Inhaled Nitric Oxide Therapy

Policy Number: 2026T0607N
Effective Date: September 1, 2026

➲ Instructions for Use

Table of Contents **Page**

Application 1
Coverage Rationale 1
Definitions 1
Applicable Codes 2
Description of Services 2
Clinical Evidence 2
U.S. Food and Drug Administration 8
References 8
Policy History/Revision Information 10
Instructions for Use 10

Community Plan Policy

- Inhaled Nitric Oxide Therapy

Application

UnitedHealthcare Commercial

This Medical Policy applies to UnitedHealthcare Commercial benefit plans.

UnitedHealthcare Individual Exchange

This Medical Policy applies to Individual Exchange benefit plans.

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 and all the following:

- Absence of congenital diaphragmatic hernia
- 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 congenital diaphragmatic hernia
- Preterm newborns who are less than 34 weeks' gestation at birth

iNO treatment for individuals outside of the Infancy age group is experimental or investigational due to a lack of U.S. Food and Drug Administration–approved indications.

Definitions

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

Proprietary Information of UnitedHealthcare. Copyright 2026 United HealthCare Services, Inc.

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 the member specific benefit plan document 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

CPT® is a registered trademark of the American Medical Association

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. 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 airspaces 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, and congenital diaphragmatic hernia. These conditions can cause elevated pressure in the pulmonary vessels. The classic characteristics of persistent pulmonary hypertension of the newborn 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 extracorporeal membrane oxygenation using a heart/lung machine.

Clinical Evidence

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

Wang et al. (2019) conducted a systematic review and meta-analysis to determine whether inhaled nitric oxide (iNO) could improve oxygenation and reduce the rate of death or use of extracorporeal membrane oxygenation (ECMO) among infants born at 34 weeks' gestation or more. Nine randomized controlled trials (RCTs), with a total of 856 individuals, 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 nitric oxide inhalation is recommended for respiratory failure among infants born at or near term. The study is limited by the relatively small number of randomized trials and individuals included, which may reduce the strength and generalizability of its conclusions.

Barrington et al. (2017a), in a Cochrane systematic review and meta-analysis, assessed whether iNO treatment of hypoxemic term and near-term newborn infants improves oxygenation, reduces rate of death or use of ECMO, or affects long-term neurodevelopmental outcomes. Overall, 17 randomized controlled studies were identified for inclusion in the review. Some of the studies were limited to individuals with persistent pulmonary hypertension of the newborn (PPHN), but some were not. Most of the reported results were obtained from 10 studies of moderate to high quality, which compared iNO vs 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 congenital diaphragmatic hernia (CDH) may respond differently than other near-term infants, results in these

Proprietary Information of UnitedHealthcare. Copyright 2026 United HealthCare Services, Inc.

infants were evaluated separately. The authors found that hypoxemic term and near-term infants treated with iNO appear to have improved outcomes due to a reduction in the incidence of the combined end point of death or use of ECMO (high-quality evidence). Infants who received iNO with 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 individuals 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 who are experiencing hypoxic respiratory failure and who do not have a diaphragmatic hernia. The review is limited by differences across the included studies, with some trials focused specifically on infants with PPHN, while others enrolled broader hypoxemic populations, making comparisons challenging. It also relied heavily on 10 moderate- to high-quality studies, while several smaller trials used different illness-severity thresholds and timing of iNO initiation, which could affect consistency of results.

Wu et al. (2016) conducted an RCT to investigate the effect of iNO for treating PPHN. Overall, 86 infants with neonatal pulmonary hypertension (PH) were included in this study. In total, 12% 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 in 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 in 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. The study is limited because it is unclear whether the premature infants were born before or after 34 weeks of gestation, making it difficult to know which gestational-age groups the results truly apply to. It is also limited by its small sample size of only 86 infants, which reduces how confidently the findings can be generalized to a broader population.

Clinical Practice Guidelines

American Academy of Pediatrics (AAP)

The AAP published a policy statement in 2000 (reaffirmed 2009) 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 U.S. Food and Drug Administration.

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

The AHA and ATS's guideline on pediatric PH 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 exists, the body of evidence, including systematic reviews and meta-analyses of RCTs, fails to demonstrate a clear clinically or statistically significant benefit of iNO in premature newborns who are born at less than 34 weeks for the treatment of respiratory distress syndrome 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. Therefore, the balance of iNO benefits and harms therefore remains unclear in for premature infants.

Mirza et al. (2025) conducted a single-center RCT to assess whether iNO treatment for early PH could reduce the risk of death or BPD in preterm infants who are < 29 weeks' gestation and require positive pressure ventilation. The exclusion criteria included infants born to mothers who were positive for COVID-19 and 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 to 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 them, 88 were excluded, and 413 mothers either declined participation or were not approached. iNO treatment was initiated in 51 infants due to hypoxic respiratory failure. A screening echocardiogram was performed in 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 groups (68% vs 62%; p = 0.99). Therefore, the data safety monitoring

Proprietary Information of UnitedHealthcare. Copyright 2026 United HealthCare Services, Inc.

board recommended termination of the study. The study includes several limitations: the trial was terminated after an interim analysis due to futility; the sample size was relatively small, limiting the generalizability of the results; the accurate diagnosis of PH could be challenging; 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 PH.

Feng et al. (2024) conducted a systematic review and meta-analysis to evaluate the safety and efficacy of iNO in neonates who were aged ≤ 34 weeks. The study included RCTs through June 2023 in preterm infants who were ≤ 34 weeks and receiving iNO treatment; the studies primarily reviewed outcomes such as BPD and mortality. Results included a total of 17 studies, which involved 4,080 neonates and seven follow-up studies. The results showed that in neonates, iNO treatment reduced the incidence of BPD (risk ratio, 0.92; 95% CI, 0.86-0.98). It also decreased the composite outcome of death or BPD (risk ratio, 0.94; 95% CI, 0.90-0.98) without increasing the risk of short-term [such as intraventricular hemorrhage (IVH) and 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. A 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, and treatment duration exceeding 7 days ($p < 0.05$). The authors indicated that the study has several limitations: differences in gestational age and birth weight; lung tissue at different developmental stages that responds differently to nitric oxide, which may affect the incidence of BPD, pulmonary hemorrhage, or other complications; and other baseline data, such as intervention dose, exposure time, and the sex of the infants included, being dissimilar 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 noted that iNO is considered a promising treatment for the potential prevention of BPD in premature infants. Additional data are needed to support iNO use in this specific population and to minimize its off-label use. (Hasan et al., 2017, is also 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% CI, 0.85-0.97; $p = 0.006$]. There was no significant difference in the incidence of BPD between the two groups at the initial dose of 5 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 of necrotizing enterocolitis (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 necrotizing enterocolitis compared with the control group ($p = 0.41$); those treated with an initial dosage of 5 ppm of iNO had a significantly greater rate of necrotizing enterocolitis 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, IVH (grade 3/4), or periventricular leukomalacia and pulmonary hemorrhage between the two treatment groups. The study has several limitations: the clinical criteria must be updated to evaluate the severity and long-term prognosis of BPD, and the reliability of the study may be affected by the small sample size and number of research samples. Additionally, there was no subgroup analysis on birth weight, the start time of inhalation, and iNO inhalation dose range in preterm infants. The authors 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 was similar. Additional studies are needed based on the findings and limitations. (Hasan et al., 2017, is included in this study.)

Greenough et al. (2020) conducted a long-term follow-up of an RCT to evaluate the long-term effects of iNO use at 7 years of age for the prevention of BPD in premature infants. A 7-year follow-up was undertaken in infants who had been entered into the European Union Nitric Oxide (EUNO) trial, which was a multicenter, double-blinded, randomized, placebo-controlled trial of iNO for the prevention of BPD in premature infants who were born between 24 and 28 weeks plus 6 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. Overall, 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, health-related quality of life, 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 in very prematurely born infants at 7 years of age who had been entered into a neonatal randomized trial of iNO. A major limitation is 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

Proprietary Information of UnitedHealthcare. Copyright 2026 United HealthCare Services, Inc.

balanced, with characteristics like those of the original randomized population, which reflects the overall population. Another study limitation is that a proportion of the population was not intubated; therefore, they may not have received enough iNO. The authors concluded that iNO for the 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 the prevention of BPD in preterm infants.

A Hayes Health Technology Assessment (2018; updated 2023) 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 that indicates that iNO use does not decrease the risk of BPD. The Hayes review also found moderate-quality evidence that indicates that routine prophylactic iNO use does not improve outcomes in preterm infants with respiratory failure.

Askie et al. (2018) conducted a meta-analysis of selected studies to assess whether iNO improves survival without BPD in preterm African American infants. The review included three randomized , placebo-controlled trials that enrolled infants who were born at less than 34 weeks of gestation and receiving respiratory support; had at least 15% of African American individuals; and used a starting iNO of greater than 5 ppm, with the intention to treat for a minimum of 7 days . In contrast to individuals 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 in 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 who are at a high risk for BPD. As subgroup analyses by race were 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. Overall, 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 3 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 3 days of age) because of an 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 in 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 with iNO in this population. Furthermore, while no clear effect was found on the incidence of neurodevelopmental impairment or on the frequency of 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 in preterm infants who require positive pressure respiratory support improves the rate of survival without BPD. An intent-to-treat RCT analysis was performed in participants at 33 U.S. and Canadian neonatal intensive care units and included 451 neonates who were younger than 30 weeks' gestation and 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' 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 for the systematic reviews above for the lack of benefit of iNO in infants who are younger than 30 weeks at birth.

Proprietary Information of UnitedHealthcare. Copyright 2026 United HealthCare Services, Inc.

Clinical Practice Guidelines

American Academy of Pediatrics (AAP)

In 2014 (reaffirmed 2025), the AAP Committee on the Fetus and Newborn released guidance on the use of iNO in preterm infants. The AAP indicates 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 2009) on the use of iNO in infants with respiratory distress. This policy statement indicates that there are limited data on the use of low-dose iNO for hypoxic preterm neonates. The authors state that available data suggest that iNO improves oxygenation but does not improve survival in this patient population.

European Pediatric Pulmonary Vascular Disease Network (EPPVDN)

The EPPVDN has published an updated consensus statement regarding iNO for the diagnosis and treatment of pediatric PH. Regarding PPHN and PH associated with BPD/neonatal chronic lung disease, the EPPVDN states that 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 if (1) PaO_2 is less than 100 mm Hg (while receiving 100% oxygen) or (2) the oxygenation index exceeds 25 [class of evidence: I, evidence and/or general agreement that a given treatment or procedure is beneficial, useful, or effective (is recommended/is indicated); level of evidence: A, data derived from multiple randomized clinical trials or meta-analyses]. The EPPVDN further states that it is not well established that iNO in preterm infants who are < 34 weeks of gestation with respiratory failure reduces the incidence of BPD [class of recommendation: IIb, usefulness/efficacy is less well established by evidence/opinion (may be considered); level of evidence: C, consensus of opinion of the experts and/or small studies, retrospective studies, or registries] and that iNO may be considered in preterm infants who are < 34 weeks of gestation with respiratory failure and confirmed PH (class of recommendation: IIb; level of evidence: C) (Hansmann et al., 2019).

National Institute for Health and Care Excellence (NICE)

A 2019 NICE guideline titled *Specialist Neonatal Respiratory Care for Babies Born Preterm* states, “Do not routinely use iNO 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 notes that the use of iNO for pulmonary hypoplasia or PH in babies who are 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 that consisted 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 in preterm infants who are less than 34 weeks’ gestation and require respiratory support (Cole et al., 2011).

Newborns With Congenital Diaphragmatic Hernia

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 in newborns with CDH beyond temporary oxygenation improvement. A few observational studies were recently published regarding CDH, but no recent RCTs for CDH were identified that would impact the conclusions of the systematic reviews.

Sescleifer et al. (2025) conducted a national multicenter cohort study that examined the use of iNO in 2,565 newborns with CDH across 48 major U.S. children’s hospitals between 2016 and 2023. The investigators assessed how differing hospital-level patterns of iNO use influenced outcomes such as mortality, ECMO use, mechanical ventilation duration, length of stay, and hospital charges. Their analysis showed that iNO use in infants with CDH has declined over time, dropping from 51.4% to 42.9% during the study period, which indicates a measurable shift in clinical practice patterns. Importantly, hospitals categorized as having high iNO use had significantly higher mortality (19.9%) than low-use hospitals (12.4%), along with longer durations of mechanical ventilation and longer hospitalization. These findings contribute to meaningful validity data, which are strengthened by the study’s large sample size, multicenter design, and consistent temporal trend analysis; this reinforces that routine iNO use in infants with CDH is ineffective at best and potentially harmful. However, the study’s observational design inherently limits causal inference, and differences in illness severity,

Proprietary Information of UnitedHealthcare. Copyright 2026 United HealthCare Services, Inc.

clinician decision-making, and institutional management strategies could influence outcomes. Additionally, because the dataset reflects care at large U.S. children's hospitals, generalizability to smaller or international centers may be limited.

Lawrence et al. (2019), in a retrospective observational study, evaluated which patients with CDH and PH benefit from iNO treatment by comparing characteristics of and outcomes in iNO responders with those in nonresponders; a retrospective chart review was performed and included infants with CDH who were treated between 2011 and 2016. In a subset of patients, iNO was initiated for hypoxemia or echocardiographic evidence of extrapulmonary right-to-left shunting. Initial posttreatment blood gases were reviewed, and patients were classified as responders (increased PaO_2 > 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 patients with CDH (73%) were treated with iNO. All patients with pretreatment echocardiograms (n = 90) had echocardiographic evidence of PH. Overall, 38 patients (40%) met the treatment response criteria. Responders had significant improvements in PaO_2 alveolar-arterial gradient and PaO_2 to fraction of inspired oxygen 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 neonates with CDH and PH and normal left ventricular systolic function, left ventricular systolic dysfunction was associated with a 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 patients. Study limitations include the retrospective design and small sample size. Also, diastolic function and additional markers of systolic function (tissue Doppler imaging, speckle tracking echocardiography, etc.) should be evaluated as other potential echocardiographic predictors of response. Ventilator measures were not followed, other than mode and fraction of inspired oxygen, 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% O_2; however, many patients in this series were treated with 100% O_2, which could have dampened a potential iNO treatment effect. As a result of this study, the use of iNO in infants with CDH, PH, and significant left ventricular 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 the rate of death or use of ECMO. The main findings in infants without CDH are reported above. The analyses in the subgroup of individuals with CDH showed no clear benefit on oxygenation.

In a Cochrane systematic review and meta-analysis, Barrington et al. (2017a) assessed whether iNO treatment in hypoxemic term and near-term newborn infants improves oxygenation, reduces the rate of death and use of ECMO, or affects long-term neurodevelopmental outcomes. The main findings in infants without CDH are reported above. Analyses limited to individuals with CDH failed to demonstrate a benefit and suggest a possible harm with 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 that iNO can "transiently improve oxygenation," but in the two RCTs [Neonatal Inhaled Nitric Oxide Study Group (NINOS), 1997; Clark et al., 2000] that analyzed data on CDH, there was no evidence of benefits on the relevant primary outcome (death or need for ECMO), and the data suggest possible but not statistically significant harm for 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 on the benefits or harm of iNO is inconclusive for this heterogeneous and relatively rare population. However, practice-based guidelines suggest that individuals may benefit from bridge therapy during the acute recovery phase.

Bizzarro et al. (2014) conducted a Cochrane review and compared the effects of postoperative administration of iNO vs placebo or conventional management or both in infants and children with congenital heart disease and PH. Randomized and quasi-randomized controlled trials that compared 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

Proprietary Information of UnitedHealthcare. Copyright 2026 United HealthCare Services, Inc.

December 2013 and found four randomized clinical trials that involved 210 individuals who were aged 1 day to 17 years and had PH either in the preoperative (one study) or postoperative period (three studies). The authors found it difficult to draw valid conclusions, given concerns regarding methodological 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 PH in children with congenital heart disease. However, based on broad CIs, the findings of this review are largely inconclusive and unable to exclude clinically significant benefits or harms. Limitations of this review include the very low quality of evidence due to small numbers of individuals and low event rates; presence of bias in most trials, aside from two with low risk; and substantial heterogeneity across studies, with different iNO concentrations, varied timing and duration of administration, and inclusion of individuals with diverse congenital heart defects that required repair.

Clinical Practice Guidelines

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

In regard to postoperative 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 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 comprises 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 the 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 March 19, 2026)

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 O_2, NO_2, 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 March 19, 2026)

Noxivent® received approval on October 2, 2018, based on the original New Drug Application 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 March 19, 2026)

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 O_2, NO_2, 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 March 19, 2026)

References

Abman SH, Hansmann G, Archer SL, et al.; American Heart Association Council on Cardiopulmonary, Critical Care, Perioperative and Resuscitation; Council on Clinical Cardiology; Council on Cardiovascular Disease in the Young; Council on Cardiovascular Radiology and Intervention; Council on Cardiovascular Surgery and Anesthesia; and the American Thoracic Society. Pediatric pulmonary hypertension: guidelines from the American Heart Association and American Thoracic Society. Circulation. 2015 Nov;132(21):2037-2099.

Proprietary Information of UnitedHealthcare. Copyright 2026 United HealthCare Services, Inc.

American Academy of Pediatrics (AAP). Committee on Fetus and Newborn. Use of inhaled nitric oxide. Pediatrics. 2000;106(2 Pt 1):344-345. Reaffirmed 2009.

Askie LM, Davies LC, Schreiber MD, et al. Race effects of inhaled nitric oxide in preterm infants: an individual participant data meta-analysis. J Pediatr. 2018 Feb;193:34-39.e32.

Barfield WD; Committee on Fetus and Newborn. Standard terminology for fetal, infant, and perinatal deaths. Pediatrics. 2016 May;137(5):e20160551.

Barrington KJ, Finer N, Pennaforte T, et al. Nitric oxide for respiratory failure in infants born at or near term. Cochrane Database Syst Rev. 2017a Jan;1(1):CD000399.

Barrington KJ, Finer N, Pennaforte T. Inhaled nitric oxide for respiratory failure in preterm infants. Cochrane Database Syst Rev. 2017b Jan;1(1):CD000509.

Bizzarro M, Gross I, Barbosa FT. Inhaled nitric oxide for the postoperative management of pulmonary hypertension in infants and children with congenital heart disease. Cochrane Database Syst Rev. 2014 Jul;2014(7):CD005055.

Clark RH, Kueser TJ, Walker MW, et al. Low-dose nitric oxide therapy for persistent pulmonary hypertension of the newborn. Clinical Inhaled Nitric Oxide Research Group. n Engl J Med. 2000 Feb;342(7):469-474.

Cole FS, Alleyne C, Barks JD, et al. NIH Consensus Development Conference statement: inhaled nitric-oxide therapy for premature infants. Pediatrics. 2011 Feb;127(2):363-369.

DiBlasi RM, Myers TR, Hess DR. Evidence-based clinical practice guideline: inhaled nitric oxide for neonates with acute hypoxic respiratory failure. Respir Care. 2010 Dec;55(12):1717-1745.

Dixon F, Ziegler DS, Bajuk B, et al. Treatment with nitric oxide in the neonatal intensive care unit is associated with increased risk of childhood cancer. Acta Paediatr. 2018 Dec;107(12):2092-2098.

Feng Z, Wu X, Xu X, et al. Efficacy of inhaled nitric oxide in preterm infants ≤ 34 weeks: a systematic review and meta-analysis of randomized controlled trials. Front Pharmacol. 2024 Jan;14:1268795.

Greenough A, Decobert F, Field D, et al. Inhaled nitric oxide (iNO) for preventing prematurity-related bronchopulmonary dysplasia (BPD): 7-year follow-up of the European Union Nitric Oxide (EUNO) trial. J Perinat Med. 2020 Sep;49(1):104-110.

Hansmann G, Koestenberger M, Alastalo TP, et al. 2019 updated consensus statement on the diagnosis and treatment of pediatric pulmonary hypertension: the European Pediatric Pulmonary Vascular Disease Network (EPPVDN), endorsed by AEPC, ESPR and ISHLT. J Heart Lung Transplant. 2019 Sep;38(9):879-901.

Hasan SU, Potenziano J, Konduri GG, et al.; Newborns Treated With Nitric Oxide (NEWNO) Trial Group. Effect of inhaled nitric oxide on survival without bronchopulmonary dysplasia in preterm infants: a randomized clinical trial. JAMA Pediatr. 2017 Nov 1;171(11):1081-1089.

Hayes, Inc. Health Technology Assessment. Inhaled nitric oxide for the treatment of respiratory failure in preterm newborns. Hayes, Inc.; November 2018. Updated March 2023.

Kumar P; Committee on Fetus and Newborn. Use of inhaled nitric oxide in preterm infants. Pediatrics. 2014 Jan;133(1):164-170. Reaffirmed 2025.

Lawrence KM, Monos S, Adams S, et al. Inhaled nitric oxide is associated with improved oxygenation in a subpopulation of infants with congenital diaphragmatic hernia and pulmonary hypertension. J Pediatr. 2020 Apr;219:167-172.

McLaughlin VV, Archer SL, Badesch DB, et al.; American College of Cardiology Foundation Task Force on Expert Consensus Documents; American Heart Association; American College of Chest Physicians; American Thoracic Society, Inc; Pulmonary Hypertension Association. ACCF/AHA 2009 expert consensus document on pulmonary hypertension a report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents and the American Heart Association developed in collaboration with the American College of Chest Physicians; American Thoracic Society, Inc.; and the Pulmonary Hypertension Association. J Am Coll Cardiol. 2009 Apr;53(17):1573-619.

Mirza H, Garcia J, Zussman M, et al. Inhaled nitric oxide treatment of early pulmonary hypertension to reduce the risk of death or bronchopulmonary dysplasia in infants born extremely preterm: a masked randomized controlled trial. J Pediatr. 2025 Mar;278:114427.

National Institute for Health and Care Excellence (NICE). NICE guideline NG124. Specialist neonatal respiratory care for babies born preterm. Available at: https://www.nice.org.uk/guidance/ng124/resources/specialist-neonatal-respiratory-care-for-babies-born-preterm-pdf-66141658884805. Accessed April 21, 2026.

Neonatal Inhaled Nitric Oxide Study Group (NINOS). Inhaled nitric oxide and hypoxic respiratory failure in infants with congenital diaphragmatic hernia. Pediatrics. 1997 Jun;99(6):838-845.

Proprietary Information of UnitedHealthcare. Copyright 2026 United HealthCare Services, Inc.

Puligandla PS, Grabowski J, Austin M, et al. Management of congenital diaphragmatic hernia: a systematic review from the APSA Outcomes and Evidence-Based Practice Committee. J Pediatr Surg. 2015 Nov;50(11):1958-1970.

Sescleifer AM, Chidiac C, Hellmann ZJ, et al. Revisiting inhaled nitric oxide utilization in congenital diaphragmatic hernia: a national cohort study of major children's hospitals in the United States. J Pediatr Surg. 2025 Sep;60(9):162423.

Wang X, Li B, Ma Y, et al. Effect of NO inhalation on ECMO use rate and mortality in infants born at or near term with respiratory failure. Medicine (Baltimore). 2019 Oct;98(41):e17139.

Wu HW, Li ZG, Liu G, et al. Effect of nitric oxide inhalation for the treatment of neonatal pulmonary hypertension. Eur Rev Med Pharmacol Sci. 2016 Nov;20(21):4607-4611.

Zheng Y, Wu Q, Han S. Inhaled nitric oxide in premature infants for preventing bronchopulmonary dysplasia: a meta-analysis. BMC Pediatr. 2023 Mar;23(1):139.

Policy History/Revision Information

Date	Summary of Changes
09/01/2026	**Supporting Information** • Updated *Clinical Evidence* and *References* sections to reflect the most current information • Archived previous policy version 2026T0607M

Instructions for Use

This Medical Policy provides assistance in interpreting UnitedHealthcare standard benefit plans. When deciding coverage, the member specific benefit plan document must be referenced as the terms of the member specific benefit plan may differ from the standard plan. In the event of a conflict, the member specific benefit plan document governs. Before using this policy, check the member specific benefit plan document and any applicable federal or state mandates. 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.

This Medical Policy may also be applied to Medicare Advantage plans in certain instances. In the absence of a Medicare National Coverage Determination (NCD), Local Coverage Determination (LCD), or other Medicare coverage guidance, CMS allows a Medicare Advantage Organization (MAO) to create its own coverage determinations, using objective evidence-based rationale relying on authoritative evidence (Medicare IOM Pub. No. 100-16, Ch. 4, §90.5).

UnitedHealthcare may also use tools developed by third parties, such as the InterQual® criteria, to assist us in administering health benefits. UnitedHealthcare Medical Policies are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.

Proprietary Information of UnitedHealthcare. Copyright 2026 United HealthCare Services, Inc.