MASSACHUSETTS

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Medical Policy
Inhaled Nitric Oxide

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Policy Number: 100

BCBSA Reference Number: 8.01.37 (For Plans internal use only)
NCD/LCD: N/A

Related Policies

None

Policy

Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity Medicare HMO Blue[SM] and Medicare PPO Blue[SM] Members

Inhaled nitric oxide may be **MEDICALLY NECESSARY** as a component of treatment of:

- Hypoxic respiratory failure in neonates born at 34 or more weeks of gestation.

Other indications for inhaled nitric oxide are **INVESTIGATIONAL** including, but not limited to:

- Treatment of premature neonates born at less than or equal to 34 weeks of gestation with hypoxic respiratory failure
- Treatment of adults and children with acute hypoxemic respiratory failure
- Postoperative use in adults and children with congenital heart disease
- In lung transplantation, during and/or after graft reperfusion.

Prior Authorization Information

Inpatient

- For services described in this policy, precertification/preauthorization **IS REQUIRED** for all products if the procedure is performed **inpatient**.

Outpatient

- For services described in this policy, see below for products where prior authorization **might be required** if the procedure is performed **outpatient**.

	Outpatient
Commercial Managed Care (HMO and POS)	Prior authorization is **not required**.
Commercial PPO and Indemnity	Prior authorization is **not required**.
Medicare HMO Blue[SM]	Prior authorization is **not required**.

Medicare PPO Blue℠	Prior authorization is **not required**.

CPT Codes / HCPCS Codes / ICD Codes

Inclusion or exclusion of a code does not constitute or imply member coverage or provider reimbursement. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage as it applies to an individual member.

Providers should report all services using the most up-to-date industry-standard procedure, revenue, and diagnosis codes, including modifiers where applicable.

CPT Codes

There is no specific CPT code for this service.

Description

Hypoxic Respiratory Failure

Hypoxic respiratory failure may result from respiratory distress syndrome, persistent pulmonary hypertension, meconium aspiration, pneumonia, or sepsis.

Treatment

Treatment typically includes oxygen support, mechanical ventilation, induction of alkalosis, neuromuscular blockade, or sedation.

Extracorporeal membrane oxygenation is an invasive technique that may be considered in neonates when other therapies fail. Inhaled nitric oxide (INO) is both a vasodilator and a mediator in many physiologic and pathologic processes. Inhaled nitric oxide has also been proposed for use in preterm infants less than 34 weeks of gestation and in adults.

Also, there are several potential uses in surgery. One is the proposed use of INO to manage pulmonary hypertension after cardiac surgery in infants and children with congenital heart disease. In congenital heart disease patients, increased pulmonary blood flow can cause pulmonary hypertension. Cardiac surgery can restore the pulmonary vasculature to normal, but there is the potential for complications, including postoperative pulmonary hypertension, which can prevent weaning from ventilation and is associated with substantial morbidity and mortality. Another potential surgical application is the use of INO in lung transplantation to prevent or reduce reperfusion injury.

Summary

Inhaled nitric oxide (INO) is a natural vasodilator and has been studied for a variety of types of respiratory failure. Most commonly, it is used as an initial treatment for neonates with hypoxic respiratory failure to improve oxygenation and reduce the need for invasive extracorporeal membrane oxygenation (ECMO). It is also proposed as a treatment for premature infants, critically ill children, and adults with respiratory failure, as well as in the postoperative management of children undergoing repair of congenital heart disease and patients after lung transplantation to prevent or reduce reperfusion injury.

For individuals who are neonates, are term or late preterm at birth, and have hypoxic respiratory failure who receive INO, the evidence includes randomized controlled trials (RCTs) and a systematic review. Relevant outcomes are overall survival (OS), hospitalizations, resource utilization, and treatment-related morbidity. Evidence from RCTs and a meta-analysis have supported the use of INO in term or late preterm infants. Pooled analyses of RCT data have found that use of INO significantly reduced the need for ECMO and the combined outcome of ECMO or death. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who are neonates, are premature at birth, and have hypoxic respiratory failure who receive INO, the evidence includes RCTs and systematic reviews. Relevant outcomes are OS, hospitalizations, resource utilization, and treatment-related morbidity. A large number of RCTs have evaluated INO for premature neonates, and most trials have reported no significant difference for

primary endpoints such as mortality and bronchopulmonary dysplasia (BPD). Meta-analyses of these RCTs have not found better survival rates in patients who received INO compared with a control intervention. Most meta-analyses also did not report improvements in other outcomes with INO (eg, BPD, intracranial hemorrhage). The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who are adults or children in acute hypoxemic respiratory failure who receive INO, the evidence includes RCTs and systematic reviews. Relevant outcomes are OS, hospitalizations, resource utilization, and treatment-related morbidity. A large number of RCTs have evaluated INO for treatment of acute hypoxemic respiratory failure. Meta-analyses of these RCTs have not found that INO significantly reduced mortality or shortened the duration of mechanical ventilation. Some evidence from a meta-analysis of 4 RCTs, a cohort study, and a separate meta-analysis has suggested that INO may be associated with an increased risk of renal impairment in patients with acute respiratory distress syndrome (ARDS). The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who are adults or children with congenital heart disease who have had heart surgery who receive INO, the evidence includes RCTs and a systematic review. Relevant outcomes are OS, hospitalizations, resource utilization, and treatment-related morbidity. Evidence from a number of small RCTs and a systematic review of these trials did not find a significant benefit for INO on mortality and other health outcomes in the postoperative management of children with congenital heart disease. There is less evidence on INO for adults with congenital heart disease. One RCT found that treatment with INO did not improve the postoperative outcomes of adults with congestive heart failure. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have a lung transplant who receive INO, the evidence includes RCTs and a systematic review. Relevant outcomes are OS, hospitalizations, resource utilization, and treatment-related morbidity. Several small RCTs have evaluated INO after lung transplantation; none found statistically significant improvements in health outcomes with INO. A systematic review of RCTs and observational studies concluded that available evidence did not support the routine use of INO after lung transplant. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Clinical input was sought to help determine whether the use of INO for individuals with various conditions would provide a clinically meaningful improvement in net health outcome and whether the use is consistent with generally accepted medical practice. In response to requests, clinical input on the use of INO was received from 4 respondents, including: 3 physician-level responses with academic affiliations identified through 1 specialty society and 1 physician-level response identified through BCBSA.

For individuals who are neonates, premature at birth, and have hypoxic respiratory failure, a limited quantity of clinical input indicated high confidence that the use of INO provides a clinically meaningful improvement in the net health outcome and is consistent with generally accepted medical practice. Cited evidence notes that the majority of RCTs, and meta-analyses of these RCTs, have reported no significant difference with INO therapy for primary endpoints such as survival and BPD. Guidelines from the American Heart Association/American Thoracic Society and an expert workshop consensus statement state that INO can be beneficial for a subset of preterm infants with severe hypoxemia that is primarily due to persistent pulmonary hypertension of the newborn physiology rather than parenchymal disease; however, this recommendation is based on case series. Limited quantity of clinical input and insufficient published evidence showing improved health outcomes provide insufficient support regarding the effect on net health outcome.

For individuals who are adults or children in acute hypoxemic respiratory failure, clinical input responses were mixed as to whether use of INO provides a clinically meaningful improvement in net health outcome. Clinical input indicates this use of INO is consistent with generally accepted medical practice, and some respondents suggested that INO is often used as a rescue therapy and bridge to ECMO. Cited evidence

notes improved physiologic outcomes such as transient improvement of oxygenation in the first 24 hours; however, the evidence does not demonstrate significant improvements in health outcomes such as overall mortality.

For individuals who are adults or children with congenital heart disease who have had heart surgery, clinical input responses indicate moderate confidence that the use of INO provides a clinically meaningful improvement in net health outcome and moderate to high confidence that this use is consistent with generally accepted medical practice. This appears to be based on cited evidence suggesting that INO can improve perioperative pulmonary hypertension; however, it is unclear that health outcomes are improved as no significant mortality benefit was observed in these patients. Further, some evidence suggests that use of INO may be associated with an increase in mortality for those without pulmonary hypertension.

For individuals with lung transplant, a limited quantity of clinical input respondents provided moderate to high confidence that use of INO during the perioperative period to manage pulmonary vascular resistance and pulmonary hypertension provides a clinically meaningful improvement in net health outcome and is consistent with generally accepted medical practice. Cited evidence includes small RCTs that found no statistically significant improvement in health outcomes with INO and cases series or non-randomized trials of a limited number of patients with inconsistent endpoints, suggesting that INO may decrease the incidence of graft rejection and dysfunction and potentially prevent reperfusion injury. Limited quantity of clinical input and insufficient published evidence showing improved health outcomes provide insufficient support regarding the effect on net health outcome.

Policy History

Date	Action
6/2022	Annual policy review. Description, summary, and references updated. Policy statements unchanged.
7/2021	Annual policy review. Description, summary, and references updated. Policy statements unchanged.
7/2020	Annual policy review. Description, summary, and references updated. Policy statements unchanged.
6/2019	Annual policy review. Description, summary, and references updated. Policy statements unchanged.
6/2018	Annual policy review. Description, summary, and references updated. Policy statements unchanged.
6/2017	Annual policy review. New references added.
10/2016	Annual policy review. Investigational statement reformatted for clarity. Added investigational bullet points: Postoperative use in adults and children with congenital heart disease and in lung transplantation during and/or after graft reperfusion. Effective 10/1/2016.
12/2014	Annual policy review. New references added
1/2014	Annual policy review. New references added
4/2013	Annual policy review. Changes to policy statement. Effective 4/2013.
11/2011-4/2012	Medical policy ICD 10 remediation: Formatting, editing and coding updates. No changes to policy statements.
5/2011	Reviewed - Medical Policy Group - Pediatrics and Endocrinology. No changes to policy statements.
4/2011	Reviewed - Medical Policy Group - Cardiology and Pulmonology. No changes to policy statements.
5/2010	Reviewed - Medical Policy Group - Pediatrics and Endocrinology. No changes to policy statements.
3/2010	Reviewed - Medical Policy Group - Allergy and ENT/Otolaryngology. No changes to policy statements.

6/2009	Medical policy #100, effective 6/2009, describing covered and non-covered indications.

Information Pertaining to All Blue Cross Blue Shield Medical Policies

Click on any of the following terms to access the relevant information:

Medical Policy Terms of Use
Managed Care Guidelines
Indemnity/PPO Guidelines
Clinical Exception Process
Medical Technology Assessment Guidelines

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