Medical Coverage Policy

Subject: Inhaled Nitric Oxide
Policy #: MED
Status: New

Current Effective Date: 11/10/14
Last Review Date: 11/10/14

Description/Scope

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. Inhaled nitric oxide (INO or iNO) has been investigated as a technique to improve oxygenation in critically ill individuals, both to reduce mortality and, in neonates, to reduce the need for extracorporeal membrane oxygenation (ECMO).

Position Statement

Medically Necessary:

Except where regulatory requirements for a particular plan would apply:

Inhaled nitric oxide (INO) is considered **medically necessary** as a component of the treatment of hypoxic respiratory failure* in term and near-term (born at 34 or more weeks of gestation) neonates when both of the following criteria are met:

1. Conventional therapies have failed or are expected to fail, e.g., administration of high concentrations of oxygen, hyperventilation, high frequency ventilation, the induction of alkalosis, neuromuscular blockade and sedation; and
2. Neonate does not have a congenital diaphragmatic hernia (CDH).

*Hypoxic respiratory failure is defined as 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 cms 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.

Investigational and Not Medically Necessary:

Other indications for treatment using inhaled nitric oxide (INO) are considered **investigational and not medically necessary,** including, but not limited to its use in treating adult respiratory distress syndrome, premature neonates (less than 34 weeks of gestation), post-operative management of congenital heart disease, and as a method of assessing pulmonary vaso-reactivity in persons with pulmonary hypertension.

Rationale

Term and Near Term Neonates

Published clinical studies report that INO therapy improves oxygenation and ventilation, reduces the need for ECMO and lowers 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). One study suggested a maximum of four days of INO should be tried before ECMO is considered. Limiting the duration of INO may avoid delaying ECMO beyond the point at which its effectiveness may be reduced. Konduri (2004) randomized 299 infants in respiratory failure to receive early (OI 15-25) versus control (OI equal or > 25) treatment with INO and found no significant reduction in the incidence of ECMO/ mortality in the early treatment group. Additionally, infants with CDH have not demonstrated benefit from INO therapy (Finer, 2006). A randomized controlled trial of infants 34 weeks gestation or more with CDH did not find any significant improvement in survival or oxygenation (Nitric Oxide Study Group, 1997a).

In 1999, the U.S. Food and Drug Administration (FDA) approved INOmax® (nitric oxide for inhalation) (INO Therapeutics, Clinton, NJ) for use, in conjunction with ventilatory support and other appropriate agents, for 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, where it improves oxygenation and reduces the need for extracorporeal membrane oxygenation. The FDA approved label (2010) advises that INO is contraindicated in neonates known to be dependent on right-to-left shunting of blood.

The American Academy of Pediatrics (AAP) (2000) policy statement regarding the use of INO in neonates with respiratory failure supports use of this therapy for the indications, dosing, administration and monitoring guidelines as outlined on the product label and approved by the U.S. FDA. A statement of reaffirmation for their policy was published on April 1, 2010. 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.
- In 2010, the American Association for Respiratory Care (AARC) published an evidence-based clinical practice guideline for INO in neonates with acute hypoxic respiratory failure. The AARC recommendations include that: "INO should not be used routinely in newborns with congenital diaphragmatic hernia."

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 [±SD] 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 are promising, an accompanying editorial points out that the significant difference between the 2 groups was in part related to the unexpectedly high rate of unfavorable outcomes (i.e., death or chronic lung disease) in the control group (Martin, 2003). The author also notes there is still 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 two 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 percent) 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 percent) in the placebo group (relative risk, 0.53; 95 percent confidence interval, 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 g, 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 percent in the INO group, as compared with 82 percent in the placebo group (relative risk, 0.97; 95 percent confidence interval, 0.86 to 1.06; P=0.52), and the rate of BPD was 60 percent versus 68 percent (relative risk, 0.90; 95 percent confidence interval, 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 g, whereas infants weighing 1000 g 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 g does not decrease the rates of death or BPD and suggested further trials are required to determine whether inhaled nitric oxide benefits infants with a birth weight of 1000 g or more.

According to a review by Kinsella (2006a) trials of INO in premature newborns have resulted in conflicting outcomes. The results of ongoing trials will help clarify the potential risks and benefits of INO therapy in this population.

Kinsella and colleagues (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 (5ppm) 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 g or less who required ventilation between 7 and 21 days of age. Two hundred ninety four infants received INO and 288 received a placebo. The survival rate without BPD at 36 weeks postmenstrual age was 43.9 percent in the group receiving INO and 36.8 percent 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 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 small sample size limited definite conclusions, but suggested that INO does not affect the rate of bronchopulmonary dysplasia and death.

Barrington and Finer (2007) conducted a systematic review to analyze the safety and efficacy of INO for respiratory failure in preterm infants. The effects of treatment with INO on death rates, BPD, intraventricular hemorrhage (IVH), or neurodevelopmental disability in preterm newborn infants with respiratory disease were evaluated. Eleven randomized controlled trials of INO therapy in the preterm infant were included in the report. The authors concluded INO as rescue therapy for very ill ventilated preterm infants does not appear to be effective and may increase the risk of severe IVH and later use of INO to prevent BPD does not appear to be effective. Also, it was noted that the routine use of INO in mildly sick preterm infants may decrease brain injury and may improve survival without BPD. Further studies are needed to confirm findings and to describe long term results.

In 2010, Barrington and Finer performed a subsequent systematic review to evaluate the effect of INO treatment in the preterm infant. Fourteen randomized controlled trials of INO therapy in preterm infants were found for this review. The authors again concluded that INO as rescue therapy for the very ill preterm infant does not appear to be effective

and that early routine use of INO in preterm infants with respiratory disease does not affect serious brain injury or improve survival without BPD. Also, it was noted that later use of INO to prevent BPD requires further study.

Di Fiore and colleagues (2007) assessed the effect of INO on resistance and compliance in ventilated preterm infants with evolving BPD. Seventy one ventilated preterm infants were enrolled in a randomized, double-blinded, placebo controlled multicenter study. Thirty-seven 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 a small sample size and a number of infants lost to follow-up due to extubation and other factors.

Huddy and colleagues (2008) reported on a multi-center randomized controlled trial which studied neonatal ventilation with INO versus ventilatory support without INO for severe respiratory failure in preterm infants with follow-up to age four to five years. This study, the INNOVO trial recruited 108 infants (55 INO arm and 53 controls) from 15 neonatal units. By one year of age 59% had died and 84% of the survivors had signs of impairment or disability. Researchers reported the long-term clinical effectiveness and costs of adding NO to the ventilator gases of preterm infants with severe respiratory failure. Children were assessed at age four to five 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 eight children of the original 108 recruited to the trial were classified as normal across all of the domains at four to five years of age. There was no indication of any differences in the levels of impairment or disability between the two groups in the domains studied, or of cost differences, among the survivors. The authors concluded for this group of infants with severe respiratory failure there was no evidence of difference in the longer-term outcome between those babies allocated to INO and those who were allocated to no INO.

Mercier and colleagues (2010) studied 800 preterm infants with a gestational age between 24 and 28 weeks plus six days with a weight of at least 500 g, 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 seven days and a maximum of 21 days in a double–blind European multi-center 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: 0.92-1.01, 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: 0.98-1.28, p=0.09. Sub analyses, (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 two-year outcomes of the European Union Nitric Oxide trial, a randomized controlled trial 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 two 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.

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: "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 AHRQ-sponsored systematic review of the literature noted above. NIH conclusions include: "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."

A recent 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 metaanalysis 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.

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.

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 end points.

A 2010 Cochrane review 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 hypoxaemic 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 ARDS (PaO2/FIO2 ≤ 100 mm Hg) as compared to those with mild-moderate ARDS (100 < PaO2/FIO2 ≤ 300 mm Hg). Parallel-group randomized controlled trials 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 = 1,142 subjects) met inclusion criteria. Nitric oxide was not observed to reduce mortality in individuals with severe ARDS (risk ratio, 1.01 [95% CI, 0.78-1.32]; p = 0.93; n = 329, six trials) or mild-moderate ARDS (risk ratio, 1.12 [95% CI, 0.89-1.42]; p = 0.33; n = 740, seven trials). The authors concluded there was no beneficial effect off 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.

Currently there is also insufficient evidence to support the use of INO for the prevention of ischemia-reperfusion injury/acute rejection following lung transplantation, or the treatment of acute lung injury, or vaso-occlusive crises in those with sickle cell disease (Dellinger, 1998; Lundin, 1999; Taylor, 2004; Weiner, 2003; Reiter Meade, 2003).

A 2005 Cochrane review identified four randomized controlled trials comparing the effects of postoperative INO versus placebo or conventional management of 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 methodologic 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.

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 five 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 cross-over 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.

INO has also been studied as a diagnostic method of assessing pulmonary vaso-reactivity in persons with pulmonary hypertension. Other vasodilators have been used for this purpose; however, there is limited published evidence in support of INO for this use. 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. A total of 71 subjects divided into two groups 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) (mean+/-SEM) from 17.2+/-2.1 U.m2 to 11.1+/-1.5 U.m2 ($p < 0.05$). Nitric oxide caused a comparable decrease from 17.8+/-2.2 U.m2 to 11.7+/-1.7 U.m2 ($p < 0.05$). In group 2, PVR decreased from 20.1+/-2.6 U.m2 to 14.3+/-1.9 U.m2 in O2 ($p < 0.05$) and further to 10.5+/-1.7 U.m2 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. This study was limited by its small size and heterogeneous study population.

A small 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 parts per million NO to evaluate pulmonary vascular reactivity. Seventy-eight individuals were determined to be operable. Of those, 74 had undergone surgery at the time data was collected. Twelve persons 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. However, they further noted:

> Unfortunately, death is a genuine risk for patients who may be selected inappropriately for surgery based on a false-positive response to oxygen and nitric oxide inhalation. In receiver operating characteristic analysis, an ideal test is portrayed by a curve with a high gain in sensitivity and little loss in specificity. This study suggests that the reliability of preoperative testing is limited, even when a combination of oxygen and inhaled nitric oxide is used.

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. One hundred thirty six children were enrolled and 121 completed the study. Children four 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 NO/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. Although initial studies may show promise, larger randomized trials are needed to investigate safety and clinical utility of INO as a method of assessing pulmonary vaso-reactivity in persons with pulmonary hypertension.

In summary, there is insufficient evidence in the published literature demonstrating the safety and efficacy of INO for any use, other than as a component of the treatment of hypoxic respiratory failure in term and near-term (born at 34 or more weeks of gestation) neonates under specific circumstances.

Background/Overview

INO has been investigated for a variety of uses. However, the only FDA approved indication is in conjunction with ventilatory support and other appropriate agents, for 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, where it improves oxygenation and reduces the need for extracorporeal membrane oxygenation.

Acute respiratory failure is the most common problem 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. Management of infants with respiratory failure may include one or more of the following: administration of high concentrations of oxygen, hyperventilation, high-frequency ventilation, the induction of alkalosis, neuromuscular blockade, ante-natal steroids for the prevention of RDS, use of post-natal steroids for the prevention of chronic lung disease, as well as INO therapy (INO is a selective pulmonary vasodilator without significant effects on the systemic circulation). Treatment of preterm infants usually involves exogenous surfactant administration. Some near term and term infants with certain respiratory disorders may receive surfactant also.

Acute respiratory failure in both term and near-term neonates is usually a consequence of meconium aspiration syndrome, sepsis, pulmonary hypoplasia, and primary pulmonary hypertension of the newborn. INO therapy

improves oxygenation and ventilation, reduces the need for ECMO, and lowers the incidences of chronic lung disease and death among term and near-term infants with respiratory failure. In term and near-term neonates, the role of INO functions primarily as a vasodilator to treat pulmonary hypertension, often due to meconium aspiration or bacterial pneumonia.

In preterm neonates, the most common cause of acute respiratory failure is RDS as a result of surfactant deficiency. In preterm neonates with respiratory failure, pulmonary hypertension with shunting is less of a clinical problem. Therefore, these two groups of neonates (term/near term and preterm) represent different clinical issues and the results of INO in term/near-term neonates cannot be extrapolated to preterm neonates. In addition, there is concern regarding the possible risk of intraventricular hemorrhage associated with INO in premature infants.

Definitions

Extracorporeal membrane oxygenation (ECMO): Is 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.

Coding

The following codes for treatments and procedures applicable to this document 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-9 Procedure	***[For dates of service prior to]***
00.12	Administration of inhaled nitric oxide

ICD-9 Diagnosis	***[For dates of service prior to 10/01/2015]***
747.83	Persistent fetal circulation (primary pulmonary hypertension of newborn)
748.5	Agenesis, hypoplasia, and dysplasia of lung
765.27	Weeks of gestation; 33-34 completed weeks of gestation
765.28	Weeks of gestation; 35-36 completed weeks of gestation
765.29	Weeks of gestation; 37 or more completed weeks of gestation
769	Respiratory distress syndrome (newborn)
770.10	Fetal and newborn aspiration, unspecified
770.12	Meconium aspiration with respiratory symptoms
770.18	Other fetal and newborn aspiration with respiratory symptoms
770.84	Respiratory failure of newborn
770.9	Unspecified respiratory condition of fetus and newborn
786.09	Other dyspnea and respiratory abnormalities (respiratory distress)

ICD-10 Procedure	***[For dates of service on or after]***
3E0F7SD	Introduction of nitric oxide gas into respiratory tract, via natural or artificial opening

ICD-10 Diagnosis	***[For dates of service on or after]***
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

When services are Investigational and Not Medically Necessary:
For the procedure and diagnosis codes listed above when criteria are not met, for all other diagnoses not listed; or when the code describes a procedure indicated in the Position Statement section as investigational and not medically necessary.

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. 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.
3. 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.
4. 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.
5. 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.
6. Barst RJ, Agnoletti G, Fraisse A; NO Diagnostic Study Group. Vasodilator testing with nitric oxide and/or oxygen in pediatric pulmonary hypertension. Pediatr Cardiol. 2010; 31(5):598-606.
7. Calfee CS, Matthay MA. Recent advances in mechanical ventilation. Am J Med. 2005; 118(6):584-591.
8. 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; 342:469-474.
9. Dellinger RP, Zimerman 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; 26:15-23.
10. 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.
11. 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):e695-703.
12. 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; 115:926-936.
13. Finer NN, Sun JW, Rich W, et al. Randomized prospective study of low-dose versus high-dose inhaled nitric oxide in the neonate with hypoxic respiratory failure. Pediatrics. 2001; 106(2 Pt 1):344-345.
14. Finer NN. Inhaled nitric oxide for preterm infants: a therapy in search of an indication? The search continues. J Ped. 2005; 146(3):301-303.
15. Hamon I, Fresson J, Nicolas M-B, et al. Early inhaled nitric oxide improves oxidative balance in very preterm infants. Pediatr Res. 2005; 57:637-643.
16. 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.e1-3.
17. 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.
18. Kinsella JP. Inhaled nitric oxide therapy in premature newborns. Curr Opin Pediatr. 2006a; 18(2):107-111.
19. 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.
20. Kinsella JP, Parker TA, Ivy DD, Abman SH. Non-invasive delivery of inhaled nitric oxide therapy for late pulmonary hypertension in newborn infants with congenital diaphragmatic hernia. Journ of Pediatrics. 2003; 142(4): 397-401.
21. Konduri GG. New approaches for persistent pulmonary hypertension of newborns. Clin Perinatol. 2004; 31(3):591-611.
22. Konduri GG. 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.

23. 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.
24. Martin RJ. Nitric oxide for preemies – not so fast. N Engl J Med 2003; 349(22):2157-2159.
25. 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.
26. Mestan KK, Marks JD, Kurt Hecox K, et al. Neurodevelopmental outcomes of premature infants treated with inhaled nitric oxide N Engl J Med. 2005; 353:23-32.
27. 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.
28. 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; 336:597-604.
29. 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.
30. 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.
31. 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.
32. Subhedar N, Dewhurst C. Is nitric oxide effective in preterm infants? Arch Dis Child Fetal Neonatal Ed. 2007; 92(5):F337-341
33. Taylor RW, Zimmerman JL, Dellinger RP, et al. Low-dose inhaled nitric oxide in patients with acute lung injury: A randomized controlled trial. JAMA. 2004; 291:1603-1609.
34. 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.
35. Van Meurs KP, Wright LL, Ehrenkranz RA, et al. for the Preemie Inhaled Nitric Oxide Study. Inhaled nitric oxide for premature infants with severe respiratory failure. N Engl J Med. 2005; 353:13-22.
36. 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.

Government Agency, Medical Society, and Other Authoritative Publications:

1. 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.
2. 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 February 28, 2014.
3. American Academy of Pediatrics. Committee on Fetus and Newborn Use of inhaled nitric oxide. Pediatrics 2000. Reaffirmed 2010; 106:344-345.
4. Barrington KJ, Finer NN. Inhaled nitric oxide for respiratory failure in preterm infants. Cochrane Database of Systematic Reviews 2006, Issue 1. Art. No.: CD000509. DOI: 10.1002/14651858.CD000509.pub2.
5. Barrington KJ, Finer NN. Inhaled nitric oxide for respiratory failure in preterm infants. Cochrane Database Syst Rev. 2007; (3):CD000509.
6. Bizzarro M, Gross I. Inhaled nitric oxide for the postoperative management of pulmonary hypertension in infants and children with congenital heart disease. Cochrane Database of Systematic Reviews 2005, Issue 4. Art. No.: CD005055. DOI: 10.1002/14651858.CD005055.pub2.
7. 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.
8. 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.
9. Finer NN, Barrington KJ. Nitric oxide for respiratory failure in infants born at or near term. Cochrane Database Syst Rev. 2006; (4):CD000399.
10. INOmax® [Product Information], Clinton, NJ. INO Therapeutics; March 2013. Available at: http://www.inomax.com/pdf/prescribing_information.pdf. Accessed on February 27, 2014.
11. Kumar P; Committee on Fetus and Newborn; American Academy of Pediatrics. Use of inhaled nitric oxide in preterm infants. Pediatrics. 2014; 133(1):164-170.

12. Nitric Oxide. In: DrugPoints® System [electronic version]. Truven Health Analytics, Greenwood Village, CO. Updated October 11, 2013. Available at: http://www.micromedexsolutions.com. Accessed on February 28, 2014.
13. Nitric Oxide Monograph. Lexicomp® Online, American Hospital Formulary Service® (AHFS®) Online, Hudson, Ohio. Lexi-Comp., Inc. Last reviewed 2014. Accessed on February 28, 2014.
14. Sokol J, Inhaled nitric oxide for acute hypoxemic respiratory failure in children and adults. Cochrane Database Systematic Reviews. 2003(1): CD0027877.

Index

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.

Document History

Status	Date	Action

Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Coverage Policy and must be considered first in determining eligibility for coverage. The member's contract benefits in effect on the date that services are rendered must be used. Medical Coverage Policy, which addresses medical efficacy, should be considered before utilizing medical opinion in adjudication. Medical technology is constantly evolving, and Sendero Health Plans reserves the right to review and update Medical Policy periodically.