

# Inhaled nitric oxide

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

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## Coverage policy

Inhaled nitric oxide is clinically proven and, therefore, may be medically necessary for the management of preterm 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  $\geq 35$  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; Witek, 2023).

### 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 serving 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

Guidelines support inhaled nitric oxide as the preferred pulmonary vasodilator for treating preterm infants with 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 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.

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 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 indicates that inhaled nitric oxide treatment is generally safe; potential side effects, including methemoglobinemia, inhibition of platelet aggregation, and systemic, are clinically manageable. Inhaled nitric oxide is effective for treating persistent pulmonary hypertension in term and late preterm infants, but the results in premature infants are less certain and conflicting. There is insufficient evidence supporting the safety and efficacy of inhaled nitric oxide for other indications.

In 2017, we found three Cochrane reviews (Barrington, 2017a, 2017b [update of 2010]; Gebistorf, 2016) for this policy update. The new evidence found that inhaled nitric oxide is effective at an initial concentration of 20 ppm for term and near-term infants with hypoxic respiratory failure who do not have a diaphragmatic hernia, but it is not an effective treatment for preterm infants (Barrington, 2017a, 2017b). For adults with acute respiratory distress syndrome, inhaled nitric oxide results in a transient improvement in oxygenation but not a reduction in mortality, and may increase renal impairment (Gebistorf, 2016). These results do not change previous findings. Therefore, no policy changes are warranted.

In 2018, we identified one meta-analysis (Askie, 2018) and one multisite randomized controlled trial (Hasan, 2017) that addressed the effects of inhaled nitric oxide on survival in high-risk preterm infants without bronchopulmonary dysplasia. Both studies lacked a standardized approach to treatment and enrollment criteria and produced conflicting results. 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 (Wang, 2019) of nine randomized controlled trials 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 added a Cochrane review that described inhaled nitric oxide as the only treatment proven to improve clinical outcomes for persistent pulmonary hypertension in newborns (Shivanna, 2019). Another Cochrane review reported a 30% rate of neonatal pulmonary hypertension cases that are refractory to inhaled nitric oxide (Kelly, 2017).

In 2023, we added a systematic review of six studies (n = 284) concluding oxygenation in preterm infants with hypoxemic respiratory failure (77% of which also had pulmonary hypertension) was improved by inhaled nitric oxide, based on a 36% death rate after treatment. Quality of evidence was rated low to very low (Mullaly, 2023).

In 2024, we deleted several older references and added a systematic review/meta-analysis of five studies (n = 400) showing preterm infants < 34 weeks gestational age without congenital anomalies or genetic disorders with hypoxemic respiratory failure and pulmonary hypertension treated with inhaled nitric oxide within 72 hours of birth had significantly reduced odds of mortality (Baczynski, 2023). Another meta-analysis of 11 studies (n = 3,651) of premature infants found inhaled nitric oxide significantly reduced the incidence of bronchopulmonary dysplasia, especially at 10 (versus five) parts per million. However, there were no differences between groups in in-hospital mortality and adverse events (Zheng, 2023). No policy changes are warranted.

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

## References

On April 8, 2025, 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.