Inhaled Nitric Oxide

Clinical Policy ID: CCP.1086

Recent review date: 5/2026

Next review date: 9/2027

Policy contains: Inhaled nitric oxide; pediatric pulmonary hypertension; respiratory distress.

First Choice Next has developed clinical policies to assist with making coverage determinations. First Choice Next's clinical policies are based on guidelines from established industry sources, such as the Centers for Medicare & Medicaid Services (CMS), state regulatory agencies, the American Medical Association (AMA), medical specialty professional societies, and peer-reviewed professional literature. These clinical policies along with other sources, such as plan benefits and state and federal laws and regulatory requirements, including any state- or plan-specific definition of "medically necessary," and the specific facts of the particular situation are considered, on a case by case basis, by First Choice Next when making coverage determinations. In the event of conflict between this clinical policy and plan benefits and/or state or federal laws and/or regulatory requirements, the plan benefits and/or state and federal laws and/or regulatory requirements shall control. First Choice Next's clinical policies are for informational purposes only and not intended as medical advice or to direct treatment. Physicians and other health care providers are solely responsible for the treatment decisions for their patients. First Choice Next's clinical policies are reflective of evidence-based medicine at the time of review. As medical science evolves, First Choice Next will update its clinical policies as necessary. First Choice Next's clinical policies are not guarantees of payment.

Coverage policy

Inhaled nitric oxide is clinically proven and, therefore, may be medically necessary for the management of newborn infants at risk for pulmonary hypertension when all of the following criteria are met (Abman, 2015; Kinsella, 2016; U.S. Food and Drug Administration, 1999):

- Inhaled nitric oxide is a component treatment of respiratory failure associated with pulmonary hypertension.
- Infants are ≥ 35 weeks of gestation.
- There is no presence of congenital diaphragmatic hernia.
- Inhaled nitric oxide is performed in centers with Level 3 or Level 4 neonatal intensive care units and referral access to extracorporeal membrane oxygenation.

Inhaled nitric oxide is investigational/not clinically proven and, therefore, not medically necessary for respiratory distress in infants less than 35 weeks of gestation (Kumar, 2014).

Limitations

All other uses of inhaled nitric oxide are not medically necessary.

Contraindications include severe left ventricular dysfunction, congenital heart disease involving a right to left

shunt, and cyanotic heart disease. Abrupt discontinuation of the treatment can worsen oxygenation and increase pulmonary artery pressure, and can cause rebound pulmonary hypertension syndrome (Witek, 2023).

Alternative covered services

Standard medical care as found in the peer-reviewed medical journals for the treatment of asthma, respiratory distress, chronic lung disease, and pulmonary disease in infants and newborns.

Background

Persistent pulmonary hypertension in newborns results from failure of successful postnatal transition of fetal pulmonary circulation. The incidence of the condition ranges from 0.4 to 2.0 cases per 1000 live births, with a mortality rate of 11% (Shivanna, 2019).

Nitric oxide is a free radical gas formed from the actions of nitric oxide synthase catalyzing the abduction of guanidine nitrogen from arginine, raising intracellular levels of cyclic-guanosine 3', 5'-monophosphate and yielding nitric oxide and water (Wang, 2019). The nitric oxide synthase isoenzymes are expressed in the epithelium of the airways in both normal and asthmatic subjects. Physiologically, nitric oxide causes vasodilatation and relaxation of airway smooth muscles. It inhibits platelet aggregation, induces disaggregation of aggregated platelets, and inhibits platelet adhesion to the vascular endothelium. In the face of inflammatory processes, more nitric oxide is produced and, in turn, is reduced in the face of glucocorticosteroids (Ruan, 2015).

Inhaled nitric oxide has been proposed as a treatment option for pulmonary hypertension and hypoxemic respiratory failure. The U.S. Food and Drug Administration (1999) approved inhaled nitric oxide (marketed as INOmax gas, Mallinckrodt Hospital Products IP Limited, Hampton, New Jersey) as a vasodilator to improve oxygenation and reduce the need for extracorporeal membrane oxygenation in term and near-term (> 34 weeks of gestation) neonates with hypoxic respiratory failure associated with clinical or echocardiographic evidence of pulmonary hypertension, in conjunction with ventilatory support and other appropriate agents. The U.S. Food and Drug Administration (2004) warns of rebound pulmonary hypertension syndrome following abrupt discontinuation from inhaled nitric oxide, methemoglobinemia, airway injury, and heart failure as a result of nitric oxide.

Inhaled nitric oxide can cause adverse effects, primarily those associated with dose. These effects can include worsening heart failure, hypotension, pulmonary vasospasm, and methemoglobinemia. Off-label uses are emerging (Witek, 2023).

Findings

Guidelines support inhaled nitric oxide as the preferred pulmonary vasodilator for treating severe hypoxemia primarily due to persistent pulmonary hypertension in the newborn. Inhaled nitric oxide therapy lowers the need for extracorporeal membrane oxygenation therapy in term and late preterm infants with no serious long-term adverse effects. There is less consensus on the role of inhaled nitric oxide in premature infants; infants most likely to benefit are those with severe hypoxemia primarily due to persistent pulmonary hypertension of the newborn physiology, particularly if associated with lung hypoplasia, sepsis, and oligohydramnios.

More studies are needed to more precisely define the role of inhaled nitric oxide in premature neonates (< 34 weeks of gestation) and in adults. Inhaled nitric oxide is not recommended for prevention of bronchopulmonary dysplasia but may be considered to treat established bronchopulmonary dysplasia with symptomatic pulmonary hypertension and congenital diaphragmatic hernia with severe pulmonary hypertension, and as initial therapy for pulmonary hypertension crises/acute right ventricular failure.

Guidelines

An American Academy of Pediatrics' literature review found insufficient evidence to support treating preterm infants who have respiratory failure with inhaled nitric oxide and no evidence of a salutary impact on neurodevelopmental processes for infants who received inhaled nitric oxide compared to controls. The review made the following points (Kumar, 2014):

- 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 favorable impacts as a smooth muscle relaxant on pulmonary vascular system and bronchiolar tree.
- Inhaled nitric oxide should not be used for more than four days because of toxicity, nor should it be used to treat hypoxemia related to congenital diaphragmatic hernia.
- Inhaled nitric oxide for treatment of preterm infants with respiratory distress, bronchopulmonary dysplasia, or pulmonary hypertension has not been standardized, and its impact is not known.
- The effectiveness of inhaled nitric oxide in adults with acute respiratory distress syndrome has not been demonstrated.
- The above recommendations for the use of inhaled nitric oxide are based on controlled clinical trials, except as mentioned in the first bullet.

The Pediatric Pulmonary Hypertension Network recognizes that inhaled nitric oxide has been studied inadequately in the premature infant (< 34 weeks of gestation). Limited case series and safety data suggest inhaled nitric oxide may have benefit for preterm infants with severe hypoxemia primarily due to persistent pulmonary hypertension of the newborn physiology rather than parenchymal lung disease, particularly if associated with lung hypoplasia, sepsis, and oligohydramnios. The Network recommends against inhaled nitric oxide to prevent bronchopulmonary dysplasia in this population (Kinsella, 2016).

According to an American Heart Association and American Thoracic Society joint guideline (Abman, 2015), the highest quality evidence supports inhaled nitric oxide to reduce the need for extracorporeal membrane oxygenation support in term and late preterm infants with persistent pulmonary hypertension of the newborn or hypoxemic respiratory failure who have an oxygenation index that exceeds 25 (Class I; Level of Evidence A) and as initial therapy for pulmonary hypertension crises/acute right ventricular failure (Class I; Level of Evidence B).

Lower quality evidence suggests a potential role in preterm infants with severe hypoxemia due primarily to persistent pulmonary hypertension of the newborn physiology rather than parenchymal lung disease, particularly if associated with prolonged rupture of membranes and oligohydramnios (Class IIa; Level of Evidence B) and in infants with established bronchopulmonary dysplasia and symptomatic pulmonary hypertension (Class IIa; Level of Evidence C). Inhaled nitric oxide may improve oxygenation in infants with congenital diaphragmatic hernia and severe pulmonary hypertension but should be used cautiously in infants with suspected left ventricular dysfunction (Class IIa; Level of Evidence B) (Abman, 2015).

Evidence review

The evidence from systematic reviews and meta-analyses indicates that inhaled nitric oxide treatment is generally safe; potential adverse effects, including methemoglobinemia, rebound pulmonary hypertension upon withdrawal, and nitrogen dioxide toxicity, are clinically manageable. As a selective pulmonary vasodilator, inhaled nitric oxide is effective for treating term and late preterm infants with persistent pulmonary hypertension of the newborn and hypoxemic respiratory failure, but the results in premature infants (≤ 34 weeks of gestation) are less certain and conflicting. Inhaled nitric oxide in this population represents an off-label use. There is insufficient evidence supporting the safety and efficacy of inhaled nitric oxide for other indications.

For term or near-term, mechanically-ventilated newborns with hypoxemic respiratory failure and no diaphragmatic hernia, inhaled nitric oxide is effective at an initial concentration of 20 parts per million in reducing the use of extracorporeal membrane oxygenation for those with an oxygenation index of 25 or greater or a partial

pressure of arterial oxygen less than 100 mmHg on 100% oxygen. Inhaled nitric oxide can improve ventilation/perfusion mismatching and may improve oxygenation in infants with or without documented pulmonary hypertension (Barrington, 2017a).

Similarly, in Wang's 2019 meta-analysis (nine randomized controlled trials, n = 856), inhaled nitric oxide also resulted in the significantly lower composite endpoint of death or use of extracorporeal membrane oxygenation, and in significantly lower use of extracorporeal membrane oxygenation before hospital discharge compared to the control group. The change in partial pressure of oxygen in arterial blood was significantly higher among infants without a diaphragmatic hernia after treatment (mean difference = 50.40, 95% confidence interval 32.14 to 68.66, $P < .00001$).

In preterm populations, the evidence supporting inhaled nitric oxide is less certain, in light of a potential increased risk of severe intracranial hemorrhage. Although oxygenation may be improved in the short term, the treatment has an uncertain effect on mortality or incidence of bronchopulmonary dysplasia when used as rescue therapy on the basis of oxygenation criteria during the first three days of life. In preterm infants with evidence of pulmonary disease, early routine use along with ventilatory support does not reduce the incidence of death or bronchopulmonary dysplasia. In late preterm infants (after three days of age) at an elevated risk of bronchopulmonary dysplasia, inhaled nitric oxide does not prevent serious brain injury or improve survival without bronchopulmonary dysplasia (Barrington, 2017b).

Recent syntheses of preterm infants provided conflicting findings (Baczynski, 2023; Mullaly, 2023; Zheng, 2023; Zhou, 2025). Inhaled nitric oxide administered within 72 hours of birth may improve oxygenation, but its effects on mortality or on the incidence of bronchopulmonary dysplasia are less certain. Adverse effects such as increased risk of retinopathy at prematurity, intraventricular hemorrhage, necrotizing enterocolitis, and periventricular leukomalacia require further study. The quality of the evidence is very low to low, and underlying genetic variants, presence of pulmonary disease, and variable treatment protocols may contribute to the uncertainty in the findings.

The majority of preterm participants in the above syntheses were non-Hispanic White. An individual patient data meta-analysis of three randomized, placebo-controlled trials (n = 1,240) determined that Black infants at 36 weeks of gestational age (n = 202) had a significant reduction in the composite outcome of death or bronchopulmonary dysplasia with inhaled nitric oxide treatment compared with control infants (relative risk = 0.77, 95% confidence interval 0.65 to 0.91, $P = .003$). There was no respiratory benefit for infants whose maternal self-reported race was White, Hispanic, or classified as other and who were treated with inhaled nitric oxide starting at a dose of greater than 5 parts per million. No other imbalances in other factors influenced death or bronchopulmonary dysplasia outcomes. Since the trials lacked a standardized approach to treatment and enrollment criteria, the authors recommended a multicenter randomized trial to determine other environmental and social factors affecting long-term outcomes in this population (Askie, 2018).

Other indications

For adults with acute respiratory distress syndrome, including the phenotype associated with COVID-19, inhaled nitric oxide results in a transient improvement in oxygenation but not a reduction in mortality or reduction in extracorporeal membrane oxygenation use, and may increase the need for renal replacement therapy. The authors recommended against routine use in this population (Nakamura, 2026).

In 2017, we updated the references and added evidence from two Cochrane reviews (Barrington, 2017a, 2017b) for this policy update. These results do not change previous findings. Therefore, no policy changes are warranted.

In 2018, we updated the references. These findings are consistent with earlier conclusions, and no policy changes are warranted.

In 2019, we identified no newly published, relevant literature to add to the policy. The policy ID was changed from CP# 11.02.02 to CCP.1086.

In 2020, we added one meta-analysis to the policy. The findings are consistent with the current policy, and no policy changes are warranted.

In 2021, we removed one reference and added two guidelines to the policy with no policy changes warranted.

In 2022, we updated the references with no policy changes warranted.

In 2023, we updated the references with no policy changes warranted.

In 2024, we deleted several older references and added new evidence to the policy. No policy changes are warranted.

In 2025, we updated the references and reorganized the guidelines with no policy changes warranted.

In 2026, we updated the references and organized the findings section with no policy changes warranted.

References

On March 13, 2026, we searched PubMed and the databases of the Cochrane Library, the U.K. National Health Services Centre for Reviews and Dissemination, the Agency for Healthcare Research and Quality, and the Centers for Medicare & Medicaid Services. Search terms were “nitric oxide” (MeSH), “inhaled nitric oxide,” and “respiratory distress.” We included the best available evidence according to established evidence hierarchies (typically systematic reviews, meta-analyses, and full economic analyses, where available) and professional guidelines based on such evidence and clinical expertise.

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Policy updates

2/2014: initial review date and clinical policy effective date: 6/2014

9/2016: Policy ID added.

3/2017: Policy references updated.

3/2018: Policy references updated.

3/2019: Policy references updated. Policy ID changed.

3/2020: Policy references updated.

3/2021: Policy references updated.

4/2022: Policy references updated.

4/2023: Policy references updated.

4/2024: Policy references updated.

5/2025: Policy references updated.

5/2026: Policy references updated.

Related codes

Below are the most commonly submitted codes for the service(s)/item(s) subject to this policy CCP.1086. This is not an exhaustive list of codes. Providers are expected to consult the appropriate coding manuals and bill accordingly.

Code	Code description
J3490	Unclassified drugs
ICD-10-PCS Procedure Code 3E0F7SD	Introduction of Nitric Oxide Gas into Respiratory Tract, Via Natural or Artificial Opening
94799	Unlisted pulmonary service or procedures