a composite of low cardiac output syndrome, extracorporeal life support, or death; length of stay in the intensive care unit; length of stay in the hospital; and postoperative troponin levels. At study end, the primary outcome, number of ventilator-free days, did not differ significantly between the nitric oxide and standard care group (p=0.92). Study authors conclude, in "children younger than 2 years undergoing cardiopulmonary bypass surgery for congenital heart disease, the use of nitric oxide via cardiopulmonary bypass did not significantly affect the number of ventilator-free days. These findings do not support the use of nitric oxide delivered into the cardiopulmonary bypass oxygenator during heart surgery."

Potapov and colleagues (2011) conducted a study to evaluate the prophylactic use of INO in adults undergoing left ventricular assist device (LVAD) implantation for congestive heart failure. A double-blind trial was conducted between 2003 and 2008 at eight centers in the United States and Germany. Individuals were randomized to receive INO (40 ppm) (n=73) or placebo (n=77) beginning at least 5 minutes before the first weaning attempt from

mechanical ventilation. The primary study outcome was right ventricular dysfunction (RVD). Continued use of INO or placebo occurred until the study participants were extubated, reached the study criteria for RVD, or were treated for 48 hours, whichever occurred first. Individuals were permitted to crossover to open-label INO if they failed to wean from mechanical ventilation, still required pulmonary vasodilator support at 48 hours, or met criteria for RVD. Thirteen of 150 randomized participants (9%) did not receive the study treatment. In addition, crossover to open-label INO occurred in 15 of 73 participants (21%) in the INO group and 20 of 77 (26%) in the placebo group. In an intention-to-treat (ITT) analysis, the RVD criteria were met by 7 of 73 (9.6%) participants in the INO group and 12 of 77 (15.6%) participants in the placebo group. This difference was not statistically significant (p=0.33). Other outcomes also did not differ significantly between groups. For example, the mean number of days on mechanical ventilation was 5.4 in the INO group and 11.1 in the placebo group (p=0.77), and the mean number of days in the hospital was 41 in each group.

A prospective randomized single center trial (Trzeciak, 2014) evaluated 50 adults with severe sepsis and systolic blood pressure less than 90 mm Hg despite intravascular volume expansion and/or serum lactate greater than or equal to 4.0 mmol/L. After macrocirculatory resuscitation goals were met, participants were randomized to 6 hours of iNO (40 ppm) or sham inhaled nitric oxide administration. The primary outcome measure was microcirculatory flow index change. Secondary outcome measures were lactate clearance and change in Sequential Organ Failure Assessment score. Of the 50 adults enrolled, 28 (56%) required vasopressor agents and 15 (30%) died. Despite increased levels of plasma nitrite with iNO treatment, no improvement was observed in microcirculatory flow, lactate clearance, or organ dysfunction. No association was found between changes in microcirculatory flow and lactate clearance or organ dysfunction.

Tal and colleagues (2018) conducted a double-blind RCT to assess the safety, tolerability, and efficacy of INO for infants with moderately severe bronchiolitis. A total of 43 participants, aged 2-11 months old, were randomized to either receive INO (n=21) or a placebo (n=22). The mean clinical score, which included respiratory rate, use of accessory muscles, wheezes/crackles, and percentage of room-air oxygen saturation, was 7.86 (± 1.1) for the INO group and 8.09 (± 1.2) for the placebo group. Adverse events were reported for 47.6% of the INO group and 59.1% for the placebo group, and each group had 4 participants who experienced serious adverse events. There were no deaths or incidences of bleeding. In terms of tolerability, 4 participants in the INO group discontinued treatment compared to 2 participants in the placebo group. The authors concluded that the results are encouraging, but large-scale trials are needed to further assess the safety and benefits.

Goldbart (2023) reported the results of another double-blind RCT involving 89 infants with bronchiolitis receiving 150 ppm NO plus supporting treatment (n=28), 85 ppm NO plus supporting treatment (n=32), or oxygen or air plus supporting treatment (n=29). Treatment was applied for 40 minutes, 4 times a day for up to 5 days. The primary endpoint was a composite measure, referred to as “fit for discharge”, which included time to 1) sustained oxygen saturation ≥ 92% on room air and 2) reaching a clinical modified Tal (mTal) score < 5. The mTal score is itself a composite measure composed of four measurements: respiratory rate, lung sound, room-air SpO2, and use of accessory muscles. A significant difference between groups in favor of the 150 ppm group was found vs. both the 85 ppm and control groups (Hazard Ratio [HR], 2.11; p=0.041 and HR, 2.32; p=0.0486, respectively). No significant differences were reported between the 85 ppm and control groups (p=0.76). Time to sustained room-air

SpO_2 > 92% was significantly better in the 150 ppm group compared to the control group (HR, 2.62; p=0.039), but not compared to the 85 ppm group (p=0.56). Time to hospital discharge was significantly better in the 150 ppm group compared to both the 85-ppm and the control groups (HR, 2.01; p=0.046 and HR, 2.28; p=0.043, respectively). No significant differences between groups was reported in regard to adverse events. The authors noted several limitations to this study, including no acceptable definitive outcomes defined in the literature regarding acute viral bronchiolitis, viral load not expected to change significantly within 3 days of treatment, and lung function tests being difficult to perform in this age group. They also note that the sample size is of concern, as no power calculations were conducted. They concluded:

> The goal of this study was to obtain information about the trend of the therapeutic dose response to 85 and 150 ppm NO compared with standard treatment empirically, and it was not powered to demonstrate statistical significance but rather to evaluate the dose–response relationship in the efficacy endpoints.

Gujja (2023) published the results of an RCT involving 80 participants with total anomalous pulmonary venous connection (TAPVC) undergoing corrective surgery and treated postoperatively with either milrinone alone after opening aortic cross clamp (n=40) or milrinone post clamping plus iNO in the ICU (n=40). At 24 hours and 48 hours post-procedure, a significant reduction in pulmonary artery pressure (p=0.00 4 and p<0.0001, respectively) and significant improvement in systemic arterial pressure (MAP) (p=0.0081 and p<0.00004, respectively) were reported in the iNO group. With the exception of reintubations (n=4 in the milrinone group vs, n=1 in the iNO group; p=0.0478), no significant differences between groups was reported with regard to adverse events. The authors noted several limitations to their study, including not measuring pulmonary vascular resistance, cardiac output, or pulmonary artery pressures to monitor the effectiveness of iNO therapy.

Di Fenza (2023) studied 200 adults with acute ventilation-dependent hypoxemic respiratory failure related to COVID-19 infection in an RCT comparing iNO to standard care (n=100 per group). Participants in the iNO arm received 80 ppm for the first 42 hours following enrollment. The median duration of inhaled iNO therapy of > 20 ppm was 10.8 days. The final analysis included 99 iNO group participants and 94 control group participants. The primary outcome was change in arterial oxygenation (PaO_2 /FIO_2) at 48 hours. The mean change in PaO_2/FIO_2 at 48 hours in the iNO group was 28.3 mm Hg and -1.4 mm Hg in the usual care arm (no p=value provided). iNO group participants had a 71.9% and 71.4% probability of having a lower risk of death at 28 days and 90 days, respectively compared to control group participants (RR for 28-day mortality, 0.85 and 90-day mortality, 0.87). No serious adverse events related to iNO therapy were reported. The authors concluded that iNO therapy improved PaO_2/FIO_2 in critically ill individuals with ventilation-dependent COVID infections, but did not alter mortality or duration of ventilation. The authors noted that the study was not powered to test whether iNO therapy reduces mortality, but indicate the need for further study. Further, treating providers were not blinded and no placebo was used in the control group leaving open a potential source of bias in the results.

Freidkin (2024) reported on an RCT evaluating the acute effect of iNO on the exercise capacity of individuals with advanced interstitial lung disease. A total of 44 participants were treated with either iNO or placebo prior to a 6-Minute Walk Test (6-MWT). The authors reported no significant differences between groups with regard to 6-

MWT distance (p=0.29). The authors concluded that the use of iNO was safe but did not provide any benefits with regard to 6-MTW outcomes.

Summary

In summary, INO is not considered clinically appropriate or effective for indications beyond use as a component of hypoxic respiratory failure treatment in term and near-term (born at 34 or more weeks of gestation) neonates under specific circumstances and as a method of assessing pulmonary vasoreactivity in individuals with pulmonary hypertension.

Definitions

Acute respiratory distress syndrome (ARDS): A buildup of fluid in the small air sacs (alveoli) in the lungs which makes it difficult for oxygen to get into the bloodstream. Although it is sometimes called adult respiratory distress syndrome, it may also affect children. This is a life-threatening condition that usually results from illness or injury.

Congenital diaphragmatic hernia (CDH): Occurs when the diaphragm, the muscle that separates the chest from the abdomen, fails to close during prenatal development. This opening allows contents of the abdomen (stomach, intestines and/or liver) to migrate into the chest, impacting the growth and development of the lungs.

Congenital heart disease: A problem with the structure of the heart that is present at birth. Congenital heart defects are the most common type of birth defect. The defects can involve the walls of the heart, the valves of the heart, and the arteries and veins near the heart. Some of the most common defects include ventricular/atrial septal defects, tetralogy of Fallot, patent ductus arteriosus, and valve stenosis.

Corrected age: Otherwise known as gestationally corrected age (GCA) is based on the age the child would be if the pregnancy had actually gone to term. Generally, after a corrected postnatal age of 24 months, no further correction will be made.

Extracorporeal membrane oxygenation (ECMO): An invasive technique used in neonates to treat hypoxic respiratory failure. ECMO therapy involves the use of a heart/lung machine to bypass the infant's circulation through the heart and lungs in an effort to improve circulatory oxygenation levels until the infant is able to breathe more efficiently on their own. It is generally considered a surgical procedure and performed in the intensive care setting.

Gestational age: A term used during pregnancy to describe how far along the pregnancy is. It is measured in weeks, from the first day of the mother's last menstrual cycle to the current date. The average, healthy, pregnancy ranges from 38 to 42 weeks.

Hypoxic respiratory failure: an oxygenation index (OI) of at least 25 recorded on 2 measurements made at least 15 minutes apart. The OI is calculated as the mean airway pressure in centimeters (cms) of water multiplied by the

fraction of inspired oxygen divided by the partial pressure of arterial oxygen times 100. An OI of 25 is associated with a 50% risk of requiring ECMO or dying. An OI of 40 is often used as a criterion to initiate ECMO therapy.

Neonate: A child under 28 days (4 weeks) of age.

Pulmonary hypertension: High blood pressure in the arteries that supply circulation to the lungs caused by hardening and narrowing of the vessels; left untreated, it can lead to the development of heart failure.

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Nitric Oxide (Inhaled) as a Treatment of Respiratory Failure

The use of specific product names is illustrative only. It is not intended to be a recommendation of one product over another, and is not intended to represent a complete listing of all products available.

History

Status	Date	Action
	03/06/2025	Revised typo in References section.
Revised	08/08/2024	Medical Policy & Technology Assessment Committee (MPTAC) review. Revised MN criteria related to prior conventional therapies. Reformatted NMN section. Revised Description, Discussion/General Information, and References sections.
Reviewed	08/10/2023	MPTAC review. Updated Discussion/General Information and References sections.
Revised	08/11/2022	Medical Policy & Technology Assessment Committee (MPTAC) review. Added NMN criteria for pre-operative and intraoperative management of congenital heart disease. Updated Discussion/General Information and References sections.
Reviewed	08/12/2021	MPTAC review. Updated Discussion/General Information and References sections.
Revised	08/13/2020	MPTAC review. Clarified MN criteria. Updated Discussion/General Information, Definitions and References sections. Reformatted Coding section.
Reviewed	02/20/2020	MPTAC review. Description, Discussion/General Information and References sections updated.
Reviewed	03/21/2019	MPTAC review. Description, Discussion/General Information and References sections updated.
New	03/22/2018	MPTAC review. Initial document development. Moved content of MED.00076 Inhaled Nitric Oxide to new clinical utilization management guideline document with the same title.