Inhaled Nitric Oxide Therapy

Policy Number: CS173.K
Effective Date: November 1, 2025

Instructions for Use

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Application

This Medical Policy does not apply to the states listed below; refer to the state-specific policy/guideline, if noted:

State	Policy
Idaho	Inhaled Nitric Oxide Therapy (for Idaho Only)
Indiana	None
Kansas	Inhaled Nitric Oxide Therapy (for Kansas Only)
Kentucky	Inhaled Nitric Oxide Therapy (for Kentucky Only)
Nebraska	None
New Jersey	None
New Mexico	Inhaled Nitric Oxide Therapy (for New Mexico Only)
North Carolina	Inhaled Nitric Oxide Therapy (for North Carolina Only)
Ohio	Inhaled Nitric Oxide Therapy (for Ohio Only)
Pennsylvania	Inhaled Nitric Oxide Therapy (for Pennsylvania Only)
Tennessee	None

Coverage Rationale

Inhaled nitric oxide (iNO) is proven and medically necessary for treating term or near-term infants (at least 34 weeks gestation at birth) with hypoxic respiratory failure or echocardiographic evidence of persistent pulmonary hypertension of the newborn (PPHN) and all of the following:
- Absence of congenital diaphragmatic hernia (CDH)
- Failure of conventional treatments (e.g., mechanical ventilation)

Note: In the postoperative management of pulmonary hypertension associated with heart or lung surgery in infants, iNO is a clinically accepted option and will be covered as bridge therapy during the acute recovery phase.

Due to insufficient evidence of efficacy, iNO is unproven and not medically necessary for treating all other newborns including but not limited to:
- Newborns with CDH

- Preterm newborns who are less than 34 weeks gestation at birth

Inhaled nitric oxide (iNO) treatment for individuals outside of the Infancy age group is experimental or investigational due to lack of Food and Drug Administration (FDA) approved indications.

Definitions

Infancy: The period from birth through the first year of life (Barfield, 2016).

Applicable Codes

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this policy does not imply that the service described by the code is a covered or non-covered health service. Benefit coverage for health services is determined by federal, state, or contractual requirements and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Guidelines may apply.

CPT Code	Description
94799	Unlisted pulmonary service or procedure

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Description of Services

Inhaled nitric oxide (iNO) therapy involves the administration of gaseous nitric oxide which dilates pulmonary vessels in ventilated areas and decreases pulmonary vascular resistance. Because nitric oxide affects vascular muscle tone regulation in the pulmonary system, it has become a treatment for hypoxemic respiratory failure which is associated with high pulmonary vascular pressure. iNO is used as one of the treatments for newborns with hypoxic respiratory failure to improve oxygenation and reduce the need for extracorporeal membrane oxygenation (ECMO). iNO may be a treatment option for the postoperative management of pulmonary hypertension associated with heart or lung surgery in infants. While iNO is generally considered safe, it results in increased levels of methemoglobin and has been associated with a more than eight-fold risk of childhood cancer (Dixon et al., 2018). These possible harms should be weighed against the benefits demonstrated in selected populations of infants.

Hypoxic respiratory failure can occur in infants of all gestational ages. In the preterm infant, respiratory failure typically presents secondary to an insufficiency of surfactant, a soap-like material that lines the air-spaces of the lungs. Respiratory failure in the term and near-term newborn can result from conditions such as sepsis, meconium aspiration at birth, pulmonary hypoplasia, or congenital diaphragmatic hernia (CDH). These conditions can cause elevated pressure in the pulmonary vessels. The classic characteristics of persistent pulmonary hypertension of the newborn (PPHN) include increased pulmonary vascular resistance, right-to-left shunting, and severe hypoxemia (McLaughlin et al., 2009).

Treatment of the preterm infant (born at less than 34 weeks gestation) with respiratory failure usually involves administration of exogenous surfactant and mechanical ventilation. In the term and near-term (≥ 34 weeks gestation) newborn, management of acute respiratory failure could also include administration of oxygen, continuous positive airway pressure, conventional or high-frequency ventilation, pharmacological intervention, or ECMO using a heart/lung machine.

Clinical Evidence

Hypoxic Respiratory Failure or Persistent Pulmonary Hypertension of the Newborn (PPHN) in Term or Near-Term Infants

Wang et al. (2019) conducted a systematic review and meta-analysis to determine whether the inhalation of nitric oxide (NO) could improve oxygenation and reduce rate of death or use of ECMO among infants born at 34 weeks gestation or more. Nine randomized controlled trials (RCTs) with a total of 856 participants were included in this meta-analysis. The analyses revealed that the iNO group was less likely to develop the combined outcome of death or use of ECMO than the control group. This difference was clinically (relative decrease in risk of 34%) and statistically significant. According to the authors, the use of NO inhalation is recommended for respiratory failure among infants born at or near term.

In a Cochrane systematic review and meta-analysis, Barrington et al. (2017a) assessed whether iNO treatment of hypoxemic term and near-term newborn infants improves oxygenation and reduces rate of death or use of ECMO or affects long-term neurodevelopmental outcomes. A total of 17 randomized controlled studies were identified for inclusion in the review. Some of the studies were limited to subjects with PPHN, but some were not. Most of the reported results were obtained from 10 studies of moderate to high quality, which compared iNO versus standard therapy without iNO. Six smaller trials enrolled infants with moderate severity of illness scores and randomized them to immediate iNO treatment or iNO treatment only after deterioration to more severe criteria. As infants with CDH may respond differently from other near-term infants, results for these infants were evaluated separately. The authors found that hypoxemic term and near-term infants treated with iNO appears to have improved outcomes by reducing the incidence of the combined endpoint of death or use of ECMO (high-quality evidence). Infants who received iNO at less severe criteria did not have better clinical outcomes than those who were enrolled but received treatment only if their condition deteriorated. The data did not suggest that iNO given earlier was more beneficial. Incidence of disability, incidence of deafness and infant development scores were all similar between participants who received iNO and those who did not. The authors concluded that iNO 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.

Wu et al. (2016) conducted an RCT (not included in the Wang or the Barrington meta-analysis) to investigate the effect of iNO for treating PPHN. Eighty-six infants with neonatal pulmonary hypertension were included in this study. Twelve percent of these infants were premature, but it is unclear whether they were born before or after 34 weeks of gestation. The infants were randomly divided into an iNO group (n = 43) or a control group (n = 43). Infants in the control group were treated with high-frequency oscillatory ventilation, while those in the observation group were treated with high-frequency oscillatory ventilation combined with iNO therapy. Pulmonary artery pressure decreased at each time point, and the levels in the iNO group were lower than those of the control group. The differences were statistically significant. The duration of mechanical ventilation, duration of oxygen therapy, and mortality in the iNO group were significantly lower than those of the control group. The investigators concluded that the use of iNO to treat PPHN can significantly improve oxygen supply, reduce pulmonary artery pressure, shorten treatment time, and reduce mortality.

Clinical Practice Guidelines

American Academy of Pediatrics (AAP)

The AAP published a policy statement in 2000 (reaffirmed in 2010) on the use of iNO in infants with respiratory distress. The AAP supports the use of iNO for the indications, dosing, administration, and monitoring outlined on the product information label and approved by the FDA.

American Heart Association (AHA) and American Thoracic Society (ATS)

The AHA and ATS's guideline on pediatric pulmonary hypertension recommends the use of iNO to reduce the need for ECMO in term and near-term infants with PPHN or hypoxemic respiratory failure who have an oxygenation index that exceeds 25 [Class I; Level of Evidence A (the procedure/treatment was deemed useful/effective with sufficient evidence from multiple randomized trials or meta-analyses)] (Abman et al., 2015).

Preterm Newborns

While some inconsistency in findings exist, the body of evidence, including systematic review and metanalyses of RCTs, fails to demonstrate clear clinically or statistically significant benefit of iNO among premature newborns born at less than 34 weeks for the treatment of respiratory distress syndrome (RDS) or the prevention or treatment of bronchopulmonary dysplasia (BPD). Furthermore, the evidence (Barrington et al., 2017b) suggests possible harm for that population [grade 3 or 4 intraventricular hemorrhage (IVH)] and the findings from Zheng et al. (2023) suggest an increased risk of necrotizing enterocolitis. The balance of iNO benefits and harms therefore remains unclear for premature infants.

Mirza et al. (2025) conducted a single-center RCT to assess whether iNO treatment for early pulmonary hypertension (PH) could reduce the risk of death or bronchopulmonary dysplasia (BPD) in preterm infants < 29 weeks gestation requiring positive pressure ventilation. Exclusion criteria included infants born to COVID-19 positive mothers, those with large patent ductus arteriosus, left ventricle dysfunction (ejection fraction < 40%), significant congenital anomalies/genetic disorders, or iNO treatment prior to the index echocardiogram. Infants with early PH were randomized into iNO or placebo groups based on an echocardiogram performed at 72 ±24 hours of life. Serial echocardiograms were conducted every 24-48 hours for up to 14 days. iNO was weaned until PH resolved or if no improvement was observed for ≥ 72 hours. The primary outcome was death or BPD at 36 weeks postmenstrual age. From July 2019 to October 2023, 683 eligible infants were admitted. Of these, 88 were excluded, and 413 mothers either declined participation or were not approached. iNO treatment was initiated for 51 infants due to hypoxic respiratory failure. A screening echocardiogram was performed on 180 infants, and 32 with early PH were randomized to iNO or placebo groups. In a preplanned intermediate analysis, the primary outcome was similar between the active and the control group (68% vs 62%, p = .99). Therefore, the Data Safety Monitoring Board recommended termination of the study. The limitations of the study included the following: the trial was terminated after an interim analysis due to futility, the sample size was relatively small, limiting the generalizability of the results, the challenges of accurately diagnosing pulmonary hypertension, and the study did not account for long-term outcomes beyond the neonatal period. In conclusion, iNO treatment did not reduce the risk of BPD or mortality in extremely preterm infants with early signs of pulmonary hypertension.

Feng et al. (2024) conducted a systematic review and meta-analysis to evaluate the safety and efficacy of iNO in neonates ≤ 34 weeks. The study included RCTs through June 2023 on preterm infants ≤ 34 weeks, receiving iNO treatment, and primarily reviewed outcomes such as bronchopulmonary dysplasia (BPD) and mortality. Results included a total of 17 studies involving 4,080 neonates and 7 follow-up studies. The results showed that in neonates, iNO treatment reduced the incidence of BPD (RR: 0.92; 95% CI: 0.86-0.98). It also decreased the composite outcome of death or BPD (RR: 0.94; 95% CI: 0.90-0.98), without increasing the risk of short-term (such as intraventricular hemorrhage, periventricular leukomalacia) and long-term neurological outcomes (including Bayley mental developmental index < 70, cerebral palsy and neurodevelopmental impairment). Also, iNO did not significantly affect other neonatal complications such as sepsis, pulmonary hemorrhage, necrotizing enterocolitis, and symptomatic patent ductus arteriosus. Subgroup analysis revealed that iNO significantly reduced BPD incidence in neonates at 36 weeks under specific intervention conditions, including age less than 3 days, birth weight over 1,000 g, iNO dose of 10 ppm or higher, or treatment duration exceeding 7 days ($p < 0.05$). The authors indicate the limitations include the following: differences in gestational age and birth weight; lung tissue at different developmental stages responds differently to NO, which may affect the incidence of BPD, pulmonary hemorrhage, or other complications; other baseline data, such as intervention dose and exposure time, as well as the sex of the infants included, were not identical among the included trials, which may also alter results. Due to the limited number of studies, it is difficult to evaluate the interference factors accurately. Larger multicenter clinical studies are needed to explore the efficacy and safety of iNO. iNO reduced the incidence of BPD in selected neonates at 36 weeks of gestation, and this depended on neonatal age, birth weight, duration and dose of iNO. The authors note that iNO is considered a promising treatment for the potential prevention of BPD in premature infants. Additional data is needed to support iNO use in this specific population, to minimize its off-label use. (Hasan 2017 included in this study.)

Zheng et al. (2023) conducted a systematic review and meta-analysis to evaluate the safety and efficacy of iNO in the prevention of BPD in premature infants. There were 11 RCTs that met the screening criteria for this study. The analysis showed that the iNO group had a significantly lower incidence of BPD than the control group [relative risk (RR) = 0.91, 95% confidence interval (CI) 0.85-0.97, $p = 0.006$]. Three was no significant difference in the incidence of BPD between the two groups at the initial dose of 5 ppm (ppm) ($p = 0.09$) but those treated with 10 ppm iNO had a significantly lower incidence of BPD (RR = 0.90, 95%CI 0.81-0.99, $p = 0.03$). However, it should be noted that although the iNO group had an increased risk for necrotizing enterocolitis (NEC) (RR = 1.33, 95%CI 1.04-1.71, $p = 0.03$), cases treated with an initial dose of 10 ppm revealed no significant difference in the incidence of NEC compared with the control group ($p = 0.41$), while those treated with an initial dosage of 5 ppm of iNO had a significantly greater NEC rates than the control group (RR = 1.41, 95%CI 1.03-1.91, $p = 0.03$). There were no statistically significant differences in the incidence of in-hospital mortality, intraventricular hemorrhage (IVH) (Grade 3/4) or periventricular leukomalacia (PVL) and pulmonary hemorrhage (PH) between the two treatment groups. Several study limitations: clinical criteria must be updated to evaluate the severity and long-term prognosis of BPD; reliability of the study may be affected by the small sample size and number of research samples; There was no subgroup analysis on birth weight, the start time of inhalation, and iNO inhalation dose range of preterm infants. The author's indicated that iNO at an initial dosage of 10 ppm seemed more effective in reducing the risk of BPD than conventional treatment and iNO at an initial dosage of 5 ppm in preterm infants at a gestational age of ≤ 34 weeks who required respiratory support. Yet, the incidence of in-hospital mortality and adverse events between the overall iNO and control group were similar. Additional studies are needed based on the findings and limitations. (Hasan 2017 included in this study.)

Greenough et al. (2020) conducted a long-term follow-up of a RCT to evaluate the long-term effects of iNO usage at 7 years of age for prevention of BPD in premature infants. A 7-year follow-up was undertaken of infants who had been entered into the European Union Nitric Oxide (EUNO) trial, a multicenter, double-blind, randomized, placebo-controlled trial of iNO for prevention of BPD in premature infants born between 24 and 28 weeks plus six days of gestation. At 7 years, survival, and hospital admissions since the 2-year follow-up, home oxygen therapy in the past year, therapies used in the previous month and growth assessments were determined. Questionnaires were used to compare general health, well-being, and quality of life. A total of 305 children were assessed. No deaths were reported. This study suggests that iNO had no significant effect on mortality, growth, hospitalization, outpatient therapy, medication use, HRQOL and overall health outcomes at 7 years of follow-up in premature infants. This study had strengths and some limitations. This was the first study to assess the outcomes of very prematurely born infants at 7 years of age who had been entered into a neonatal randomized trial of iNO. A major limitation was that 11 of the original 35 study centers did not participate in the 7-year follow-up. Nevertheless, the iNO and placebo groups were well balanced, with characteristics like those of the original randomized population which reflects the overall population. Another study limitation was that a proportion of the population was not intubated, and hence they may not have received enough iNO. The authors conclude that iNO for prevention of BPD in very premature infants with respiratory distress did not result in long-term benefits or adverse long-term consequences and that routine use of iNO cannot be recommended for prevention of BPD in preterm infants.

A Hayes report evaluated the use of iNO therapy to reduce mortality and prevent early lung injury in preterm newborns (less than 35 weeks gestation at birth). This systematic review was designed to identify good quality systematic reviews and health technology assessments, as well as subsequently published primary data to update the findings of earlier reviews. The review found that a consistent body of high-quality evidence indicates that early rescue iNO does not increase survival, decrease pulmonary morbidity, or improve neurodevelopmental outcomes in preterm infants who require respiratory support. Hayes found moderate quality evidence indicating that iNO use does not decrease the risk of BPD. The Hayes review also found moderate quality evidence indicating that routine prophylactic iNO use does not improve outcomes in preterm infants with respiratory failure (Hayes, 2018, Annual review 2023).

Askie et al. (2018) conducted a meta-analysis of selected studies to assess whether iNO improves survival without BPD for preterm African American infants. The review included 3 randomized, placebo-controlled trials that enrolled infants born at less than 34 weeks of gestation receiving respiratory support, had at least 15% of African American participants, and used a starting iNO of greater than 5 parts per million with the intention to treat for 7 days minimum. In contrast with participants of other races, African American infants had a significant reduction in the composite outcome of death or BPD with iNO treatment: 49% treated vs 63% controls. There was also a significant difference between races of iNO treatment for BPD in survivors, with the greatest effect in African American infants. There were no differences between racial groups for death, the use of postnatal steroids, pulmonary air leak, pulmonary hemorrhage, or other measures of respiratory support. The investigators concluded that iNO therapy should be considered for preterm African American infants at high risk for BPD. As subgroup analyses by race was not pre-specified in all included studies, these findings should be considered post hoc and hypothesis-generating rather than conclusive evidence of benefit in African American infants.

In a Cochrane systematic review, Barrington et al. (2017b) analyzed the effects of iNO treatment on survival and brain or lung injury in preterm newborn infants with hypoxic respiratory failure. A total of 17 randomized controlled studies were identified for inclusion in the review. These trials studied preterm infants with very different baseline characteristics; therefore, it was decided to divide them into three groups: (1) infants treated over the first three days of life because of defects in oxygenation, (2) preterm infants with evidence of pulmonary disease treated routinely with iNO and (3) infants treated later (after three days of age) because of elevated risk of BPD. Eight studies addressed iNO use for early rescue with no significant effect on mortality or BPD demonstrated. The routine use of iNO for infants with pulmonary disease was addressed in four studies and no significant decrease in death or BPD was reported. The authors did not find any clinically or statistically significant benefit of iNO in this population. Furthermore, while no clear effect was found on the incidence of neurodevelopmental impairment or on the frequency of the IVH of any grade, the meta-analysis suggested a possible increased risk of grade 3 or 4 IVH with iNO. The investigators concluded that iNO does not appear to be effective as rescue therapy for the very ill preterm infant and indicated that early routine use of iNO in preterm infants with respiratory disease does not prevent serious brain injury or improve survival without BPD.

Hasan et al. (2017) conducted a randomized clinical trial to evaluate whether the administration of iNO to preterm infants requiring positive pressure respiratory support improves the rate of survival without BPD. An intent-to-treat RCT analysis was performed for participants at 33 US and Canadian neonatal intensive care units, including 451 neonates younger than 30 weeks' gestation receiving mechanical ventilation or positive pressure respiratory support on postnatal days 5 to 14. Placebo (nitrogen) or iNO initiated at 20 ppm was decreased to 10 ppm between 72 and 96 hours after starting treatment and then to 5 ppm on day 10 or 11. Infants remained on the 5-ppm dose until completion of therapy (24 days). The primary outcome was the rate of survival without BPD at 36 weeks' postmenstrual age (PMA). In total, 222 infants received placebo, and 229 infants received iNO. Survival without BPD at 36 weeks' PMA was similar between the placebo and iNO groups (31.5% vs 34.9%). Rates for severe BPD, postnatal corticosteroid use for BPD and the mean days of positive pressure respiratory support, oxygen therapy, and hospitalization were equivalent between the two groups. No differences in the incidence of common morbidities were observed. Respiratory outcomes on discharge to home, at 1 year, and at age 18 to 24 months' PMA and neurodevelopmental assessments at 18 to 24 months' PMA did not differ between groups. This study provides additional support to the systematic reviews above for the lack of benefit of iNO in infants younger than 30 weeks at birth.

Clinical Practice Guidelines

American Academy of Pediatrics (AAP)

In 2014, the AAP Committee on Fetus and Newborn released guidance on the use of inhaled nitric oxide (iNO) in preterm infants. The AAP indicated that neither rescue nor routine use of nitric oxide in preterm infants with respiratory failure improves survival (Grade of recommendation: strong; Evidence quality: A). The AAP also states that evidence does not support the use of iNO for preventing BPD, severe IVH, or other neonatal comorbidities in preterm infants with respiratory failure (Grade of recommendation: strong; Evidence quality: A) (Kumar, 2014).

The AAP published a policy statement in 2000 (reaffirmed in 2010) on the use of iNO in infants with respiratory distress. This policy statement indicates that there is limited data on the use of low-dose iNO for hypoxic preterm neonates. The authors state that available data suggests iNO improves oxygenation but does not improve survival in this patient population.

European Paediatric Pulmonary Vascular Disease Network (EPPVDN)

The EPPVDN has published an updated consensus statement regarding iNO for the diagnosis and treatment of pediatric pulmonary hypertension. Regarding PPHN and pulmonary hypertension associated with bronchopulmonary dysplasia (BPD)/neonatal chronic lung disease, the Network stated iNO is indicated for the treatment of PPHN in mechanically ventilated term and near-term newborn infants to improve oxygenation and to reduce the need for ECMO (a) if PaO2 is less than 100 mm Hg (while receiving 100% oxygen), or (b) if the oxygenation index exceeds 25 [COE I Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective (is recommended/is indicated); LOE A: Data derived from multiple randomized clinical trials or meta-analyses]. The Network further stated that it is not well established that iNO in preterm infants < 34 weeks of gestation with respiratory failure reduces the incidence of BPD [COR IIb: Usefulness/efficacy is less well established by evidence/opinion (may be considered); LOE C Consensus of opinion of the experts and/or small studies, retrospective studies, registries]; and that INO may be considered in preterm infants < 34 weeks of gestation with respiratory failure and confirmed PH. (COR IIb; LOE C) (Hansmann, et al., 2019)

National Institute for Health and Care Excellence (NICE)

In 2019, NICE indicated in a guideline "Specialist neonatal respiratory care for babies born preterm": "Do not routinely use inhaled nitric oxide for preterm babies who need respiratory support for respiratory distress syndrome (RDS), unless there are other indications such as pulmonary hypoplasia or pulmonary hypertension. The guideline noted that the use of INO for pulmonary hypoplasia or pulmonary hypertension in babies less than 34 weeks gestation is "off-label".

National Institutes of Health (NIH)

In 2011, the NIH released a Consensus Development Conference Statement on the use of iNO therapy for premature infants. The statement was developed by a conference panel consisting of 16 members from pertinent fields and was based on published scientific literature and evidence presented in an open forum. The statement indicates that early routine, early rescue, or later rescue use of iNO is not recommended for preterm infants less than 34 weeks gestation requiring respiratory support (Cole et al., 2011).

Newborns With Congenital Diaphragmatic Hernia (CDH)

The benefits of iNO are not clear in newborns with CDH and possible harm is a concern in this population. Systematic reviews of RCTs suggest that iNO is ineffective or has minimal effect in newborns with CDH. The evidence indicates that the net health outcome of iNO was not improved for newborns with CHD beyond temporary oxygenation improvement. A few observational studies were recently published regarding CDH but no recent randomized controlled trials for CDH were identified that would impact the conclusions of the systematic reviews.

Lawrence et al. (2019) in a retrospective observational study, evaluated which individuals with CDH and pulmonary hypertension (PH) benefit from iNO treatment by comparing characteristics and outcomes of iNO responders to nonresponders using a retrospective chart review of infants with CDH treated between 2011 and 2016. In a subset of individuals, iNO was initiated for hypoxemia or echocardiographic evidence of extrapulmonary right to left shunting. Initial post-treatment blood gases were reviewed, and individuals were classified as responders (increased PaO2 > 20 mm Hg) or nonresponders. Baseline characteristics, echocardiograms and outcomes were compared between groups with Fisher exact tests and Mann-Whitney tests, as appropriate. During the study period, 95 of 131 individuals with CDH (73%) were treated with iNO. All individuals with pretreatment echocardiograms (n = 90) had echocardiographic evidence of PH. Thirty-eight (40%) individuals met treatment response criteria. Responders had significant improvements in PaO_2 alveolar-arterial gradient and PaO_2 to FiO_2 ratio. Nonresponders were more likely to have left ventricular systolic dysfunction on echocardiogram. Responders were less likely to require extracorporeal membrane support. While iNO was associated with improved oxygenation in a subpopulation of CDH neonates with PH and normal LV systolic function, LV systolic dysfunction was associated with lack of response to treatment and subsequent ECMO treatment, potentially suggesting that pulmonary vasodilation and increased pulmonary venous return could precipitate cardiorespiratory failure in this subset of individuals. Study limitations included this was retrospective and a small sample size. Also, diastolic function and additional markers of systolic function (tissue Doppler imaging, speckle tracking echo, etc.) should be evaluated as other potential echocardiographic predictors of response. Ventilator measures were not followed other than mode and FiO2 during the treatment period, therefore the contribution of ventilator management to oxygenation improvements could not be assessed. Lastly, the institutional practice was to initially resuscitate neonates with CDH and with 50% O2, but still many individuals in this series were treated with 100% O2 which could have dampened a potential iNO treatment effect. As a result of this study, the use of iNO in infants with CDH with PH and significant LV dysfunction is not recommended. Future studies are needed to identify additional individual characteristics and echocardiographic parameters that predict iNO response to further refine individual selection for therapy.

Wang et al. (2019) conducted a systematic review and meta-analysis to determine whether the inhalation of iNO could improve oxygenation and reduce rate of death or use of ECMO. The main findings for infants without CDH are reported above. The analyses for the subgroup of participants with CDH showed no clear benefit on oxygenation.

In a Cochrane systematic review and meta-analysis, Barrington et al. (2017a) assessed whether iNO treatment of hypoxemic term and near-term newborn infants improves oxygenation and reduces rate of death and use of ECMO or affects long-term neurodevelopmental outcomes. The main findings for infants without CDH are reported above. Analyses limited to individuals with CDH failed to demonstrate a benefit and suggest a possible harm of iNO for the combined outcome of death or use of ECMO, despite a possible benefit on short-term oxygenation.

Puligandla et al. (2015) performed a systematic review on the management of CDH. The available studies indicated iNO can "transiently improve oxygenation," but in the two randomized controlled trials [Neonatal Inhaled Nitric Oxide Study Group (NINOS), 1997; Clark et al., 2000] that analyzed data on CDH, there was no evidence for benefits on the relevant primary outcome (death or need for ECMO) and the data suggested possible but not statistically significant harm on this combined outcome. The authors recommended that multi-institutional studies be done to identify best practices.

Clinical Practice Guidelines

American Association for Respiratory Care (AARC)

The AARC published an evidence-based clinical practice guideline on iNO for neonates with acute hypoxic respiratory failure in 2010. This guideline recommends that iNO should not be used routinely in newborns with CDH (DiBlasi et al., 2010).

Postoperative Management of Pulmonary Hypertension Associated With Heart or Lung Surgery in Infants

Evidence for the benefits or harm of iNO is inconclusive for this heterogeneous and relatively rare population. However, practice-based guidelines suggest that individual individuals may benefit from bridge therapy during the acute recovery phase.

In an updated Cochrane systematic review, Bizzarro et al. (2014) compared the effects of postoperative administration of iNO versus placebo or conventional management, or both, on infants and children with congenital heart disease (CHD) and pulmonary hypertension. Randomized and quasi-randomized controlled trials comparing iNO with placebo or conventional management, or both were included in the review. The original review was published in 2005 and updated in 2008. The authors reran the searches to December 2013 and found four randomized clinical trials involving 210 participants aged from one day to 17 years with PH either in the preoperative (one study) or postoperative period (three studies). The authors found it difficult to draw valid conclusions given concerns regarding methodologic quality, sample size, and heterogeneity. The authors concluded that the results of this review do not appear to show any significant clinical benefit with the use of postoperative iNO to treat pulmonary hypertension in children with CHD. However, based on broad confidence intervals, the findings of this review are largely inconclusive and unable to exclude clinically significant benefits or harms.

Clinical Practice Guidelines

American Heart Association (AHA) and American Thoracic Society (ATS)

In regard to postoperative pulmonary hypertension (PH), the AHA and ATS guideline on pediatric PH recommends that in addition to conventional postoperative care, iNO and/or inhaled prostacyclin (PGI_2) should be used as the initial therapy for PH crises (PHCs) and failure of the right side of the heart [Class I; Level of Evidence B (the procedure/treatment was deemed useful/effective with data derived from a single randomized trial or nonrandomized studies)] (Abman et al., 2015).

U.S. Food and Drug Administration (FDA)

This section is to be used for informational purposes only. FDA approval alone is not a basis for coverage.

Nitric oxide gas is regulated by the FDA as a drug. A complete nitric oxide delivery system is comprised of a nitric oxide administration apparatus, a nitric oxide gas analyzer, and a nitrogen dioxide gas analyzer.

INOmax® (nitric oxide gas) was initially cleared by the FDA in December 1999. INOmax is indicated for treatment of term and near-term (> 34 weeks) neonates with hypoxic respiratory failure associated with clinical or echocardiographic evidence of pulmonary hypertension. Multiple supplemental approvals have been issued for INOmax. INOmax is not approved for use in preterm infants (≤ 34 weeks). INOmax is contraindicated in infants known to be dependent on right-to-left shunting. Refer to the following websites for more information:

- https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm?ID=K061901
- https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=020845

(Accessed April 16, 2025)

The INOmax delivery system received FDA clearance in September 2006. This delivery system can administer the iNO in conjunction with a ventilator or other mechanical gas administration system such as INOmax DSIR®, INOmax DS®, and INOvent®. These delivery systems allow the administration of an operator-determined amount of nitric oxide and should be calibrated using a precise calibration mixture of nitric oxide and nitrogen dioxide such as INOcal®. They also provide monitoring of inspired O2, NO2, and NO with an alarm system. Refer to the following website for more information: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm?ID=K061901. (Accessed April 16, 2025)

Noxivent® received approval on October 2, 2018, based on the original New Drug Application (NDA) for INOmax. Refer to the following website for more information:
https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=207141.
(Accessed April 16, 2025)

The GeNOsyl™ MV-1000 nitric oxide delivery device received 510(K) clearance from the FDA in 2012. It is approved to provide a constant set concentration of nitric oxide to the patient via mechanical ventilation and also includes monitoring of inspired O2, NO2, and NO with an alarm system. Refer to the following website for more information: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm?ID=K120216. (Accessed April 16, 2025)

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Policy History/Revision Information

Date	Summary of Changes
04/01/2026	**Template Update** • Removed content/language pertaining to the state of Louisiana

Date	Summary of Changes
02/01/2026	**Application** ***Louisiana*** • Added reference link to state-specific policy version (effective Feb. 1, 2026)
11/01/2025	**Application** ***North Carolina*** • Added language to indicate this Medical Policy does not apply to the state of **North Carolina**; refer to the state-specific policy version **Supporting Information** • Updated *Description of Services*, *Clinical Evidence*, and *References* sections to reflect the most current information • Archived previous policy version CS173.J

Instructions for Use

This Medical Policy provides assistance in interpreting UnitedHealthcare standard benefit plans. When deciding coverage, the federal, state, or contractual requirements for benefit plan coverage must be referenced as the terms of the federal, state, or contractual requirements for benefit plan coverage may differ from the standard benefit plan. In the event of a conflict, the federal, state, or contractual requirements for benefit plan coverage govern. Before using this policy, check the federal, state, or contractual requirements for benefit plan coverage. UnitedHealthcare reserves the right to modify its Policies and Guidelines as necessary. This Medical Policy is provided for informational purposes. It does not constitute medical advice.

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