Purpose: To provide an understanding of inhaled nitric oxide (iNO) treatment in the neonatal population.

Goal: To support an evidence-based approach to inhaled nitric oxide therapy and describe the limitations of and recommendations for this treatment.

Target Client Population: This guideline applies to term or late preterm neonates in acute hypoxic respiratory failure who have not responded to conventional therapies.

Background

Acute respiratory failure can commonly occur in infants of all gestational ages. In the preterm infant, respiratory failure typically presents secondary to an insufficiency of surfactant, a soap-like material that lines the air-spaces of the lungs. Respiratory failure in the term and near-term neonate can result from conditions such as sepsis, meconium aspiration at birth, pulmonary hypoplasia or congenital diaphragmatic hernia (CDH). These conditions can cause elevated pressure in the pulmonary vessels. The classic characteristics of persistent pulmonary hypertension of the newborn (PPHN) include increased pulmonary vascular resistance, right-to-left shunting and severe hypoxemia. (ACCR/AHA, 2009)

Treatment of the preterm infant with respiratory failure usually involves administration of exogenous surfactant. In the term and near-term neonate, management of acute respiratory failure could include administration of oxygen, conventional or high-frequency ventilation, pharmacological intervention or extracorporeal membrane oxygenation (ECMO) using a heart/lung machine.

Inhaled nitric oxide therapy involves the administration of gaseous nitric oxide which dilates pulmonary vessels and decreases pulmonary vascular resistance. Because nitric oxide affects vascular muscle tone regulation in the pulmonary system, it has emerged as a new treatment for hypoxemic respiratory failure which is associated with high pulmonary vascular pressure. This treatment provides a less invasive alternative to ECMO treatment although the American Academy of Pediatrics recommends centers that provide iNO therapy either have ECMO available or have a transfer plan in place to an ECMO center in the event that iNO treatment is not successful. (AAP, 2010) Multicenter randomized clinical trials have demonstrated improved oxygenation and reduction in the need for ECMO in neonates with refractory hypoxemia. (ACCR/AHA, 2009)

INOmax® is a commercially available gaseous nitric oxide product which received 510(K) approval from the FDA in 1999. There are INOmax delivery systems which can administer the inhaled nitric oxide in conjunction with a ventilator or other mechanical gas administration system such as INOmax DSIR®, INOmax DS® and INOvent®. These delivery systems allow the administration of an operator-determined amount of nitric oxide and should be calibrated using a precise calibration mixture of nitric oxide and nitrogen dioxide such as INOcal®.

The GeNOsyl™ MV-1000 nitric oxide delivery device received 510(K) clearance from the FDA in 2012. It is approved to provide a constant set concentration of nitric oxide to the patient via mechanical ventilation and also includes monitoring of inspired O2, NO2 and NO with an alarm system.
## Inhaled Nitric Oxide Medical Policy

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### General Information

- **INOmax®** is contraindicated in infants known to be dependent on right-to-left shunting. (INOMAX [package insert]. Clinton, NJ: INO Therapeutics LLC, 2010)

- There is a risk of methemoglobinemia and increased NO2 levels when nitric oxide is administered at doses >20 ppm. (INOMAX [package insert]. Clinton, NJ: INO Therapeutics LLC, 2010)

- The recommended dose of INOmax® is 20 ppm and treatment should be maintained up to 14 days or until the underlying oxygen desaturation has resolved and the neonate is ready to be weaned from INOmax® therapy. (INOMAX [package insert]. Clinton, NJ: INO Therapeutics LLC, 2010)

- Although there is variation in iNO dosing between facilities, a retrospective study by Guthrie et al (2004) comparing low-dose (< 18ppm), mid-dose (18-22ppm) and high-dose (>22ppm) nitric oxide administration showed no evidence that a higher dose of iNO improved patient outcomes.

- Inhaled nitric oxide may become necessary when a neonate has an oxygenation index > 20 to 25 or when their PaO2 is < 100 mmHg while they are receiving 100% oxygen. (Finer, 2006; Konduri, 2004; Roberts, 1997; NINOS, 1997)

### Treatment Criteria

Clinical evidence supports the use of inhaled nitric oxide in the following situations:

The administration of inhaled nitric oxide would be considered appropriate for term or late preterm newborns (at least 34 weeks gestation) who:

- Have hypoxic respiratory failure associated with clinical and/or echocardiographic evidence of persistent pulmonary hypertension of the newborn syndrome **AND** have failed conventional treatments for hypoxic respiratory failure such as IV fluids and mechanical ventilation,

  **OR**

- Have pulmonary hypertension in the acute phases of recovery following surgery for congenital heart defects,

  **AND**

- Do not have congenital diaphragmatic hernia.

There is insufficient clinical evidence to support the use of inhaled nitric oxide for any indication in preterm infants < 34 weeks gestation. This includes routine administration in intubated infants, early rescue based on decreased oxygenation levels, and late rescue based on the risk of bronchopulmonary dysplasia BPD.

There is insufficient clinical evidence to support the use of inhaled nitric oxide for treatment of chronic lung conditions.
Preterm infants

- An AAP clinical report, specific to the use of iNO in preterm infants, was published in January 2014. This document evaluated the evidence and subsequently provided guidance on iNO use in this infant population. Following review of RCT results, meta-analyses and an individualized patient data meta-analysis study, a strong recommendation based on high quality evidence indicated neither rescue nor routine use of iNO improves survival in preterm neonates with respiratory failure. Another strong recommendation also indicates high quality evidence does not support the use of iNO for preventing or reducing the incidence of BPD, severe intraventricular hemorrhage or other neonatal morbidities.

- In 2011 the National Institutes of Health (NIH) published a Consensus Development Conference Statement which indicated the available evidence did not support the use of iNO in early-routine, early-rescue or later-rescue protocols for preterm infants < 34 weeks gestation who required respiratory support. This statement was supported by the information from a 2010 AHRQ Evidence Report/Technology Assessment which indicated there was currently no evidence to support iNO administration to preterm infants with respiratory failure outside of a rigorously conducted randomized clinical trial.

- The American Academy of Pediatrics (AAP) published a policy statement in 2000 (reaffirmed in 2010) on the use of inhaled nitric oxide in infants with respiratory distress. This statement indicates that there is limited data on the use of low-dose iNO for hypoxic preterm neonates. The available data suggests iNO improves oxygenation but does not improve survival in this patient population. The AAP calls for additional large randomized trials of iNO for premature infants as they may experience more toxic effects than the term and near-term infants.

- INOmax® (nitric oxide gas) was FDA approved on 12/23/1999. The approved indication includes treatment of term and near-term (>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. (INOMAX [package insert]. Clinton, NJ: INO Therapeutics LLC, 2010)

- In a multicenter randomized trial, Kinsella et al (2006) concluded iNO administration decreased the overall risk of brain injury in premature (≤ 34 weeks) infants but did not decrease the overall incidence of bronchopulmonary dysplasia (BPD) except in the infants that weighed at least 1,000 grams.

- Although Ballard et al (2006) concluded iNO improved survival without BPD in preterm infants with a gestational age of 26 weeks and birth weight ≤ 1,205 grams, the authors indicated that additional long-term follow-up of infants at high risk for BPD is needed before definitive recommendations for this population can be made.

- A systematic review and subsequent systematic review by Barrington and Finer (2007 and 2010) reached similar conclusions: inhaled nitric oxide for treatment of preterm infants with respiratory failure does not appear to be effective. Both of these reviews note additional studies are needed.

- A multi-center randomized controlled study was reviewed by Huddy et al (2008). The INNOVO trial studied ventilated preterm infants with severe respiratory distress and compared the effectiveness of including nitric oxide to the ventilator gases of a portion of these subjects. The authors concluded that there was no evidence of difference in the long-term outcome between infants that received iNO therapy versus those infants that did not receive iNO.
Clinical Evidence (continued)

- In 2010, Mercier et al reviewed the results of a multi-center double-blind European study and concluded the use of low-dose iNO for very preterm infants (gestational age of 24-28 weeks +6 days) with mild to moderate respiratory distress does not improve their survival without BPD.

- A meta-analysis by Askie et al (2011) included data from 12 randomized controlled trials and 3,298 infants assessing the effectiveness of iNO therapy in infants < 37 weeks gestation. They indicated this data did not show a statistically significant effect of iNO on death or chronic lung disease in these infants.

Congenital Diaphragmatic Hernia (CDH)

- Systematic review of 14 randomized controlled studies concluded the use of iNO for term or near-term infants with hypoxic respiratory failure who did not have a diaphragmatic hernia was reasonable. The outcome of infants with diaphragmatic hernia was not improved and possibly even worsened following iNO treatment. (Finer, 2006)

- A randomized, double-masked, controlled multicenter trial conducted by the Neonatal Inhaled Nitric Oxide Study Group in 1997 evaluated the effects of iNO in term and near-term infants with CDH. They concluded that inhaled nitric oxide therapy did not reduce the need for ECMO or death in infants with CDH and hypoxemic respiratory failure.

- A case series of 4 infants with CDH and severe respiratory insufficiency received iNO in order to assess the effects of this therapy. The conclusion of this evaluation indicated that even though select infants with CDH may respond to iNO therapy, the positive effects may be temporary. (Shah, 1994)

- A clinical trial was conducted to determine whether low-dose iNO reduces the need for ECMO in infants with pulmonary hypertension who were at least 34 weeks gestation. Administration of iNO reduced the need for ECMO in infants with meconium aspiration syndrome, pneumonia, idiopathic pulmonary hypertension, respiratory distress syndrome and pulmonary hypoplasia. However, it did not reduce the need for ECMO or improve the outcome of infants who had CDH. (Clark, 2000)

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

Bronchopulmonary Dysplasia (BPD)/Chronic Lung Disease (CLD)

- Per December 2010 new pediatric labeling, the efficacy of INOmax® in preventing BPD in premature infants had not been demonstrated by additional studies. (INOMAX [package insert]. Clinton, NJ: INO Therapeutics LLC, 2010)

- Clark et al (2002) reviewed the results of an open trial of iNO administered to very low birth weight (VLBW) infants with early chronic lung disease (CLD). The authors concluded iNO administered at ≤ 20 ppm improved oxygenation in these infants. They also acknowledged that long term efficacy could not be inferred from their study and additional trials utilizing iNO in early or evolving CLD were needed.

- Schreiber et al (2003) conducted a randomized, double-blind, placebo-controlled trial including premature infants < 34 weeks gestation who were receiving mechanical ventilation for respiratory distress syndrome. Out of 207 infants enrolled in this study, 51 infants who received iNO either died or had CLD versus 65 infants in the placebo group. The authors concluded that premature infants with respiratory distress syndrome had a decreased incidence of CLD and death when administered iNO.
Clinical Evidence (continued)

- Kinsella et al (2006) performed a multicenter, randomized trial including preterm infants 34 weeks or less with respiratory failure requiring mechanical ventilation. 793 neonates were randomized to either receive iNO or placebo. The authors concluded that low-dose (5 ppm) did not reduce the overall incidence of BPD except for those infants with a birth weight of at least 1,000 grams.

- In 2008, Hibbs et al reviewed the 12-month outcomes of preterm infants (<1,250 grams) from the Nitric Oxide Chronic Lung Disease Trial, a randomized clinical trial which sought to assess whether iNO treatment decreased long-term pulmonary morbidities in this patient population. The group of infants who had received iNO therapy contained fewer infants with BPD than the group of preterm infants who had not received iNO therapy. According to the authors, however, this difference did not reach statistical significance.

- A systematic review of the literature on the use of iNO in preterm infants (≤ 34 weeks gestation) was performed by Donohue et al in 2011. Fourteen randomized controlled trials, 7 follow-up studies and one observational study was included in their review. Twelve of these RCTs provided information on BPD in infants 36 weeks PMA. Even though the definition of BPD varied among the studies, the authors indicated there were no statistically significant differences in the rates of BPD found among the infants who received iNO and the infants who did not. The authors concluded that the use of iNO in preterm infants with respiratory failure was not supported at that time.

- In 1999, Banks et al reviewed the results of an open-labeled, non-controlled phase II pilot study evaluating the use of iNO in 16 preterm infants with severe BPD. There was great variability not only in the gestational age of these infants (23 to 29 weeks) but also in their chronological age at time of iNO delivery (age 1 to 7 months). Eleven of the 16 infants were reported to have had a significant increase in their PaO2 after one hour of iNO administration and subsequent reduction in FIO2 after 72 hours of iNO. However, four of these responders died and only four (36%) were able to be successfully weaned from mechanical ventilation. Although this small study appears to have demonstrated safety in regards to iNO administration with no adverse effects documented, the efficacy of iNO treatment in these very preterm infants cannot be substantiated. The authors conclude that randomized clinical trials of low-dose iNO for BPD are warranted.

- Soll (2012) performed a systematic review including 14 randomized controlled trials evaluating the use of iNO in preterm infants with respiratory failure. Nine of these trials involved early rescue based on oxygenation criteria with results demonstrating no significant effect on mortality or BPD. The additional studies which focused on routine use for pulmonary disease and later treatment based on increased BPD risk also provided no evidence to support improved outcomes in these preterm infants.

Recovery after surgical intervention for Congenital Heart Disease (CHD)

- Ichinose and Zapol (2009) address the use of iNO following congenital heart disease surgery in the 7th ed. of Miller’s Anesthesia. Based on the results of studies by Roberts et al (1993), Russell et al (1998), and Goldman et al (1996) the use of iNO appears to improve postoperative pulmonary hypertension and decrease the need for postoperative extracorporeal membrane oxygenation.

- Bernstein (2011) outlines the general principles of treatment of congenital heart disease in the 19th ed. of Kliegman: Nelson Textbook of Pediatrics. This text indicates “postoperative pulmonary hypertension can be managed with hyperventilation and inhaled nitric oxide”.

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Clinical Evidence (continued)

- In 2003, Hermon et al described a retrospective review on the use of iNO following pediatric cardiac surgery. The authors concluded that the postoperative use of iNO for treatment of pulmonary hypertension was feasible and safe for this population of children with congenital heart disease.
- Kawakami and Ichinose (2004) discussed the treatment of pulmonary hypertension following congenital heart surgery. They address the widespread use of iNO for this indication and its ability to decrease pulmonary vascular resistance and improve oxygenation in this patient population. The authors also indicate additional multicenter, randomized clinical trials are needed in several areas including the treatment of post-operative pulmonary hypertension.

Specialty Society Guidelines

- American Academy of Pediatrics: Use of Inhaled Nitric Oxide in Preterm Infants (2014)
- Canadian Paediatric Society: Inhaled Nitric Oxide Use in Newborns (2012)

Bibliography


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### Revision History

The following are approved changes incorporated into the revision numbers indicated below.

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<th>Revision</th>
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<td>V1.0</td>
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