Subject: Inhaled Nitric Oxide in Newborns

Background: Inhaled nitric oxide (iNO) is used to improve oxygenation and reduce the need for extracorporeal membrane oxygenation (ECMO) in term and late preterm infants with severe persistent pulmonary hypertension of the newborn (PPHN).

Policy and Coverage Criteria:
Harvard Pilgrim Health Care (HPHC) considers inhaled nitric oxide as medically necessary for term or near-term neonates (>34 weeks gestational age) when documentation confirms ALL the following:

- Hypoxic respiratory failure with clinical or echocardiographic evidence of pulmonary hypertension; AND
- No congenital diaphragmatic hernia; AND
- Use is in conjunction with ventilatory support and other appropriate agents

Exclusions: Harvard Pilgrim Health Care (HPHC) considers use of inhaled nitric oxide in neonates as investigational/experimental for all other indications, including its use in premature neonates (<34 weeks gestational age).

Supporting Information:
Nitric Oxide inhalation (iNO) therapy is a noninvasive treatment for PPHN that involves inhalation of gaseous nitric oxide in conjunction with ventilator support. The potential of exogenous NO as a therapeutic agent is based on its potent vasodilator properties and its ability to be delivered as a gas to the lung. Exogenous NO increases the partial pressure of arterial oxygen by dilating pulmonary vessels in better ventilated areas of the lung. NO inhalation therapy, in conjunction with ventilatory support, has been investigated for the treatment of term and near-term newborns, ≥ 34 weeks gestational age, with hypoxic respiratory failure associated with clinical or echocardiographic evidence of pulmonary hypertension.

Ryan and Tobias (2007) retrospectively reviewed their experience with iNO in a pediatric ICU. In 19 patients who presented with respiratory failure, 15 of 19 showed an increase in oxygenation with iNO treatment. The 15 patients who responded to iNO treatment survived, while the other 4 patients who did not respond died. In 19 patients with pulmonary hypertension following cardiopulmonary bypass and surgery for CHD, iNO was used to treat the pulmonary hypertension. A high pulmonary artery pressure was documented in 13 of these 19 patients and iNO resulted in a decrease in the PA pressure in 9 of these patients.

Finer and Barrington (2006) conducted a review to determine whether treatment of hypoxic term and near-term newborn infants with iNO improves oxygenation and reduces the rates of death, the requirement for ECMO, or affects long term neurodevelopmental outcomes. Fourteen RCTs were included in the review. Seven of these trials compared iNO to control in infants with moderate or severe illness. Four of these trials compared iNO to control, but allowed iNO backup treatment for some infants over time. Two trials enrolled infants with moderate severity of illness and randomized to immediate iNO treatment or iNO treatment only if they deteriorated to more severe criteria. One trial studied only infants with congenital diaphragmatic hernia, and one trial enrolled both preterm and term infants, but reported the majority of the results separately for the two groups. Inhaled nitric
oxide appears to improve outcome in hypoxemic term and near-term infants by reducing the incidence of the combined endpoint of death or need for ECMO. The reduction seems to be entirely a reduction in need for ECMO; mortality is not reduced. Oxygenation improves in approximately 50% of infants receiving nitric oxide. Whether infants have clear echocardiographic evidence of PPHN or not does not appear to affect outcome. The outcome of infants with diaphragmatic hernia was not improved and there is a suggestion that outcome was slightly worsened. The authors concluded that the use of iNO is reasonable for term and near-term infants with hypoxic respiratory failure who do not have a diaphragmatic hernia.

Sadiq et al. (2003) conducted a randomized, prospective multicenter study to assess whether iNO in patients with moderate PPHN would improve PaO2, prevent progression to severe PPHN, and improve outcomes. A total of 80 patients were randomized to receive either standard medical therapy or standard medical therapy plus iNO. In the iNO group, iNO concentration was increased in steps of 10-20 ppm every 30 minutes until there was no further improvement in PaO2. 58% of control patients compared to 15% of iNO patients failed assigned therapy and developed severe PPHN. PaO2 improved from 112 +/- 48 to 133 +/- 100 in the control group compared to an improvement of 101 +/- 29 to 208 +/- 118 in the iNO group. For the first 36 hours after the study, entry AaDO2 levels and ventilator support were significantly lower in the iNO group compared to control. The authors concluded that treatment with iNO improves PaO2, reduces the amount of ventilator support needed, and prevents progression to severe PPHN in patients with moderate PPHN.

Clark et al. (2000) conducted a clinical trial to determine whether low-dose iNO would reduce the use of ECMO in neonates with PPHN who were born after 34 weeks' gestation, were 4 days or older, required assisted ventilation, and had hypoxic respiratory failure as defined by an oxygenation of 25 or higher. A total of 248 neonates were included and 126 were randomly assigned to the NO group and 122 to the control group. ECMO was used in 64% of the control group and 38% of the NO group. There was a similar 30-day mortality rate in the two groups. Neonates in the NO group developed less chronic lung disease than in the control group. The authors concluded that iNO reduces the extent to which ECMO is needed in neonates with hypoxic respiratory failure and pulmonary hypertension.

Davidson et al. (1998) assessed the dose-related effects of iNO as a specified adjunct to early conventional therapy for 155 term infants with PPHN, with regards to neonatal outcome, oxygenation, and safety. Infants were randomized to receive either a control or NO and treatment was administered until success or failure criteria were met. The authors found that for term infants with PPHN, early iNO as the sole adjunct to conventional management produced an acute and sustained improvement in oxygenation for 24 hours without short-term side effects, and suggests ECMO use may be reduced.

A study conducted by the Neonatal Inhaled Nitric Oxide Study Group (1997) sought to determine whether inhaled NO would reduce mortality or the initiation of extracorporeal membrane oxygenation in infants with hypoxic respiratory failure. Infants who were included in the study consisted of 235 infants born after gestation of >/= 34 weeks who were 14 days old or less, had no structural heart disease, and required assisted ventilation and whose oxygenation index was 25 or higher on two measurements. Infants were randomly assigned to receive NO at 20 ppm (n=114) or control of oxygen only (n=121). 64% of the control group and 46% of the NO group died within 120 days or were treated with ECMO. Significantly fewer infants in the NO group received ECMO. The NO group had significantly greater improvement in PaO2 and in the oxygenation index. The authors concluded that NO therapy reduced the use of ECMO, but had no apparent effect on mortality in critically ill infants with hypoxic respiratory failure.

Roberts et al. (1997) studied whether iNO decreases severe hypoxemia in infants with persistent pulmonary hypertension. The study included 58 full-term infants with severe hypoxemia and PPHN who were randomized to
either breathe a control gas of nitric oxide, mixed with oxygen from a ventilator. Systematic oxygenation doubled with iNO in 53% of infants. Conventional therapy without iNO increased oxygenation in only 7% of infants. Long-term therapy with iNO sustained systemic oxygenation in 75% of the infants who showed initial improvement. ECMO was required in 21% of the control group and 40% of the iNO group. The authors concluded that iNO improves systemic oxygenation in infants with PPHN and may reduce the need for more invasive treatments.

Kinsella et al (1997) conducted a randomized, multicenter clinical trial to determine the relative roles of iNO and high-frequency oscillatory ventilation (HFOV) in the treatment of severe PPHN in 205 neonates. Infants were stratified by disease then randomly assigned to either HFOV (n=98) or iNO (n=107). 26% of infants recovered with the initially assigned therapy without crossover. Of infants whose initial treatment failed, crossover treatment with the alternative therapy was successful in 21% for INO and 14% for HFOV. Both treatment strategies failed in 125 infants and 32% of these infants responded to combination therapy with iNO plus HFOV. Overall, 60% responded to either treatment alone or combination therapy. The authors concluded that the treatment with HFOV plus iNO is often more successful than treatment with HFOV or iNO alone in severe PPHN.

Wessel et al. (1997) conducted a prospective, randomized trial to determine the effect of iNO on clinical outcome in 49 mechanically ventilated newborns with PPHN. Infants were randomized to receive treatment with iNo or without iNO. Mortality (8%), use of ECMO (33%), median days on mechanical ventilation (9 days), and duration of supplemental oxygen (13 days) were not different between treatment groups. PaO2, oxygen saturation, and OI improved in the NO group compared with baseline and to control patients at 15 minutes. The median percent change in OI (-31%) in the NO group was significantly different from baseline and from the control group. Before cannulation for ECMO, oxygenation was better in the NO group compared with control patients. There was a tendency to observe fewer adverse neurologic events (seizure and intracranial hemorrhage) in the NO group (4/26 vs 8/23). The authors concluded that sustained improvement in oxygenation with NO and better oxygenation at initiation of ECMO may have important clinical benefits.

INOmax® is a vasodilator, which, in conjunction with ventilator support and other appropriate agents, is indicated for the treatment of term and near-term (>34 weeks gestation) 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.

Guidelines:
The American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines (ACCF/AHA, 2009) reported that persistent PH [pulmonary hypertension] of the newborn is a syndrome characterized by increased pulmonary vascular resistance, right to left shunting, and severe hypoxemia. Treatment options include inhaled nitric oxide (iNO) and extracorporeal membrane oxygenation. Pediatric IPAH [idiopathic pulmonary arterial hypertension] is treated similar to that in adults. A higher percentage of children are acute responders and candidates for calcium channel blockers.

American Academy of Pediatrics (AAP), 2000: Recommendations:

- 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.
- 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.
The 2014 American Academy of Pediatrics (AAP) reported the following on the use of inhaled nitric oxide in preterm infants:

- The results of randomized controlled trials, traditional meta-analyses, and an individualized patient data meta-analysis study indicate that neither rescue nor routine use of iNO improves survival in preterm infants with respiratory failure (Evidence quality, A; Grade of recommendation, strong).
- The preponderance of evidence does not support treating preterm infants who have respiratory failure with iNO for the purpose of preventing/ameliorating BPD, severe intraventricular hemorrhage, or other neonatal morbidities (Evidence quality, A; Grade of recommendation, strong).
- The incidence of cerebral palsy, neurodevelopmental impairment, or cognitive impairment in preterm infants treated with iNO is similar to that of control infants (Evidence quality, A).
- The results of 1 multicenter, randomized controlled trial suggest that treatment with a high dose of iNO (20 ppm) beginning in the second postnatal week may provide a small reduction in the rate of BPD. However, these results need to be confirmed by other trials.
- An individual-patient data 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.
- There are limited data and inconsistent results regarding the effects of iNO treatment on pulmonary outcomes of preterm infants in early childhood.

The National Institute of Health (NIH, 2010) guidelines state the following:

- Taken as a whole, the available evidence does not support use of inhaled nitric oxide in early routine, early rescue, or later rescue regimens in the care of premature infants <34 weeks gestation who require respiratory support.
- There are rare clinical situations, including pulmonary hypertension or hypoplasia, that have been inadequately studied in which inhaled nitric oxide may have benefit in infants <34 weeks gestation. In such situations, clinicians should communicate with families regarding the current evidence on its risks and benefits as well as remaining uncertainties.
- Basic research and animal studies have contributed to important understandings of inhaled nitric oxide benefits on lung development and function in infants at high risk of bronchopulmonary dysplasia. These promising results have only partly been realized in clinical trials of inhaled nitric oxide treatment in premature infants. Future research should seek to understand this gap.
- Predefined subgroup and post hoc analyses of previous trials showing potential benefit of inhaled nitric oxide have generated hypotheses for future research for clinical trials. Prior strategies shown to be ineffective are discouraged unless new evidence emerges. The positive results of one multicenter trial, which was characterized by later timing, higher dose, and longer duration of treatment, require confirmation. Future trials should attempt to quantify the individual effects of each of these treatment related variables (timing, dose, and duration), ideally by randomizing them separately.
- Based on assessment of currently available data, hospitals, clinicians, and the pharmaceutical industry should avoid marketing inhaled nitric oxide for premature infants <34 weeks gestation.

The Canadian Pediatric Society (CPS, 2012) guidelines state that iNO use in the term infant with severe hypoxic respiratory failure improves oxygenation and decreases the combined outcome of death or need for ECMO, mainly by decreasing the use of ECMO. iNO use is not effective for most infants with congenital diaphragmatic hernia. Its role in the management of the preterm infant has yet to be established. iNO use is safe when administered in tertiary care NICUs under strict protocols and monitoring. The starting dose in term infants is 20 ppm, with gradual reduction of the dose following improvement of oxygenation. At the recommended doses, iNO is associated with minimal toxicity.

HPHC Clinical Medical Policy

INHALED NITRIC OXIDE IN NEWBORNS

HPHC policies are based on medical science, and written for the majority of people with a given condition.

Coverage described in this policy is standard under most HPHC plans. Specific benefits may vary by product and/or employer group. Please reference appropriate member materials (e.g., Benefit Handbook, Certificate of Coverage) for member-specific benefit information.
Coding:
Codes are listed below for informational purposes only, and do not guarantee member coverage or provider reimbursement. The list may not be all-inclusive. Deleted codes and codes which are not effective at the time the service is rendered may not be eligible.

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<tr>
<th>CPT® Code</th>
<th>Description</th>
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<tr>
<td>93463</td>
<td>Pharmacologic agent administration (eg, inhaled nitric oxide, intravenous infusion of nitroprusside, dobutamine, milrinone, or other agent) including assessing hemodynamic measurements before, during, after and repeat pharmacologic agent administration, when performed</td>
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Billing Guidelines:
Member’s medical records must document that services are medically necessary for the care provided. Harvard Pilgrim Health Care maintains the right to audit the services provided to our members, regardless of the participation status of the provider. All documentation must be available to HPHC upon request. Failure to produce the requested information may result in denial or retraction of payment.

References:

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Summary of Changes

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<thead>
<tr>
<th>Date</th>
<th>Change</th>
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<tbody>
<tr>
<td>3/18</td>
<td>References updated, minor language revision</td>
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<tr>
<td>4/17</td>
<td>Policy Reviewed; Removed Benchmarks</td>
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<tr>
<td>1/16</td>
<td>New Policy</td>
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Approved by Medical Policy Review Committee: 3/20/2018
Reviewed/Revised: 1/16; 4/17; 3/18
Initiated: 1/13/16

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