

Clinical Policy: Inhaled Nitric Oxide

Reference Number: CP.MP.87

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Description

Inhaled nitric oxide (iNO) is a selective pulmonary vasodilator in which its mechanism of action results in smooth muscle relaxation. Several studies have suggested that iNO improves oxygenation, particularly in trials of term and near-term neonates with hypoxic respiratory failure. iNO has been shown to reduce the need for ECMO (extracorporeal membrane oxygenation) without increasing neurodevelopmental, behavioral, or medical abnormalities at 2 years of age.

Policy/Criteria

- I. It is the policy of health plans affiliated with Centene Corporation® that inhaled nitric oxide (iNO) therapy is **medically necessary** when meeting the following:
 - A. *Initiation* of therapy, both of the following*:
 1. iNO will be administered via endotracheal tube or tracheostomy;
 2. One of the following indications:
 - a. Hypoxic respiratory failure in newborns \geq 34 weeks gestational age **at birth** with all:
 - i. Evidence of pulmonary artery hypertension (PAH), one of the following:
 - a) Well-documented, clear clinical evidence of pulmonary hypertension despite maximal respiratory support;
 - b) Echocardiogram suggestive of PAH;
 - ii. Absence of unrepaired congenital diaphragmatic hernia except when used as a bridge to surgical repair of congenital diaphragmatic hernia;
 - iii. Conventional therapies such as mechanical ventilation, administration of high concentrations of oxygen (80-100%), high-frequency ventilation, induction of alkalosis, neuromuscular blockade, and/or sedation have failed or are expected to fail;
 - iv. Oxygen index (OI) \geq 25. The OI is calculated as the mean airway pressure divided by the partial pressure of arterial oxygen times 100;
 - v. Response seen with administration of up to 40 ppm trial of iNO (defined as a PaO₂ increase \geq 20 mm Hg or a 20% decrease in OI);
 - b. Perioperative management in children, and infants \geq 34 weeks gestational age **at birth**, both of the following:
 - i. One of the following indications:
 - a) Congenital heart defect and one of the following:
 - 1) iNO therapy for vasodilation is used in response to cardiac bypass surgery to repair a congenital heart defect that is causing PAH;
 - 2) Perioperative stabilization and management of hypoxia;
 - b) Pulmonary hypertensive crisis associated with heart or lung surgery (including immediately pre-operatively for congenital diaphragmatic hernia);

- ii. Initiation of alternative vasodilator therapies during iNO administration with the intent to wean iNO* (e.g. sildenafil or others).

B. *Continuation* of iNO therapy, one of the following*:

1. Member continues to require iNO as evidenced by a continued O₂ requirement of 80-100%;
2. A weaning protocol has been initiated after a 4-6 hour period of stability, indicated by O₂ requirement decreased/decreasing to 60-80% or OI \leq 10.

***Note:** Extended administration of iNO beyond 48 hours requires secondary review by a medical director.

II. It is the policy of health plans affiliated with Centene Corporate that iNO is **not medically necessary** for any other indications such as preterm infants < 34 weeks gestation at birth, acute bronchiolitis, bronchopulmonary dysplasia (BPD), congenital diaphragmatic hernia (CDH) (except as noted above), adult respiratory distress syndrome or acute lung injury, treatment in adults with positive vaso-reactivity testing, post-op cardiac surgery in adults, and vaso-occlusive crises in members with sickle cell disease because safety and effectiveness have not been established.

Treatment Regimen

The American Academy of Pediatrics (AAP) recommends that iNO should only be administered according to a formal protocol that has been approved by the Food and Drug Administration (FDA) and the institutional review board and with informed consent.

Since no one standard protocol has been issued for iNO treatment, the following is one guideline to assist in determining appropriate initiation and continuation of treatment. The recommended starting dose of iNO for term infants is 20ppm. A positive response generally occurs in less than 30 minutes with a PaO₂ increase \geq 20 mmHg (or 20% decrease in OI). If there is no response, the dose may be increased up to 40 ppm. In premature infants, the initial dose used in studies was 10 ppm with an increase up to 20 ppm in non-responders. Doses of up to 80 ppm have been used, but the potential for increasing toxicity without additional benefits occurs at doses greater than 40 ppm.

Per Peliowski, weaning can occur following improvement in oxygenation and after a 4 to 6 hour period of stability, during which the inspired oxygen concentration is decreased to 60% to 80%, or the OI falls to \leq 10. At 4-6 hour intervals, the dose can be decreased by 50%, as long as the OI remains \leq 10. When stability is maintained at iNO dose of 5 ppm, weaning should occur by 1 ppm every 4 hours and discontinued at 1 ppm if oxygenation status remains with <60% oxygen with PaO₂ consistently >50 mmHg. If deterioration occurs during or after weaning occurs, the dose should be increased to the previous level or iNO restarted. Once the infant stabilizes again, weaning should occur more slowly, taking place over a 24 to 48 hour period.

In general, patients who responded to iNO therapy typically require treatment for only 3-4 days, with randomized trials demonstrating that 90% of treated infants were off iNO therapy within one week of initiation. Patients should be monitored for potential toxic effects by measuring the

serum methemoglobin concentration, levels of nitrogen dioxide at the airway opening, and ambient air contamination. Decreased platelet aggregation, increased risk of bleeding (including intracranial hemorrhage), and surfactant dysfunction can also occur from iNO toxicity.

Background

A large and well-designed multicenter trial was conducted by the Neonatal Research Network in 235 infants with gestational age ≥ 34 weeks who had severe hypoxic respiratory failure (OI ≥ 25) and did not have congenital diaphragmatic hernia. Infants were randomly assigned to iNO or to control (100% oxygen). Fewer infants in the treatment group died within 120 days or received ECMO therapy, (46% versus 64%; relative risk 0.72, 95% CI 0.57-0.91) compared to control. This difference was entirely due to decreased requirement for ECMO (39% versus 54%); there was no difference between groups in mortality.

In a systemic review by the Cochrane database, similar findings of fewer requirements for ECMO and no difference in mortality were noted. Fourteen randomized trials were found in term or near term infants with hypoxia. iNO improved oxygenation in approximately 50% of the treated infants. Within 30 to 60 minutes of beginning therapy, PaO₂ increased by a mean of 53 mmHg and OI decreased by a mean of 15.1. Outcome did not appear to be affected by whether infants had echocardiographic evidence of persistent pulmonary hypertension. No benefit was noted in those with congenital diaphragmatic hernia, indeed there is a suggestion that outcome was slightly worsened.

In preterm infants <35 weeks gestation, a systematic review by the Cochrane database found 14 randomized controlled trials of iNO. The authors concluded that iNO as a rescue therapy for the very ill ventilated preterm infant does not appear to be effective and may increase the risk of severe intraventricular hemorrhage. Later use to prevent BPD does not appear to be effective. Early routine use of iNO in mildly sick preterm infants may improve survival without BPD and decrease serious brain injury; further studies are needed to confirm these findings.

Furthermore, a 2018 retrospective analysis of 993 extremely preterm infants (born at 22 to 29 weeks' gestation) compared infants receiving iNO with propensity-matched controls, and did not find a significant association between iNO exposure and mortality.

iNO has been well-studied in patients with acute lung injury and acute respiratory distress syndrome (ALI/ARDS). While iNO may improve oxygenation temporarily, it has not been shown to improve clinically important outcomes such as duration of mechanical ventilation, 28-day mortality or one-year survival. Furthermore, iNO does not improve oxygenation in all patients and the factors that may predict a good response are still uncertain.

In an updated Cochrane database review, the evidence was insufficient to support iNO in any category of critically ill adults and children with acute respiratory distress syndrome. Although iNO results in a transient improvement in oxygenation, it does not reduce mortality and may be harmful, as it seems to increase renal impairment.²²

A Cochrane Summary for the use of iNO for pulmonary hypertension (PH) following surgery in infants and children with congenital heart disease found no benefit of it to assist in recovery. In

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the four randomized trials reviewed, there was no difference found in mortality or other outcomes reviewed. Due to the minimal data that was available, the authors found it difficult to draw valid conclusions regarding effectiveness and safety of this treatment in the select population. In a later study, iNO was effective in reducing the risk of development of PH crisis in PAH-congenital heart defect patients after cardiac repair in a placebo-controlled study.¹⁶ Infants with PAH-congenital heart defects receiving iNO had fewer PH crises and shorter postoperative courses without concomitant side effects related to the medication.

2015 guidelines on pediatric pulmonary hypertension, issued by the American Heart Association and American Thoracic Society, make a class 1, level B recommendation for use of iNO in post-operative pulmonary hypertensive crises. The guidelines state that iNO is an established therapy for postoperative pulmonary hypertension due to its selective pulmonary vasodilator properties, rapid effect onset, and ease of administration.

Research on iNO use in adults with PH is limited to case reports and small case series, which leaves the impact of iNO on survival uncertain. It has been found to successfully stabilize a variety of acutely ill and hemodynamically compromised patients with severe PH, but the outcomes data are limited and thus cannot be considered standard of care. Acute vasodilator testing is the only well established and widely accepted use of iNO in patients with PAH. Patients with a positive vasoreactivity test are candidates for a trial of calcium channel blocker therapy

INO has numerous potential harms that must be considered when determining the risks and benefits of treatment. These potential harms include renal dysfunction, DNA strand breakage and base alterations which are potentially mutagenic, immunosuppression that could increase the risk of nosocomial infection, and a possible increase in methemoglobin and NO2 concentrations, which must be monitored frequently. Also, iNO may produce toxic free radicals; however, it is unknown if these are more harmful than ongoing exposure to high fractions of inspired oxygen.

Coding Implications

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CPT® Codes	Description
94799	Unlisted pulmonary service or procedure

HCPCS Codes	Description
N/A	

ICD-10-CM Diagnosis Codes that Support Coverage Criteria

ICD-10-CM Code	Description
I16.0-I16.9	Hypertensive crisis
I27.0	Primary pulmonary hypertension
I27.2	Other secondary pulmonary hypertension
P07.37	Preterm newborn, gestational age 34 completed weeks
P07.38	Preterm newborn, gestational age 35 completed weeks
P07.39	Preterm newborn, gestational age 36 completed weeks
P22.0	Respiratory distress syndrome of newborn
P28.5	Respiratory failure of newborn
P29.3	Persistent fetal circulation
Q21.0	Ventricular septal defect
Q21.2	Atrial septal defect
Z98.890	Other specified postprocedural states

Reviews, Revisions, and Approvals	Date	Approval Date
Policy developed, Neonatologist reviewed	08/13	08/13
Split criteria into initiation and continuation of therapy Added Treatment Regimen section Neonatologist reviewed	08/14	09/14
Literature researched and bibliography updated Converted to new template Neonatologist reviewed	09/15	09/15
Updated template and disclaimer language	03/16	
Added criteria for iNO therapy in perioperative management for PAH in pediatrics. Reviewed by Pediatric Cardiology, Adult Cardiology, and Neonatologist.	08/16	09/16
References reviewed and updated. ICD-10 and CPT codes added.	09/17	09/17
Added indication for pediatric post-op management of pulmonary hypertension associated with heart or lung surgery. Background updated. Reviewed by pediatric pulmonologist.	09/18	09/18

Reviews, Revisions, and Approvals	Date	Approval Date
Newborn hypoxic respiratory failure: removed exclusion of infant with congenital heart defect; added clinical evidence of PH as a diagnostic option; added that congenital diaphragmatic hernia is excluded except when a bridge to surgical repair. Perioperative criteria: combined indications into I.A.2; specified criteria applies to infants ≥ 34 weeks of age and children; removed restriction that congenital heart defect criteria applies only in the presence of pulmonary hypertension; added perioperative stabilization and management of hypoxia as an indication for members with congenital heart defect; removed requirement that iNO be delivered via endotracheal tube; for pulmonary hypertensive crisis associated with heart or lung surgery, added immediate pre-op treatment of congenital diaphragmatic hernia; to all perioperative criteria, added requirement that alternative vasodilators must be initiated with the intent to wean iNO. For Continuation criteria: removed restriction to newborns only; removed restriction to one week of iNO or less. Added note applying to all indications that iNO administration beyond 48 hours requires medical director review. Reviewed by a pediatric pulmonologist, pediatric critical care physician, and pediatric emergency medicine physicians. Added ICD-10- CM codes I16.0-I16.9 and Z98.890.	04/19	04/19
Added requirement that iNO be delivered via endotracheal tube or tracheostomy.	05/19	05/19

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Important Reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. “Health Plan” means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan’s affiliates, as applicable.

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Note: For Medicaid members, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.

Note: For Medicare members, to ensure consistency with the Medicare National Coverage Determinations (NCD) and Local Coverage Determinations (LCD), all applicable NCDs, LCDs, and Medicare Coverage Articles should be reviewed prior to applying the criteria set forth in this clinical policy. Refer to the CMS website at <http://www.cms.gov> for additional information.

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