

Clinical Policy: Therapeutic Utilization of Inhaled Nitric Oxide

Reference Number: CP.MP.87

Date of Last Revision: 04/25

[Revision Log](#)

See [Important Reminder](#) at the end of this policy for important regulatory and legal information.

Description

Inhaled nitric oxide (iNO) is a selective pulmonary vasodilator with a mechanism of action which results in smooth muscle relaxation. Many studies have suggested that iNO improves oxygenation, particularly in trials done in term and near-term neonates with hypoxic respiratory failure.^{3,10} Further, iNO has been shown to reduce the need for extracorporeal membrane oxygenation (ECMO) without increasing neurodevelopmental, behavioral, or medical abnormalities evaluated at two years of age.¹⁰

Policy/Criteria

- I. It is the policy of health plans affiliated with Centene Corporation® that *initiation* of inhaled nitric oxide (iNO) therapy is **medically necessary** when meeting one of the following:
 - A. Hypoxic respiratory failure in newborns \geq 34 weeks gestational age **at birth** with all of the following:
 1. Evidence of pulmonary arterial hypertension (PAH), one of the following:
 - a. Well-documented, clear clinical evidence of pulmonary hypertension despite maximal respiratory support;
 - b. Echocardiogram suggestive of PAH;
 2. Absence of unrepaired congenital diaphragmatic hernia (CDH), except when used as a bridge to surgical repair of congenital diaphragmatic hernia;
 3. Conventional therapies such as mechanical ventilation, administration of high concentrations of oxygen (80 to 100%), high-frequency ventilation, induction of alkalosis, neuromuscular blockade, and/or sedation have failed;
 4. Oxygen index (OI) > 25 . The OI is calculated as the mean airway pressure (cm H₂O) times the fraction of inspired oxygen (FiO₂) times 100 divided by the partial pressure of arterial oxygen (mm Hg);
 - B. Perioperative management in children and infants \geq 34 weeks gestational age **at birth**, both of the following:
 1. One of the following indications:
 - a. Congenital heart defect and one of the following:
 - 1) iNO therapy for vasodilation is used in response to cardiac bypass surgery to repair a congenital heart defect that is causing PAH;
 - 2) Perioperative stabilization and management of hypoxia;
 - 3) Right ventricular heart failure;
 - b. Pulmonary hypertensive crisis associated with heart or lung surgery (including immediately pre- or post-operatively for congenital diaphragmatic hernia);
 2. Initiation of alternative vasodilator therapies (e.g., sildenafil or others) during iNO administration with the intent to wean or discontinue iNO (see continuation criteria in section III);
 - C. COVID-19 diagnosis**, both of the following:
 1. Severe acute respiratory distress syndrome (ARDS);
 2. Hypoxemia despite optimized ventilation and other rescue strategies.

****Note:** If no rapid improvement in oxygenation is observed, treatment should be tapered off.

II. It is the policy of health plans affiliated with Centene Corporation that, while the medical literature predominantly does not support the use of inhaled nitric oxide (iNO) in premature infants < 34 weeks gestational age at birth, requests for initiation of iNO therapy in these infants may be **reviewed on a case-by-case basis** with consideration of the criteria for premature newborns ≥ 34 weeks gestational age at birth in section I.

III. It is the policy of health plans affiliated with Centene Corporation that *continuation* of iNO therapy is **medically necessary** when meeting the following:

A. Member/enrollee has previously met initial approval criteria and one of the following*:

1. Response seen with administration of up to 40 ppm trial of iNO with a recommended dose of 20 ppm (response defined as a partial pressure of oxygen (PaO₂) increase of ≥ 20 mm Hg or a 20% decrease in OI);
2. A weaning protocol for the iNO has been initiated after a four-to-six-hour period of stability, indicated by O₂ requirement decreased/decreasing to 60 to 80% or OI ≤ 10.

***Note:** Extended administration of iNO beyond 72 hours requires secondary review by a medical director.

IV. It is the policy of health plans affiliated with Centene Corporate that inhaled nitric oxide is **not medically necessary** for any other indications, including but not limited to acute bronchiolitis, bronchopulmonary dysplasia (BPD); congenital diaphragmatic hernia (CDH) (except as noted above), acute respiratory distress syndrome (except as noted above), acute lung injury, treatment in adults with positive vaso-reactivity testing, post-op cardiac surgery in adults, or vaso-occlusive crises in members/enrollees with sickle cell disease because safety and effectiveness have not been established.

Treatment Regimen

In 2000, the American Academy of Pediatrics (AAP) recommended that inhaled nitric oxide (iNO) should only be administered according to a formal protocol that has been approved by the Food and Drug Administration (FDA) and the institutional review board and with informed consent.

Since no single standard protocol has been issued for iNO treatment, the following is one guideline to assist in determining appropriate initiation and continuation of treatment. The recommended starting dose of iNO for term infants is 20 ppm.^{3,5-7,10} A positive response generally occurs in less than 30 minutes with a partial pressure of oxygen (PaO₂) increase ≥20 mmHg or 20% decrease in oxygen index (OI). If there is no response, the dose may be incrementally increased up to 40 ppm.⁵ In premature infants, the initial dose used in studies was 10 ppm with an increase up to 20 ppm in non-responders. Doses of up to 80 ppm have been used but the potential for increasing toxicity without additional benefits occurs at doses greater than 40 ppm.⁶

Therapeutic Utilization of Inhaled Nitric Oxide

Weaning of iNO can occur following improvement in oxygenation and after a four-to-six-hour period of stability, during which the inspired oxygen concentration is decreased to 60 to 80%, or the OI falls to ≤ 10 . At four-to-six-hour intervals, the dose can be decreased by 50%, as long as the OI remains ≤ 10 . When stability is maintained at iNO dose of 5 ppm, weaning should occur by 1 ppm every four hours and be discontinued at 1 ppm if oxygenation status remains with $< 60\%$ FiO₂ with PaO₂ consistently > 50 mmHg. If deterioration occurs during or after weaning occurs, the dose should be increased to the previous level or iNO restarted. Once the infant stabilizes again, weaning should occur more slowly, taking place over a 24-to-48-hour period.¹⁵

In general, patients who respond to iNO therapy typically require treatment for only three to four days, with randomized trials demonstrating that 90% of treated infants were off iNO therapy within one week of initiation. Patients should be monitored for potential toxic effects by measuring the serum methemoglobin concentration, levels of nitrogen dioxide at the airway opening, and ambient air contamination.⁷ Decreased platelet aggregation, increased risk of bleeding (including intracranial hemorrhage; especially in premature infants), and surfactant dysfunction can also occur from iNO toxicity.

Background

A large and well-designed multicenter trial was conducted by the Neonatal Research Network in 235 infants whose gestational age was ≥ 34 weeks. Infants included in this trial had severe hypoxic respiratory failure with oxygen index (OI) ≥ 25 and did not have congenital diaphragmatic hernia. Infants were randomly assigned to inhaled nitric oxide (iNO) or to control (100% oxygen). Fewer infants in the treatment group died within 120 days or received extracorporeal membrane oxygenation (ECMO) therapy (46% versus 64%; relative risk 0.72, 95% CI 0.57-0.91) compared to control. This difference was entirely due to decreased requirement for ECMO (39% versus 54%). Results also revealed that there was no difference in mortality between the groups.¹¹

In a systemic review by the Cochrane database, similar findings of fewer requirements for ECMO and no difference in mortality were noted. Fourteen randomized trials were found in term or near-term infants with hypoxia. iNO improved oxygenation in approximately 50% of the treated infants, and within 30 to 60 minutes of beginning therapy, PaO₂ increased by a mean of 53 mmHg, and there was a mean decrease of 15.1 in OI. The outcome did not appear to be affected by whether infants had echocardiographic evidence of persistent pulmonary hypertension, and no benefit was noted in those with congenital diaphragmatic hernia.

In preterm infants < 35 weeks gestation, a systematic review by the Cochrane database found 14 randomized controlled trials of iNO. The authors concluded that iNO as a rescue therapy for the very ill ventilated preterm infant does not appear to be effective and may increase the risk of severe intraventricular hemorrhage. Later use to prevent bronchopulmonary dysplasia (BPD) does not appear to be effective. Early routine use of iNO in mildly sick preterm infants without BPD may improve survival and decrease serious brain injury, but further studies are needed to confirm these findings. Extremely preterm infants and infants with pulmonary hypoplasia may develop pulmonary hypertension, and there are no clinical trials available to guide prediction of response to iNO in these cohorts. A trial of iNO in preterm infants with documented pulmonary hypertension or in infants with pulmonary hypoplasia may be beneficial, however, the evidence

Therapeutic Utilization of Inhaled Nitric Oxide

remains inconclusive.²⁹ In addition, patient selection criteria has not been defined and additional studies are needed to identify the subset of preterm infants who would benefit from iNO.^{1,12}

Furthermore, a 2018 retrospective analysis of 993 extremely preterm infants (born at 22 to 29 weeks gestation) compared infants receiving iNO with propensity-matched controls and did not find a significant association between iNO exposure and mortality.¹⁰

iNO has been well-studied in patients with acute lung injury and acute respiratory distress syndrome (ALI/ARDS). While iNO may improve oxygenation temporarily, it has not been shown to improve clinically important outcomes such as duration of mechanical ventilation, 28-day mortality or one-year survival. Furthermore, iNO does not improve oxygenation in all patients and the factors that may predict a good response are still uncertain.

In an updated Cochrane database review, the evidence was insufficient to support iNO in any category of critically ill adults and children with acute respiratory distress syndrome. Although iNO results in a transient improvement in oxygenation, it does not reduce mortality and may be harmful, as it seems to increase renal impairment.¹⁷

A Cochrane Summary for the use of iNO for pulmonary hypertension (PH) following surgery in infants and children with congenital heart disease found no benefit of it to assist in recovery.⁴ In the four randomized trials reviewed, there was no difference found in mortality or other outcomes reviewed. Due to the minimal data that was available, the authors found it difficult to draw valid conclusions regarding effectiveness and safety of this treatment in the select population. In a later study, iNO was effective in reducing the risk of development of PH crisis in pulmonary arterial hypertension (PAH)-congenital heart defect patients after cardiac repair in a placebo-controlled study.¹⁶ Infants with PAH-congenital heart defects receiving iNO had fewer PH crises and shorter postoperative courses without concomitant side effects related to the medication.

2015 guidelines on pediatric PH, issued by the American Heart Association and American Thoracic Society, make a class 1, level B recommendation for use of iNO in post-operative pulmonary hypertensive crises.²¹ The guidelines state that iNO is an established therapy for postoperative PH due to its selective pulmonary vasodilator properties, rapid effect onset, and ease of administration.²¹

Research on iNO use in adults with PH is limited to case reports and small case series, which leaves the impact of iNO on survival uncertain. It has been found to successfully stabilize a variety of acutely ill and hemodynamically compromised patients with severe PH, but data on outcomes are limited so it cannot be considered standard of care. Acute vasodilator testing is the only well established and widely accepted use of iNO in patients with PAH. Patients with a positive vasoreactivity test are candidates for a trial of calcium channel blocker therapy.

iNO has numerous disadvantages that must be considered when determining the risks and benefits of treatment. These potential harms include renal dysfunction, DNA strand breakage and base alterations which are potentially mutagenic, immunosuppression that could increase the risk of nosocomial infection, and a possible increase in methemoglobin and NO₂ concentrations,

Therapeutic Utilization of Inhaled Nitric Oxide

which must be monitored frequently. Also, iNO may produce toxic free radicals; however, it is unknown if these are more harmful than ongoing exposure to high fractions of inspired oxygen.

Due to the rapidly evolving COVID-19 pandemic, the National Institutes of Health (NIH) has developed treatment guidelines that rely heavily on experience with other diseases and are supplemented with evolving personal clinical experience with COVID-19 and incorporate the rapidly growing published scientific literature on COVID-19.¹⁵ The guidelines will be updated frequently as published data and other authoritative information becomes available.¹⁵

In adults with COVID-19 and acute hypoxemic respiratory failure, conventional oxygen therapy may be insufficient to meet oxygen needs. Options include high-flow nasal cannula oxygen, noninvasive positive pressure ventilation, or intubation and invasive mechanical ventilation.

The recommendations for mechanically ventilated adults include the following:¹⁵

For mechanically ventilated adults with COVID-19 and refractory hypoxemia despite optimized ventilation:

- The Panel recommends prone ventilation for 12 to 16 hours per day over no prone ventilation (moderate recommendation, moderate quality of evidence).

For mechanically ventilated adults with COVID-19, severe ARDS, and hypoxemia despite optimized ventilation and other rescue strategies:

- The Panel recommends using recruitment maneuvers rather than not using recruitment maneuvers (weak recommendation, moderate quality of evidence);
- If recruitment maneuvers are used, the Panel recommends against the use of staircase or incremental positive end-expiratory pressure (PEEP) recruitment maneuvers (strong recommendation, moderate quality of evidence);
- the Panel recommends using an inhaled pulmonary vasodilator as a rescue therapy; if no rapid improvement in oxygenation is observed, the patient should be tapered off treatment (weak recommendation, expert opinion).

For mechanically ventilated adults with COVID-19 and ARDS:

- The Panel recommends using low tidal volume (VT) ventilation (VT 4 to 8 mL/kg of predicted body weight) over higher VT ventilation (VT >8 mL/kg) (AI) (strong recommendation, high quality of evidence);
- The Panel recommends targeting plateau pressures of <30 cm H₂O (strong recommendation, moderate quality of evidence);
- The Panel recommends using a conservative fluid strategy over a liberal strategy (moderate recommendation, moderate quality of evidence);
- The Panel recommends using a higher PEEP strategy over a lower PEEP strategy for mechanically ventilated adults with COVID-19 and moderate to severe ARDS (moderate recommendation, moderate quality of evidence);
- The Panel recommends against the routine use of iNO (strong recommendation, moderate quality of evidence).

Therapeutic Utilization of Inhaled Nitric Oxide

There is a lack of published studies on patients with COVID-19 and the use of iNO, but a Cochrane review of 13 trials evaluating iNO use in patients with ARDS showed a transient benefit for oxygenation. Although the Panel does not recommend routine use of iNO, it is reasonable to attempt using iNO as a rescue therapy after other options have failed in patients with COVID-19 and severe ARDS due to the results of this Cochrane review. However, iNO should be tapered quickly if it does not improve a patient's oxygenation to prevent rebound pulmonary vasoconstriction.¹⁵

Potential risks and challenges with COVID-19 patients include aerosolization and clogging of bacterial/viral filters used in ventilator circuits when pulmonary vasodilators are being administered. iNO may be preferred since it is associated with a lower need to change filters with resultant reduction in the risk to the respiratory healthcare provider.²⁸

Coding Implications

This clinical policy references Current Procedural Terminology (CPT[®]). CPT[®] is a registered trademark of the American Medical Association. All CPT codes and descriptions are copyrighted 2024, American Medical Association. All rights reserved. CPT codes and CPT descriptions are from the current manuals and those included herein are not intended to be all-inclusive and are included for informational purposes only. Codes referenced in this clinical policy are for informational purposes only. Inclusion or exclusion of any codes does not guarantee coverage. Providers should reference the most up-to-date sources of professional coding guidance prior to the submission of claims for reimbursement of covered services.

CPT [®] Codes	Description
94799	Unlisted pulmonary service or procedure

HCPCS Codes	Description
N/A	

Reviews, Revisions, and Approvals	Revision Date	Approval Date
Policy developed, Neonatologist reviewed	08/13	08/13
Added requirement that iNO be delivered via endotracheal tube or tracheostomy.	05/19	05/19
In continuation criteria, clarified that member/enrollee must have previously met initial approval criteria.	01/20	
Annual review completed. Codes and references checked and updated. P29.3 changed to P29.30-P29.38 and I27.2 changed to I27.20 - I27.29.	04/20	4/20
Added iNO as medically necessary for COVID-19, severe ARDS, and hypoxemia despite optimized ventilation and other rescue strategies. Updated background. Added the following ICD-10 codes: J80, J96.01, U07.1 and U07.2	04/20	05/20

Therapeutic Utilization of Inhaled Nitric Oxide

Reviews, Revisions, and Approvals	Revision Date	Approval Date
Corrected calculation of Oxygen Index in I.A.2.IV. Updated background with no impact on criteria. References added. Replaced “member” with “member/enrollee.”	11/20	
References reviewed and updated.	04/21	04/21
Added indications for case by case review of iNO initiation for preterm infants <34 weeks at birth to section II. Split continuation criteria into section III, and not medically necessary indications are now section IV. Minor rewording of background. Added reference 35. Changed “Review Date” in policy header to “Date of Last Revision,” and “Date” in the revision log table header to “Revision Date.”	07/21	07/21
Annual Review. Spelled out “partial pressure of oxygen” in I.B.1.e. and “inhaled nitric oxide” in IV. Updated description and background with no impact on criteria. References reviewed and updated. Specialist reviewed.	04/22	04/22
Annual review. Policy title updated from “Inhaled Nitric Oxide” to “Therapeutic Utilization of Inhaled Nitric Oxide.” Minor rewording in Description, criteria I.B.1., I.B.1.a., I.B.1.b., and I.B.1.c. Added recommended iNO dose in criteria I.B.1.e. Minor rewording in criteria I.B.2.b. Minor rewording in criteria II., II.B.1.a., II.B.1.c., and II.B.1.d. Removed response requirement of “within two hours” in criteria II.B.1.e. and added recommended iNO dose in criteria II.B.1.e. Minor rewording in criteria II.B.2.b. and in criteria III. Added clarifying language to criteria III.A.1. and minor rewording to criteria III.A.2. Updated notation in criteria III. from 48 hours to 72 hours. Minor rewording in criteria IV. and in criteria Treatment Regimen section. Background updated with no impact on criteria. Removed ICD-10 codes. References reviewed and updated. Reviewed by internal specialist.	04/23	04/23
Annual review. Condensed criteria statement II. to, “while the medical literature predominantly does not support the use of inhaled nitric oxide (iNO) in premature infants < 34 weeks gestational age at birth, requests for initiation of iNO therapy in these infants may be reviewed on a case-by-case basis with consideration of the criteria for premature newborns ≥ 34 weeks gestational age at birth in section I.” References reviewed and updated. Reviewed by external specialist.	05/24	05/24
Corrected May 2024 revision log entry to include, removed criteria I.A., “iNO will be administered via endotracheal tube or tracheostomy,” and, updated oxygen index from ≥ 25 to > 20 in criteria I.A.6. Added additional indication I.B.1.a.3) right ventricular failure.	07/24	
Updated criteria IV. from “adult respiratory distress” to “acute respiratory distress”.	11/24	11/24
Annual review. Merged changes and revision log entries from 11/24 and 7/24 policy versions. Under I.A.6. changed oxygen index (OI) >20 to 25. Moved I.A.7. to III.A.1. Removed criteria under III.A.1. Continues	04/25	04/25

Reviews, Revisions, and Approvals	Revision Date	Approval Date
to require iNO as evidenced...References reviewed and updated. Reviewed by internal specialist.		

References

1. Barrington KJ, Finer N, Pennaforte T. Inhaled nitric oxide for respiratory failure in preterm infants. *Cochrane Database Syst Rev*. 2017;1(1):CD000509. Published 2017 Jan 3. doi:10.1002/14651858.CD000509.pub5
2. Ichinose F, Roberts JD Jr, Zapol WM. Inhaled nitric oxide: a selective pulmonary vasodilator: current uses and therapeutic potential. *Circulation*. 2004;109(25):3106 to 3111. doi:10.1161/01.CIR.0000134595.80170.62
3. Barrington KJ, Finer N, Pennaforte T, Altit G. Nitric oxide for respiratory failure in infants born at or near term. *Cochrane Database Syst Rev*. 2017;1(1):CD000399. Published 2017 Jan 5. doi:10.1002/14651858.CD000399.pub3
4. Guthrie SO, Walsh WF, Auten K, Clark RH. Initial dosing of inhaled nitric oxide in infants with hypoxic respiratory failure. *J Perinatol*. 2004;24(5):290 to 294. doi:10.1038/sj.jp.7211087
5. Peliowski A; Canadian Paediatric Society, Fetus and Newborn Committee. Inhaled nitric oxide use in newborns. *Paediatr Child Health*. 2012;17(2):95 to 100. doi:10.1093/pch/17.2.95
6. Kumar P; Committee on Fetus and Newborn; American Academy of Pediatrics. Use of inhaled nitric oxide in preterm infants. *Pediatrics*. 2014;133(1):164 to 170. doi:10.1542/peds.2013-3444
7. Kinsella JP, Steinhorn RH, Krishnan US, et al. Recommendations for the Use of Inhaled Nitric Oxide Therapy in Premature Newborns with Severe Pulmonary Hypertension. *J Pediatr*. 2016;170:312 to 314. doi:10.1016/j.jpeds.2015.11.050
8. Stark AR, Eichenwald EC. Persistent pulmonary hypertension of the newborn (PPHN): management and outcome. UpToDate. www.uptodate.com. Published March 08, 2023. Accessed March 3, 2025.
9. Martin, R. Respiratory distress syndrome in preterm infants: management. UpToDate. www.uptodate.com. Published April 13, 2022. Accessed March 3, 2025.
10. Carey WA, Weaver AL, Mara KC, Clark RH. Inhaled Nitric Oxide in Extremely Premature Neonates With Respiratory Distress Syndrome [published correction appears in *Pediatrics*. 2018 Oct;142(4):]. *Pediatrics*. 2018;141(3):e20173108. doi:10.1542/peds.2017-3108
11. Gebistorf F, Karam O, Wetterslev J, Afshari A. Inhaled nitric oxide for acute respiratory distress syndrome (ARDS) in children and adults. *Cochrane Database Syst Rev*. 2016;2016(6):CD002787. Published 2016 Jun 27. doi:10.1002/14651858.CD002787.pub3
12. 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;(7):CD005055. Published 2014 Jul 3. doi:10.1002/14651858.CD005055.pub3
13. Soll RF. Inhaled nitric oxide in the neonate. *J Perinatol*. 2009;29 Suppl 2:S63 to S67. doi:10.1038/jp.2009.40
14. Abman SH, Hansmann G, Archer SL, et al. Pediatric Pulmonary Hypertension: Guidelines From the American Heart Association and American Thoracic Society [published correction

Therapeutic Utilization of Inhaled Nitric Oxide

- appears in *Circulation*. 2016 Jan 26;133(4):e368]. *Circulation*. 2015;132(21):2037 to 2099. doi:10.1161/CIR.0000000000000329
15. National Institute of Health. Coronavirus Disease 2019 (Covid-19) Treatment Guidelines. Oxygenation and Ventilation for Adults. <https://www.covid19treatmentguidelines.nih.gov/management/critical-care-for-adults/oxygenation-and-ventilation-for-adults/>. Updated March 1, 2024. Accessed March 3, 2025.
 16. Anesi GL. COVID-19: management of the intubated adult. UpToDate. www.uptodate.com. Published March 14, 2023. Accessed March 3, 2025.
 17. Hopkins W, Rubin LJ. Treatment of pulmonary arterial hypertension (group 1) in adults: Pulmonary hypertension-specific therapy. UpToDate. www.uptodate.com. Published March 15, 2023. Accessed March 3, 2025.
 18. Siegel MD, Siemieniuk R. Acute respiratory distress syndrome: Fluid management, pharmacotherapy, and supportive care in adults. UpToDate. www.uptodate.com. Published March 28, 2023. Accessed March 3, 2025.
 19. Klinger JR. Inhaled nitric oxide in adults: biology and indications for use. UpToDate. www.uptodate.com. Published June 27, 2022. Accessed March 3, 2025.
 20. Miller OI, Tang SF, Keech A, Pigott NB, Beller E, Celermajer DS. Inhaled nitric oxide and prevention of pulmonary hypertension after congenital heart surgery: a randomised double-blind study. *Lancet*. 2000;356(9240):1464 to 1469. doi:10.1016/S0140-6736(00)02869-5
 21. Granton J, Langleben D, Kutryk MB, et al. Endothelial NO-Synthase Gene-Enhanced Progenitor Cell Therapy for Pulmonary Arterial Hypertension: The PHACeT Trial. *Circ Res*. 2015;117(7):645 to 654. doi:10.1161/CIRCRESAHA.114.305951
 22. Sardo S, Osawa EA, Finco G, et al. Nitric Oxide in Cardiac Surgery: A Meta-Analysis of Randomized Controlled Trials. *J Cardiothorac Vasc Anesth*. 2018;32(6):2512 to 2519. doi:10.1053/j.jvca.2018.02.003
 23. Collura CA, Mara KC, Weaver AL, Clark RH, Carey WA. Outcomes of early inhaled nitric oxide use in premature African American neonates. *J Perinatol*. 2018;38(12):1657 to 1665. doi:10.1038/s41372-018-0232-6
 24. 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;342(7):469 to 474. doi:10.1056/NEJM200002173420704
 25. Putnam LR, Tsao K, Morini F, et al. Evaluation of Variability in Inhaled Nitric Oxide Use and Pulmonary Hypertension in Patients With Congenital Diaphragmatic Hernia. *JAMA Pediatr*. 2016;170(12):1188 to 1194. doi:10.1001/jamapediatrics.2016.2023
 26. Health Technology Assessment. Inhaled nitric oxide for the treatment of respiratory failure in preterm newborns. Hayes. www.hayesinc.com. Published November 06, 2018 (annual review January 24, 2023). Accessed March 3, 2025.
 27. DiBlasi RM, Dupras D, Kearney C, Costa E Jr, Griebel JL. Nitric oxide delivery by neonatal noninvasive respiratory support devices. *Respir Care*. 2015;60(2):219 to 230. doi:10.4187/respcare.03278
 28. Gebistorf F, Karam O, Wetterslev J, Afshari A. Inhaled nitric oxide for acute respiratory distress syndrome (ARDS) in children and adults. *Cochrane Database Syst Rev*. 2016;2016(6):CD002787. Published 2016 Jun 27. doi:10.1002/14651858.CD002787.pub3

Therapeutic Utilization of Inhaled Nitric Oxide

29. Morales-Blanchir J, Santos S, de Jover L, et al. Clinical value of vasodilator test with inhaled nitric oxide for predicting long-term response to oral vasodilators in pulmonary hypertension. *Respir Med*. 2004;98(3):225 to 234. doi:10.1016/j.rmed.2003.09.019
30. Ellsworth KR, Ellsworth MA, Weaver AL, Mara KC, Clark RH, Carey WA. Association of Early Inhaled Nitric Oxide With the Survival of Preterm Neonates With Pulmonary Hypoplasia. *JAMA Pediatr*. 2018;172(7):e180761. doi:10.1001/jamapediatrics.2018.0761
31. Soll RF. Inhaled Nitric Oxide for Preterm Infants: What Can Change Our Practice?. *Pediatrics*. 2018;141(3):e20174214. doi:10.1542/peds.2017-4214
32. Carey WA, Weaver AL, Mara KC, Clark RH. Inhaled Nitric Oxide in Extremely Premature Neonates With Respiratory Distress Syndrome [published correction appears in *Pediatrics*. 2018 Oct;142(4):]. *Pediatrics*. 2018;141(3):e20173108. doi:10.1542/peds.2017-3108
33. Mandell EW, Kratimenos P, Abman SH, Steinhorn RH. Drugs for the Prevention and Treatment of Bronchopulmonary Dysplasia. *Clin Perinatol*. 2019;46(2):291 to 310. doi:10.1016/j.clp.2019.02.011
34. Chandrasekharan P, Lakshminrusimha S, Abman SH. When to say no to inhaled nitric oxide in neonates?. *Semin Fetal Neonatal Med*. 2021;26(2):101200. doi:10.1016/j.siny.2021.101200
35. Stritzke A, Bhandari V, Lodha A. Use of Inhaled Nitric Oxide in Preterm Infants: Is There Sufficient Evidence?. *Indian J Pediatr*. 2022;89(3):262 to 266. doi:10.1007/s12098-021-03827-0
36. Society CP. Inhaled nitric oxide use in newborns | Canadian Paediatric Society. cps.ca. Accessed March 3, 2025. <https://cps.ca/en/documents/position/inhaled-nitric-oxide#:~:text=iNO%20may%20be%20considered%20as>
37. Chock V, Van Meurs K, Hintz S, et al. Inhaled Nitric Oxide for Preterm Premature Rupture of Membranes, Oligohydramnios, and Pulmonary Hypoplasia. *American Journal of Perinatology*. 2008;26(04):317-322. doi:https://doi.org/10.1055/s-0028-1104743
38. Abman SH, Hansmann G, Archer SL, et al. Pediatric Pulmonary Hypertension. *Circulation*. 2015;132(21):2037-2099. doi:https://doi.org/10.1161/cir.0000000000000329
39. Lakshminrusimha S, Gugino SF, Sekar K, et al. Inhaled Nitric Oxide at Birth Reduces Pulmonary Vascular Resistance and Improves Oxygenation in Preterm Lambs. *Children*. 2021;8(5):378. doi:https://doi.org/10.3390/children8050378
40. Schäfer M, Frank B, D. Dunbar Ivy, et al. Short-Term Effects of Inhaled Nitric Oxide on Right Ventricular Flow Hemodynamics by 4-Dimensional–Flow Magnetic Resonance Imaging in Children With Pulmonary Arterial Hypertension. 2021;10(8). doi:https://doi.org/10.1161/jaha.120.020548
41. Mourani PM, Ivy DD, Gao D, Abman SH. Pulmonary vascular effects of inhaled nitric oxide and oxygen tension in bronchopulmonary dysplasia. *Am J Respir Crit Care Med*. 2004;170(9):1006-1013. doi:10.1164/rccm.200310-1483OC
42. Sehgal A, Blank D, Roberts CT, Menahem S, Hooper SB. Assessing pulmonary circulation in severe bronchopulmonary dysplasia using functional echocardiography. *Physiol Rep*. 2021;9(1):e14690. doi:10.14814/phy2.14690
43. Konduri GG, Solimano A, Sokol GM, et al. A randomized trial of early versus standard inhaled nitric oxide therapy in term and near-term newborn infants with hypoxic respiratory failure. *Pediatrics*. 2004;113(3 Pt 1):559-564. doi:10.1542/peds.113.3.559

Therapeutic Utilization of Inhaled Nitric Oxide

44. Zheng Y, Wu Q, Han S. Inhaled nitric oxide in premature infants for preventing bronchopulmonary dysplasia: a meta-analysis. *BMC Pediatrics*. 2023;23(1). doi:<https://doi.org/10.1186/s12887-023-03923-4>
45. 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;219:167-172. doi:10.1016/j.jpeds.2019.09.052
46. Mullaly R, McCallion N, El-Khuffash A. Inhaled nitric oxide in preterm neonates with preterm prelabour rupture of membranes, a systematic review. *Acta Paediatr*. 2023;112(3):358-371. doi:10.1111/apa.16596
47. Peliowski A, Finer NN, Etches PC, Tierney AJ, Ryan CA. Inhaled nitric oxide for premature infants after prolonged rupture of the membranes. *J Pediatr*. 1995;126(3):450-453. doi:10.1016/s0022-3476(95)70467-1

Important Reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. “Health Plan” means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan’s affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment or medical care. It is not intended to dictate to providers how to practice medicine. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible

Therapeutic Utilization of Inhaled Nitric Oxide

for the medical advice and treatment of member/enrollees. This clinical policy is not intended to recommend treatment for member/enrollees. Member/enrollees should consult with their treating physician in connection with diagnosis and treatment decisions.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

This clinical policy is the property of the Health Plan. Unauthorized copying, use, and distribution of this clinical policy or any information contained herein are strictly prohibited. Providers, member/enrollees and their representatives are bound to the terms and conditions expressed herein through the terms of their contracts. Where no such contract exists, providers, member/enrollees and their representatives agree to be bound by such terms and conditions by providing services to member/enrollees and/or submitting claims for payment for such services.

Note: For Medicaid member/enrollees, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.

Note: For Medicare member/enrollees, to ensure consistency with the Medicare National Coverage Determinations (NCD) and Local Coverage Determinations (LCD), all applicable NCDs, LCDs, and Medicare Coverage Articles should be reviewed prior to applying the criteria set forth in this clinical policy. Refer to the CMS website at <http://www.cms.gov> for additional information.

©2018 Centene Corporation. All rights reserved. All materials are exclusively owned by Centene Corporation and are protected by United States copyright law and international copyright law. No part of this publication may be reproduced, copied, modified, distributed, displayed, stored in a retrieval system, transmitted in any form or by any means, or otherwise published without the prior written permission of Centene Corporation. You may not alter or remove any trademark, copyright or other notice contained herein. Centene[®] and Centene Corporation[®] are registered trademarks exclusively owned by Centene Corporation.