Clinical Policy Title: Inhaled Nitric Oxide

Clinical Policy Number: 11.02.02
Effective Date: June 1, 2014
Initial Review Date: February 19, 2014
Most Recent Review Date: March 19, 2014
Next Review Date: February 2015

Coverage policy

1.) Arbor Health Plan considers the use of inhaled nitric oxide in the management of term infants at risk for pulmonary hypertension to be clinically proven and, therefore, medically necessary when all of the following criteria are met:
   - Inhaled nitric oxide is a component treatment of respiratory failure associated with pulmonary hypertension.
   - In infants 35 weeks gestation or greater.
   - With no congenital diaphragmatic hernia.
   - In centers with Level 3 or Level 4 NICU, and referral access to extracorporeal membrane oxygenation (ECMO).

2.) Arbor Health Plan considers the use of inhaled nitric oxide for respiratory distress in infants under 35 weeks gestation to be investigational and, therefore, not medically necessary.

Limitations: All other uses of inhaled nitric oxide are not medically necessary.
**Alternative covered services:** Standard medical care as found in the peer-reviewed medical journals for the treatment of asthma, respiratory distress, chronic lung disease or pulmonary disease in infants/newborns.

**Background**

Nitric oxide (chemical designation NO) is a free radical serving as a signal for inflammatory processes and as a regulator serves as a vasodilator. Nitric oxide is formed from the actions of nitric oxide synthase (NOS) catalyzing the abduction of guanidine nitrogen from arginine raising intracellular levels of cyclic-guanosine 3', 5'-monophosphate and yielding NO and water. Three isozymes of NOS exist with a similar final common pathway. However, the iNOS is expressed in the epithelium of the airways in both normal and asthmatic subjects. In the face of inflammatory processes more NO is produced, and in turn is reduced in the face of glucocorticosteroids. Physiologically NO causes vasodilatation and relaxation of smooth muscles.

**Inhaled Nitric Oxide**

The impact of nitric oxide as a vasodilator and as a molecule with impacts on other pulmonary regulatory systems has made the use of inhaled nitric oxide (iNO) to be viewed as a potentially viable option in the treatment of preterm infants with pulmonary hypertension and hypoxemic respiratory failure. A number of small series studies initially supported this use. In 2010, the National Institutes of Health (NIH) convened a panel to review the evidence. It did not find supporting evidence for the use of iNO for rescue and care of infants less than 34 weeks gestation. The following year, Askie et al. published their meta-analysis from 14 published trials but the significant differences in the design of published trials precluded a determination of the salutary impact of iNO.

A consensus panel from the American Respiratory Care Foundation (DiBlasi, 2010) made recommendations for (1) a trial of iNO in newborns >34 weeks gestation with oxygen tension <100 mm Hg on 100 percent oxygen; (2) use of iNO be started early to reduce duration of mechanical ventilation, (3) iNO should not be used in infants with congenital diaphragmatic hernia, cardiac anomalies with right-to-left shunts, or heart failure. The ARCF recommendations indicate a reliance on Cochrane Neonatal Group (2010) which failed to find evidence for the use of iNO as rescue therapy and that early use of iNO in preterm infants with respiratory conditions does not affect brain injury or morality.

The Agency for Healthcare Research and Quality funded an evidence report on inhaled nitric oxide in preterm infants that found a 7 percent reduction is composite outcome of death or bronchopulmonary dysplasia (BPD) at 36 weeks compared to control; but that there was insufficient evidence to support the use of iNO outside of “rigorously conducted randomized clinical trials.”

The American Academy of Pediatrics’ Clinical Report: *Use of Inhaled Nitric Oxide in Preterm Infants* published January 2014, reviewed the literature for the use of inhaled nitric oxide in infants with respiratory failure and found that “the preponderance of evidence does not support treating preterm infants who have respiratory failure with iNO. Further, there is no evidence of a positive salutary impact on neurodevelopmental processes for infants who received iNO compared to controls.

The U.S. Food and Drug Administration (FDA) warns of rebound pulmonary hypertension syndrome following abrupt discontinuation from iNO, methemoglobinemia, airway injury and heart failure as a result of nitric oxide. The use of iNO in adults with acute respiratory distress syndrome (ARDS) has not been demonstrated to be effective.
Methods

Searches:
Arbor Health Plan searched PubMed and the databases of:
- UK National Health Services Centre for Reviews and Dissemination.
- Agency for Healthcare Research and Quality’s National Guideline Clearinghouse and other evidence-based practice centers.
- The Centers for Medicare & Medicaid Services.

Searches were conducted on February 5, 2014, using the terms “inhaled nitric oxide” and “respiratory distress.”

Included were:
- **Systematic reviews**, which pool results from multiple studies to achieve larger sample sizes and greater precision of effect estimation than in smaller primary studies. Systematic reviews use predetermined transparent methods to minimize bias, effectively treating the review as a scientific endeavor, and are thus rated highest in evidence-grading hierarchies.
- **Guidelines based on systematic reviews.**
- **Economic analyses**, such as cost-effectiveness, and benefit or utility studies (but not simple cost studies), reporting both costs and outcomes — sometimes referred to as efficiency studies — which also rank near the top of evidence hierarchies.

Findings:
As a summary of the findings of the studies, the following points may be made:
- There is evidence to support the use of inhaled nitric oxide in term or late preterm infants with respiratory distress and pulmonary hypertension for its acute salutary impacts as a smooth muscle relaxant on pulmonary vascular and bronchiolar tree.
- iNO should not be used for more than four days because of toxicity; nor is it effective in treatment of hypoxemia related to congenital diaphragmatic hernia.
- The use of inhaled nitric oxide for treatment of preterm infants with respiratory distress, BPD or pulmonary hypertension has not been standardized and its impact is not known.
- The recommendations for the use of inhaled nitric oxide reside with controlled clinical trials except as mentioned in the first bullet.

Summary of clinical evidence

<table>
<thead>
<tr>
<th>Citation</th>
<th>Content, Methods, Recommendations</th>
</tr>
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<tbody>
<tr>
<td>Keszler M (2012)</td>
<td><strong>Key points:</strong></td>
</tr>
<tr>
<td></td>
<td>• Inhaled nitric oxide has been FDA approved for treatment of late preterm and term infants with persistent pulmonary hypertension of the newborn.</td>
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<td></td>
<td>• Off-label use is widespread.</td>
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<tr>
<td></td>
<td>• There is limited data on the long-term use of iNO in treating infants with pulmonary hypertension with BPD, diaphragmatic hernia, and rescue therapy in preterm infants with severe respiratory failure.</td>
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<tr>
<td></td>
<td>• Need to avoid potential exposure to unknown adverse effects not balanced by documentable benefits.</td>
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| Kumar P (2014) | **Key points:**  
• The results of randomized controlled trials, traditional meta-analyses, and an individualized patient data meta-analysis study indicate 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). |
| Barrington (2010) | **Key points:**  
• Cochrane Collaborative Report, based upon 14 randomized trials of iNO in preterm infants.  
• No clear effect of iNO on frequency of all grades of intraventricular hemorrhage. |

**Glossary**

**Bronchodilation** — Refers to relaxation of the muscles around the bronchial tubes causing the airways to open further.

**Inhaled nitric oxide** — Abbreviated iNO, this is use of nitric oxide as reported therapy for premature infants with respiratory failure or other conditions.

**Nitric Oxide** — A simple molecule with one atom of nitrogen and oxygen. It is produced in the body as a result of enzyme reactions and is a potent regulator of vasodilatation and bronchodilation.

**Vasodilatation** — Refers to relaxation of the small muscles within the artery wall causing the artery to open with a wider diameter.

**Related policies**
Arbor Health Plan Utilization Management program description.
References
Professional society guidelines:


Peer-reviewed references:


Clinical trials:

Inhaled Nitric Oxide/INOpulse DS for Pulmonary Arterial Hypertension (PAH), NCT01457781, INO Therapeutics, Dec. 10, 2013.
Study of Inhaled Nitric Oxide and Respiratory Outcomes in Late Preterm Infants, NCT01748045, Dec. 2013, Tufts Medical Center, Boston.

Study in Subjects with PAH and PH Secondary to IPF Using Inhaled NITROsyl (PHiano), NCT01265888, April 2013, Geno LLC.

Centers for Medicare & Medicaid Services (CMS) national coverage determinations (NCDs)
There are no NCDs for the diagnostic or therapeutic uses of nitric oxide.

Local coverage determinations (LCDs)
There are no LCDs for the diagnostic or therapeutic uses of nitric oxide.

Commonly submitted codes
Below are the most commonly submitted codes for the service(s)/item(s) subject to this policy. This is not an exhaustive list of codes. Providers are expected to consult the appropriate coding manuals and bill in accordance with those manuals.

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<tr>
<td>94002</td>
<td>Ventilation assist and management, initiation of pressure or volume preset ventilators for assisted or controlled breathing; hospital inpatient/observation, initial day</td>
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<td>94003</td>
<td>Ventilation assist and management, initiation of pressure or volume preset ventilators for assisted or controlled breathing; hospital inpatient/observation, each subsequent day</td>
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<td>Primary and/or persistent pulmonary hypertension of newborn</td>
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