Anthem

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 considered 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 or are expected to fail, for example, administration of high concentrations of oxygen, hyperventilation, high frequency ventilation, the induction of alkalosis, neuromuscular blockade and sedation; **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:

- Treatment of hypoxic respiratory failure in premature neonates born at less than 34 weeks gestational;
- Treatment of acute respiratory distress syndrome in adults;
- 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.

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) (2000; reaffirmed 2010) policy statement regarding the use of INO in neonates with respiratory failure supports its use for the indications, dosing, administration and monitoring outlined on the product information label and approved by the FDA. The AAP’s recommendations are as follows:

- Infants with progressive hypoxic respiratory failure should be cared for in centers with the expertise and experience to provide multiple modes of ventilatory support and rescue therapies or be transferred in a timely manner to such an institution.
- INO therapy should be given using the indications, dosing, administration, and monitoring guidelines outlined on the product label. An echocardiogram to rule out congenital heart disease is recommended. Center specific criteria for treatment failure should be developed to facilitate timely consideration of alternative therapies.
- INO therapy should be directed by physicians qualified by education and experience in its use and offered only at centers that are qualified to provide multisystem support, generally including on-site ECMO capability.
- Generally, INO should be initiated in centers with ECMO capability. If INO is offered by a center without ECMO capability, for geographic or other compelling reasons, mutually acceptable treatment failure criteria and mechanisms for timely transfer of infants to a collaborating ECMO center should be established prospectively. Transfer must be accomplished without interruption of INO therapy.
- Centers that provide INO should provide comprehensive long-term medical and neuro-development follow-up.
- Centers that provide INO therapy should establish prospective data collection for treatment time course, toxic effects, treatment failure, and use of alternative therapies and outcomes.
- Administration of INO for indications other than those approved by the FDA or in other neonatal populations, including compassionate use, remains experimental. As such, INO should be administered according to a formal protocol that has been approved by the FDA and the institutional review board and with informed parental consent.

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.

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 (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 subjects 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 subjects to receive either INO (n=229) or a placebo (n=222); however, several subjects died or were withdrawn, leaving 208 subjects 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 (odds ratio [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 ($\geq$ 1 hour INO exposure). Primary outcomes included survival without disability and mortality. Overall response rate (defined as 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 subjects 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 subjects 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.”

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 subjects, 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 subjects were included for analysis in this study. In the first group, 46 subjects 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 subjects were studied in RA, 100% O2 and 80 ppm NO in oxygen (NO+O2). In group one, O2 decreased pulmonary vascular resistance (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 subjects 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 subjects 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 vs. baseline were greater with INO/O2 vs. 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 subjects 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 subjects 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 2015 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 (Galiè and colleagues) reported that INO at 10-20 parts per million (ppm) 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 subjects) 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 subjects 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 (Abourshed, 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 subjects 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 subjects (9%) did not receive the study treatment. In addition, crossover to open-label INO occurred in 15 of 73 subjects (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%) subjects in the INO group and 12 of 77 (15.6%) subjects 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, subjects 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 subjects, 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 subjects in the INO group discontinued treatment compared to 2 subjects 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.

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.

References

Peer Reviewed Publications:

1. Adhikari NK, Dellinger RP, Lundin S, et al. Inhaled nitric oxide does not reduce mortality in patients with acute respiratory distress syndrome regardless of severity: systematic review and meta-analysis. Crit Care Med. 2014; 42(2):404-412.
2. Ahmed MS, Giesinger RE, Ibrahim M, et al. Clinical and echocardiography predictors of response to inhaled nitric oxide in hypoxic preterm neonates. J Paediatr Child Health. 2019; 55(7):753-761.
3. Askie LM, Ballard RA, Cutter GR, et al.; Meta-analysis of Preterm Patients on Inhaled Nitric Oxide Collaboration. Inhaled nitric oxide in preterm infants: an individual-patient data meta-analysis of randomized trials. Pediatrics. 2011; 128(4):729-739.
4. Atz AM, Adatia I, Lock JE, Wessel DL. Combined effects of nitric oxide and oxygen during acute pulmonary vasodilator testing. J Am Coll Cardiol. 1999; 33(3):813-819.
5. Baczynski M, Ginty S, Weisz DE, et al. Short-term and long-term outcomes of preterm neonates with acute severe pulmonary hypertension following rescue treatment with inhaled nitric oxide. Arch Dis Child Fetal Neonatal Ed. 2017; 102(6):F508-F514.
6. Ballard RA, Truog WE, Cnaan A, et al.; NO CLD Study Group. Inhaled nitric oxide in preterm infants undergoing mechanical ventilation. N Engl J Med. 2006; 355(4):343-353.
7. Balzer DT, Kort HW, Day RW, et al. Inhaled nitric oxide as a preoperative test (INOP Test I): the INOP Test Study Group. Circulation. 2002; 106(12 Suppl 1):76-81.
8. Barst RJ, Agnoletti G, Fraisse A, et al.; NO Diagnostic Study Group. Vasodilator testing with nitric oxide and/or oxygen in pediatric pulmonary hypertension. Pediatr Cardiol. 2010; 31(5):598-606.
9. Bronicki RA, Fortenberry J, Schreiber M, et al. Multicenter randomized controlled trial of inhaled nitric oxide for pediatric acute respiratory distress syndrome. J Pediatr. 2015; 166(2):365-369.
10. Campbell BT, Herbst KW, Briden KE, et al. Inhaled nitric oxide use in neonates with congenital diaphragmatic hernia. Pediatrics. 2014; 134(2):e420-e426.
11. Carey WA, Weaver AL, Mara KC, Clark RH. Inhaled nitric oxide in extremely premature neonates with respiratory distress syndrome. Pediatrics. 2018, 141(3):e20173108.
12. Chandrasekharan P, Lakshminrusimha S, Chowdhury D, et al. Early Hypoxic Respiratory Failure in Extreme Prematurity: Mortality and Neurodevelopmental Outcomes. Pediatrics. 2020; 146(4):e20193318.
13. Chandrasekharan PK, Rawat M, Madappa R, et al. Congenital diaphragmatic hernia - a review. Matern Health Neonatol

Perinatol. 2017; 3:6.
14. Clark RH, Kueser TJ, Walker MW, et al. Low-dose nitric oxide therapy for persistent pulmonary hypertension of the newborn. Clinical Inhaled Nitric Oxide Research Group. N Eng J Med. 2000; 342(7):469-474.
15. Dellinger RP, Zimmerman JL, Taylor RW, et al. Effects of inhaled nitric oxide in patients with acute respiratory distress syndrome: results of a randomized phase II trial. Crit Care Med. 1998; 26(1):15-23.
16. Di Fiore JM, Hibbs AM, Zadell AE, et al. The effect of inhaled nitric oxide on pulmonary function in preterm infants. J Perinatol. 2007; 27(12):766-771.
17. Durrmeyer X, Hummler H, Sanchez-Luna M, et al; European Union Nitric Oxide Study Group. Two-year outcomes of a randomized controlled trial of inhaled nitric oxide in premature infants. Pediatrics. 2013; 132(3):e695-e703.
18. Field D, Elbourne D, Truesdale A, et al. Neonatal ventilation with inhaled nitric oxide versus ventilatory support without inhaled nitric oxide for preterm infants with severe respiratory failure: the INNOVO multicentre randomised controlled trial (ISRCTN 17821339). Pediatrics. 2005; 115(4):926-936.
19. Gien J, Kinsella JP. Management of pulmonary hypertension in infants with congenital diaphragmatic hernia. J Perinatol. 2016; 36 Suppl 2:S28-31.
20. Hamon I, Fresson J, Nicolas MB, et al. Early inhaled nitric oxide improves oxidative balance in very preterm infants. Pediatr Res. 2005; 57(5 Pt 1):637-643.
21. Hasan SU, Potenziano J, Konduri GG, et al. Effect of inhaled nitric oxide on survival without bronchopulmonary dysplasia in preterm infants: a randomized clinical trial. JAMA Pediatr. 2017; 171(11):1081-1089.
22. Hintz SR, Van Meurs KP, Perritt R, et al. Neurodevelopmental outcomes of premature infants with severe respiratory failure enrolled in a randomized controlled trial of inhaled nitric oxide. J Pediatr. 2007; 151(1):16-22, 22.e1-e3.
23. Huddy CL, Bennett CC, Hardy P, et al; INNOVO Trial Collaborating Group. The INNOVO multicentre randomized controlled trial: neonatal ventilation with inhaled nitric oxide versus ventilatory support without nitric oxide for severe respiratory failure in preterm infants: follow up at 4-5 years. Arch Dis Child Fetal Neonatal Ed. 2008; 93(6):F430-F435.
24. James C, Millar J, Horton S, et al. Nitric oxide administration during paediatric cardiopulmonary bypass: a randomised controlled trial. Intensive Care Med. 2016; 42(11):1744-1752.
25. Kinsella JP. Inhaled nitric oxide therapy in premature newborns. Curr Opin Pediatr. 2006a; 18(2):107-111.
26. Kinsella JP, Cutter GR, Steinhorn RH, et al. Noninvasive inhaled nitric oxide does not prevent bronchopulmonary dysplasia in premature newborns. J Pediatr. 2014; 165(6):1104-1108.
27. Kinsella JP, Cutter GR, Walsh WF, et al. Early inhaled nitric oxide therapy in premature newborns with respiratory failure. N Engl J Med. 2006b; 355(4):354-364.
28. Kinsella JP, Steinhorn RH, Krishnan US, et al. Recommendations for the use of inhaled nitric oxide therapy in premature newborns with severe pulmonary hypertension. J Pediatr. 2016; 170:312-314.
29. Kinsella JP, Truog WE, Walsh WF, et al. Randomized, multicenter trial of inhaled nitric oxide and high-frequency oscillatory ventilation in severe, persistent pulmonary hypertension of the newborn. J Pediatr. 1997; 131(1 Pt 1):55-62.
30. Konduri GG. New approaches for persistent pulmonary hypertension of newborns. Clin Perinatol. 2004; 31(3):591-611.
31. Konduri GG, Solimano A, Sokol GM, et al. A randomized trial of early versus standard inhaled nitric oxide therapy in term and near-term newborn infants with hypoxic respiratory failure. Pediatrics. 2004; 113(3Pt1): 559-564.
32. Krasuski RA, Devendra GP, Hart SA, et al. Response to inhaled nitric oxide predicts survival in patients with pulmonary hypertension. J Card Fail. 2011; 17(4):265-271.
33. Lawrence KM, Monos S, Adams S, et al. Inhaled nitric oxide is associated with improved oxygenation in a subpopulation of infants with congenital diaphragmatic hernia and pulmonary hypertension. J Pediatr. 2020; 219:167-172.
34. Lubinsky AS, Brosnahan SB, Lehr A, et al. Inhaled pulmonary vasodilators are not associated with improved gas exchange in mechanically ventilated patients with COVID-19: A retrospective cohort study. J Crit Care. 2022.
35. Lundin S, Mang H, Smithies M, et al. Inhalation of nitric oxide in acute lung injury: results of a European multicentre study. The European Study Group of Inhaled Nitric Oxide. Intensive Care Med. 1999; 25(9):911-919.
36. Maddux AB, Mourani PM, Banks R, etc. Inhaled nitric oxide use and outcomes in critically ill children with a history of prematurity. Respir Care. 2021; 66(10):1549-1559.
37. Malowitz JR, Hornik CP, Laughon MM, et al. Management practice and mortality for infants with congenital diaphragmatic hernia. Am J Perinatol. 2015; 32(9):887-894.
38. Martin RJ. Nitric oxide for preemies – not so fast. N Engl J Med 2003; 349(22):2157-2159.
39. Mercier JC, Hummler H, Durrmeyer X, et al.; EUNO Study Group. Inhaled nitric oxide for prevention of bronchopulmonary dysplasia in premature babies (EUNO): a randomised controlled trial. Lancet. 2010; 376(9738):346-354.
40. Mestan KK, Marks JD, Kurt Hecox K, et al. Neurodevelopmental outcomes of premature infants treated with inhaled nitric oxide N Engl J Med. 2005; 353(1):23-32.
41. Neonatal Inhaled Nitric Oxide Study Group (NINOS). Inhaled nitric oxide and hypoxic respiratory failure in infants with congenital diaphragmatic hernia. Pediatrics. 1997a; 99(6):838-845.
42. Neonatal Inhaled Nitric Oxide Study Group. Inhaled nitric oxide in full-term and nearly full-term infants with hypoxic respiratory failure. N Engl J Med. 1997b; 336(9):597-604.
43. Potapov E, Meyer D, Swaminathan M, et al. Inhaled nitric oxide after left ventricular assist device implantation: a prospective, randomized, double-blind, multicenter, placebo-controlled trial. J Heart Lung Transplant. 2011; 30(8):870-878.
44. Putnam LR, Tsao K, Morini F, et al; Congenital Diaphragmatic Hernia Study Group. Evaluation of variability in inhaled nitric oxide use and pulmonary hypertension in patients with congenital diaphragmatic hernia. JAMA Pediatr. 2016; 170(12):1188-1194.
45. Reiter Meade MO, Granton JT, Matte-Martyn A, et al. A randomized trial of inhaled nitric oxide to prevent ischemia-reperfusion injury after lung transplantation. Am J Respir Crit Care Med. 2003; 167(11):1483-1489.
46. Schlapbach LJ, Gibbons KS, Horton SB, et al. Effect of nitric oxide via cardiopulmonary bypass on ventilator-free days in young children undergoing congenital heart disease surgery: The NITRIC Randomized Clinical Trial. JAMA. 2022 Jun 27. [Epub ahead of print].
47. Schreiber MD, Gin-Mestan K, Marks JD, et al. Inhaled nitric oxide in premature infants with the respiratory distress syndrome. N Engl J Med. 2003; 349(22):2099-2107.
48. Subhedar N, Dewhurst C. Is nitric oxide effective in preterm infants? Arch Dis Child Fetal Neonatal Ed. 2007; 92(5):F337-341.
49. Tal A, Greenberg D, Av-Gay Y, et al. Nitric oxide inhalations in bronchiolitis: a pilot, randomized, double-blinded, controlled trial. Pediatr Pulmonol. 2018; 53(1):95-102.
50. Taylor RW, Zimmerman JL, Dellinger RP, et al.; Inhaled Nitric Oxide in ARDS Study Group. Low-dose inhaled nitric oxide in patients with acute lung injury: a randomized controlled trial. JAMA. 2004; 291(13):1603-1609.
51. Trzeciak S, Glaspey LJ, Dellinger RP, et al. Randomized controlled trial of inhaled nitric oxide for the treatment of microcirculatory dysfunction in patients with sepsis*. Crit Care Med. 2014; 42(12):2482-2492.
52. Van Meurs KP, Hintz SR, Ehrenkranz RA, et al. Inhaled nitric oxide in infants >1500 g and <34 weeks gestation with severe respiratory failure. J Perinatol. 2007; 27(6):347-352.
53. Van Meurs KP, Wright LL, Ehrenkranz RA, et al.; Preemie Inhaled Nitric Oxide Study. Inhaled nitric oxide for premature infants with severe respiratory failure. N Engl J Med. 2005; 353(1):13-22.

54. Villarreal EG, Aiello S, Evey LW, et al. Effects of inhaled nitric oxide on haemodynamics and gas exchange in children after having undergone cardiac surgery utilising cardiopulmonary bypass. Cardiol Young. 2020; 30(8):1151-1156.
55. Weiner DL, Hibberd PL, Betit P, et al. Preliminary assessment of inhaled nitric oxide for acute vasoocclusive crisis in pediatric patients with sickle cell disease. JAMA. 2003; 289(9):1136-1142.
56. Zheng P, Jiang D, Liu C, et al. Nitric oxide inhalation therapy attenuates postoperative hypoxemia in obese patients with acute type A aortic dissection. Comput Math Methods Med. 2022; 9612548.
57. Zheng Y, Wu Q, Han S. Inhaled nitric oxide in premature infants for preventing bronchopulmonary dysplasia: a meta-analysis. BMC pediatrics. 2023; 23(1):139.

Government Agency, Medical Society, and Other Authoritative Publications:

1. Abman SH, Hansmann G, Archer SL, et al.; American Heart Association Council on Cardiopulmonary, Critical Care, Perioperative and Resuscitation; Council on Clinical Cardiology; Council on Cardiovascular Disease in the Young; Council on Cardiovascular Radiology and Intervention; Council on Cardiovascular Surgery and Anesthesia; and the American Thoracic Society. Pediatric Pulmonary Hypertension: Guidelines From the American Heart Association and American Thoracic Society. Circulation. 2015; 132(21):2037-2099.
2. Aboursheid T, Albaroudi O, Alahdab F. Inhaled nitric oxide for treating pain crises in people with sickle cell disease. Cochrane Database Syst Rev. 2019;(10):CD011808.
3. Afshari A, Brok J, Møller AM, Wetterslev J. Inhaled nitric oxide for acute respiratory distress syndrome (ARDS) and acute lung injury in children and adults. Cochrane Database Syst Rev. 2010;(7):CD002787.
4. Allen MC, Donohue P, Gilmore M, et al. Inhaled Nitric Oxide in Preterm Infants. Evidence Report/Technology Assessment No. 195. (Prepared by Johns Hopkins University Evidence-based Practice Center under Contract No. 290-2007-10061-1). AHRQ Publication No. 11-E001. Rockville, MD: Agency for Healthcare Research and Quality. October 2010. Available at: http://www.ahrq.gov/downloads/pub/evidence/pdf/inoinfants/inoinfants.pdf. Accessed on July 1, 2023.
5. American Academy of Pediatrics. Committee on Fetus and Newborn Use of inhaled nitric oxide. Pediatrics 2000. Reaffirmed 2010; 106(2 Pt 1):344-345.
6. Barrington KJ, Finer NN, Pennaforte T. Inhaled nitric oxide for respiratory failure in preterm infants. Cochrane Database Syst Rev. 2017;(3):CD000509.
7. Barrington KJ, Finer N, Pennaforte T, Altit G. Nitric oxide for respiratory failure in infants born at or near term. Cochrane Database Syst Rev. 2017;(1):CD000399.
8. Bizzarro M, Gross I, Barbosa FT. Inhaled nitric oxide for the postoperative management of pulmonary hypertension in infants and children with congenital heart disease. Cochrane Database Syst Rev. 2014;(7):CD005055.
9. Cole FS, Alleyne C, Barks JD, et al. NIH Consensus Development Conference statement: inhaled nitric-oxide therapy for premature infants. Pediatrics. 2011; 127(2):363-369.
10. DiBlasi RM, Myers TR, Hess DR. Evidence-based clinical practice guideline: inhaled nitric oxide for neonates with acute hypoxic respiratory failure: American Association for Respiratory Care (AARC). Respir Care. 2010; 55(12):1717-1745.
11. Finer NN, Barrington KJ. Nitric oxide for respiratory failure in infants born at or near term. Cochrane Database Syst Rev. 2006; (4):CD000399.
12. Galiè N, Humbert M, Vachiery JL, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). Eur Heart J. 2016; 37(1):67-119.
13. INOmax® [Product Information], Hazelwood, MO. INO Therapeutics; 2015. Available at: https://www.inomax.com/wp-content/themes/inomax-website/dist/downloads/INOmax-PI-web-2015-10.pdf. Accessed on July 1, 2023.
14. Nitric Oxide. In: DrugPoints® System [electronic version]. Truven Health Analytics, Greenwood Village, CO. Updated March 7, 2023. Available at: http://www.micromedexsolutions.com. Accessed on July 1, 2023.
15. Puligandla PS, Grabowski J, Austin M, et al. Management of congenital diaphragmatic hernia: A systematic review from the APSA outcomes and evidence based practice committee. J Pediatr Surg. 2015; 50(11):1958-1970.
16. Sokol J, Inhaled nitric oxide for acute hypoxemic respiratory failure in children and adults. Cochrane Database Systematic Reviews. 2003;(1):CD0027877.

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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
Reviewed	08/10/2023	Medical Policy & Technology Assessment Committee (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.

the right to review and update Clinical UM Guidelines periodically. Clinical guidelines approved by the Medical Policy & Technology Assessment Committee are available for general adoption by plans or lines of business for consistent review of the medical necessity of services related to the clinical guideline when the plan performs utilization review for the subject. Due to variances in utilization patterns, each plan may choose whether to adopt a particular Clinical UM Guideline. To determine if review is required for this Clinical UM Guideline, please contact the customer service number on the member's card.

Alternatively, commercial or FEP plans or lines of business which determine there is not a need to adopt the guideline to review services generally across all providers delivering services to Plan’s or line of business’s members may instead use the clinical guideline for provider education and/or to review the medical necessity of services for any provider who has been notified that his/her/its claims will be reviewed for medical necessity due to billing practices or claims that are not consistent with other providers, in terms of frequency or in some other manner.