Inhaled nitric oxide

Clinical Policy ID: CCP.1086

Recent review date: 4/2024

Next review date: 8/2025

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 at- or near-term infants at risk for pulmonary hypertension when all of the following criteria are met (Abman, 2015; Hansmann, 2016; Kinsella, 2016; U.S. Food and Drug Administration, 1999; Witek, 2023):

- 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; Witek, 2023).

Limitations

All other uses of inhaled nitric oxide are not medically necessary (Gebistorf, 2016).

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 synthease 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 syntheses 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. Studies indicate that inhaled nitric oxide treatment is generally safe; potential side effects, including methemoglobinemia, inhibition of platelet aggregation and systemic vasodilatation, are often clinically insignificant (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. Off-label use is widespread (Keszler, 2012).

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

Findings

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 (Kumar, 2014).

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 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.

A National Institute for Health and Care Excellence guideline recommended against routine use of inhaled nitric oxide for preterm infants requiring treatment for respiratory distress syndrome, in the absence of indications such as pulmonary hypoplasia or pulmonary hypertension. The guideline found no evidence of improved outcomes for preterm babies needing respiratory support for respiratory distress syndrome (National Institute for Health and Care Excellence, 2019).

In 2017, we found three Cochrane reviews (Barrington, 2017a, 2017b [update of 2010]; Gebistorf, 2016) and one consensus statement (Hansmann, 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).

The European Paediatric Pulmonary Vascular Disease Network strongly supports inhaled nitric oxide for treating acute pulmonary vascular crisis and/or acute exacerbation of pediatric pulmonary hypertension, but only weakly supports inhaled nitric oxide for treating post-operative pediatric pulmonary hypertension in the intensive care unit (Hansmann, 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 (Abman, 2015; Kinsella, 2016) 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). We added another Cochrane review that 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) of preterm infants with hypoxemic respiratory failure and pulmonary function treated with inhaled nitric oxide within 72 hours of birth had significantly reduced odds of mortality (Baczynski, 2023).

We also added a 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.

References

On January 5, 2024, 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.