MEDICAL POLICY STATEMENT
TrueCare

Policy Name & Number	Date Effective
Inhaled Nitric Oxide-TrueCare-MM-1452	07/01/2025
Policy Type	
MEDICAL	

Medical Policy Statements are derived from literature based on and supported by clinical guidelines, nationally recognized utilization and technology assessment guidelines, other medical management industry standards, and published MCO clinical policy guidelines. Medically necessary services include, but are not limited to, those health care services or supplies that are proper and necessary for the diagnosis or treatment of disease, illness, or injury and without which the patient can be expected to suffer prolonged, increased, or new morbidity, impairment of function, dysfunction of a body organ or part, or significant pain and discomfort. These services meet the standards of good medical practice in the local area, are the lowest cost alternative, and are not provided mainly for the convenience of the member or provider. Medically necessary services also include those services defined in any Evidence of Coverage or Certificate of Coverage documents, Medical Policy Statements, Provider Manuals, Member Handbooks, and/or other plan policies and procedures.

Medical Policy Statements do not ensure an authorization or payment of services. Please refer to the plan contract (often referred to as the Evidence of Coverage or Certificate of Coverage) for the service(s) referenced in the Medical Policy Statement. Except as otherwise required by law, if there is a conflict between the Medical Policy Statement and the plan contract, then the plan contract will be the controlling document used to make the determination.

According to the rules of Mental Health Parity Addiction Equity Act (MHPAEA), coverage for the diagnosis and treatment of a behavioral health disorder will not be subject to any limitations that are less favorable than the limitations that apply to medical conditions as covered under this policy.

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A. Subject

Inhaled Nitric Oxide (iNO)

B. Background

Inhaled Nitric oxide (iNO) is a lipophilic gas naturally produced in numerous cells in the body and readily absorbed across pulmonary membranes in the ventilated lung after inhalation. In the body, nitric oxide is involved in oxygen transport to the tissues, the transmission of nerve impulses, and other physiological activities. When administered via inhalation, it is a potent endogenous vasodilator that induces relaxation of vascular and bronchial smooth muscle, vasodilation of blood vessels, and can increase the partial pressure of arterial oxygen. iNO was initially approved by the U.S. Food and Drug Administration (FDA) in 1999. 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. Additional warnings and precautions were added in 2013, including rebound hypertension following abrupt discontinuation, hypoxia from methemoglobinemia, and airway injury from nitrous dioxide.

Dilation of pulmonary vessels in well-ventilated lung areas redistributes blood flow away from lung areas where ventilation/perfusion ratios are poor. iNO has been used in conjunction with ventilator support as a treatment of hypoxic respiratory failure associated with persistent pulmonary hypertension of the newborn (PPHN), in infants who are at term or near-term (greater than 34 weeks gestation) to improve oxygenation, and to decrease the need for extracorporeal membrane oxygenation (ECMO).

Respiratory failure is a clinical state defined either by the inability to rid the body of carbon dioxide or establish an adequate blood oxygen level. Acute respiratory failure is the most common clinical problem seen in term, near-term (born at 34 or more weeks of gestation), and pre-term (less than 34 weeks of gestation) infants admitted to neonatal intensive care units. Acute respiratory failure is frequently associated with meconium aspiration syndrome, sepsis, pulmonary hypoplasia, and/or primary pulmonary hypertension of the newborn.

Management of infants with respiratory failure includes administration of high concentrations of oxygen, hyperventilation, high-frequency ventilation, neuromuscular blockade, antenatal steroids for the prevention of respiratory distress syndrome, use of post-natal steroids to decrease inflammation, as well as iNO therapy.

Clinical studies have shown that iNO is a selective pulmonary vasodilator without significant effects on the systemic circulation. There is scientific evidence that iNO therapy improves oxygenation and ventilation, reduces the need for extracorporeal membrane oxygenation (ECMO), and lowers the incidences of chronic lung disease and death among infants with respiratory failure. Moreover, the literature indicates that iNO does not appear to increase the incidence of adverse neurodevelopmental, behavioral, or medical sequelae in these high-risk neonates. Infants with congenital diaphragmatic hernia (CDH) have not been shown to benefit from iNO therapy. Clark, et al (2000)

concluded iNO does not lead to reduced ECMO use and Putnam, et al (2016) concluded iNO use in CDH may be associated with increased mortality.

In preterm infants, the most common cause of acute respiratory failure is respiratory distress syndrome as a result of surfactant deficiency. According to the available literature, treatment of preterm infants usually entails exogenous surfactant administration. A systematic review of the evidence (Barrington and Finer, 2003) concluded: "The currently published evidence from randomized trials does not support the use of inhaled nitric oxide in preterm infants with hypoxic respiratory failure." Carey, et al (2018) also concluded, “Off-label prescription of iNO is not associated with reduced in-hospital mortality among premature infants with respiratory distress syndrome (RDS).”

In an Agency for Healthcare Research and Quality’s assessment on *Inhaled Nitric Oxide in Preterm Infants*, Allen, et al (2010) systematically reviewed the evidence on the use of iNO in preterm infants born at or before 34 weeks gestation age who receive respiratory support. They searched MEDLINE, EMBASE, the Cochrane Central Register of Controlled Studies (CENTRAL) and PsycInfo in June 2010. They also searched the proceedings of the 2009 and 2010 Pediatric Academic Societies Meeting and ClinicalTrials.gov. They identified additional studies from reference lists of eligible articles and relevant reviews, as well as from technical experts. Questions were developed in collaboration with technical experts, including the chair of the upcoming National Institutes of Health Office of Medical Applications of Research Consensus Development Conference. These researchers limited their review to randomized controlled trials (RCTs) for the question of survival or occurrence of bronchopulmonary dysplasia (BPD), and for the question on short-term risks. All study designs were considered for long-term pulmonary or neurodevelopmental outcomes, and for questions about whether outcomes varied by subpopulation or by intervention characteristics. Two investigators independently screened search results and abstracted data from eligible articles. These investigators identified a total of 14 RCTs, reported in 23 articles, and 8 observational studies. Chronic Lung Disease (CLD) or BPD studies have shown that there is insufficient evidence to support iNO for the treatment of CLD or BPD.

Mortality rates in the neonatal intensive care unit (NICU) did not differ for infants treated with iNO versus those not treated with iNO (RR 0.97 (95 % CI: 0.82 to 1.15)). Broncho-pulmonary dysplasia at 36 weeks for iNO and control groups also did not differ (RR 0.93 (0.86, 1.003) for survivors). A small difference was found between iNO and control infants in the composite outcome of death or BPD (RR 0.93 (0.87, 0.99)). There was inconsistent evidence about the risk of brain injury from individual RCTs, but meta-analyses showed no difference between iNO and control groups. These researchers found no evidence of differences in other short-term risks. There was no evidence to suggest a difference in the incidence of cerebral palsy (RR 1.36 (0.88, 2.10)), neurodevelopmental impairment (RR 0.91 (0.77, 1.12)), or cognitive impairment (RR 0.72 (0.35, 1.45)). Evidence was limited on whether the effect of iNO varies by subpopulation or by characteristics of the therapy (timing, dose and duration, mode of delivery, or concurrent therapies). The authors concluded that there was a 7% reduction

in the risk of the composite outcome of death or BPD at 36 weeks PMA for infants treated with iNO compared to controls, but no reduction in death or BPD alone. They stated that further studies are needed to explore subgroups of infants and to assess long-term outcomes including function in childhood. There is currently no evidence to support the use of iNO in preterm infants with respiratory failure outside the context of rigorously conducted RCTs.

To provide health care professionals, families, and the general public with a responsible assessment of currently available data regarding the benefits and risks of iNO in premature infants, the Eunice Kennedy Shriver National Institute of Child Health and Human Development, the National Heart, Lung, and Blood Institute, and the Office of Medical Applications of Research of the National Institutes of Health (Cole, et al, 2011) convened a consensus-development conference. Findings from a substantial body of experimental work in developing animals and other model systems suggest that iNO may enhance lung growth and reduce lung inflammation independently of its effects on blood vessel resistance. Although this work demonstrates biological plausibility and the results of RCTs in term and near-term infants were positive, combined evidence from the 14 RCTs of iNO treatment in premature infants of gestation of 34 weeks or less shows equivocal effects on pulmonary outcomes, survival, and neurodevelopmental outcomes.

A National Institutes of Health Consensus Development Conference for inhaled nitric oxygen in premature infants (Cole, et al, 2010) recommended the following:

1. Taken as a whole, the available evidence does not support use of iNO in early routine, early rescue, or later rescue regimens in the care of premature infants <34 weeks gestation who require respiratory support.
2. There are rare clinical situations, including pulmonary hypertension or hypoplasia, that have been inadequately studied in which iNO may have benefit in infants <34 weeks gestation. In such situations, clinicians should communicate with families regarding the current evidence on its risks and benefits as well as remaining uncertainties.
3. Basic research and animal studies have contributed to important understandings of iNO benefits on lung development and function in infants at high risk of BPD. These promising results have only partly been realized in clinical trials of iNO treatment in premature infants. Future research should seek to understand this gap.
4. Predefined subgroup and post hoc analyses of previous trials showing potential benefit of iNO have generated hypotheses for future research for clinical trials. Prior strategies shown to be ineffective are discouraged unless new evidence emerges. The positive results of one multicenter trial, which was characterized by later timing, higher dose, and longer duration of treatment, require confirmation. Future trials should attempt to quantify the individual effects of each of these treatment-related variables (timing, dose, and duration), ideally by randomizing them separately.
5. Based on assessment of currently available data, hospitals, clinicians, and the pharmaceutical industry should avoid marketing iNO for premature infants <34 weeks gestation.

An American Academy of Pediatrics clinical report on the use of iNO in preterm infants (Kumar, et al, 2014) concluded the following:

1. The results of randomized controlled trials, traditional meta-analyses, and an individualized patient data meta-analysis study indicate that neither rescue nor routine use of iNO improves survival in preterm infants with respiratory failure (Evidence quality, A; Grade of recommendation, strong).
2. The preponderance of evidence does not support treating preterm infants who have respiratory failure with iNO for the purpose of preventing/ameliorating BPD, severe intraventricular hemorrhage, or other neonatal morbidities (Evidence quality, A; Grade of recommendation, strong).
3. The incidence of cerebral palsy, neurodevelopmental impairment, or cognitive impairment in preterm infants treated with iNO is similar to that of control infants (Evidence quality, A).
4. The results of 1 multicenter, randomized controlled trial suggest that treatment with a high dose of iNO (20 ppm) beginning in the second postnatal week may provide a small reduction in the rate of BPD. However, these results need to be confirmed by other trials.
5. An individual-patient data meta-analysis that included 96% of preterm infants enrolled in all published iNO trials found no statistically significant differences in iNO effect according to any of the patient-level characteristics, including gestational age, race, oxygenation index, postnatal age at enrollment, evidence of pulmonary hypertension, and mode of ventilation.
6. There are limited data and inconsistent results regarding the effects of iNO treatment on pulmonary outcomes of preterm infants in early childhood.

There has been a suggestion that premature infants with pulmonary hypertension and prolonged rupture of membranes or chorioamnionitis improve with initiation of inhaled nitric oxide. The numbers of infants looked at were very small and further investigation would be necessary to support this specific use.

Following surgical intervention, children and adults can experience life-threatening reactive or persistent elevated pulmonary arterial pressure, or pulmonary hypertension. Due to its specificity for the pulmonary vascular bed, iNO acts directly on pulmonary vascular smooth muscle. Because of its ability to decrease pulmonary vascular resistance (PVR) and intrapulmonary shunting, and increase oxygenation, iNO is an established treatment option for pulmonary hypertension following surgical repair of congenital heart disease.

Randomized controlled trials, non-randomized comparative studies and case series reported that iNO effectively lowered pulmonary vascular resistance and pulmonary artery pressure in children and adults with pulmonary hypertension after open heart surgery. However, it did not appear to increase the survival rate in those with severe pulmonary hypertension. Studies have shown that in children with pulmonary hypertension crises (PHC)/acute right ventricular (RV) failure, iNO may be used as the initial therapy for pulmonary hypertensive crisis (PHCs) and failure of the right side of the

heart. iNO is commonly used to treat postoperative PH in CHD patients. A retrospective review suggested that iNO may reduce mortality following repair of atrioventricular septal defects.

Studies have shown that the effectiveness of iNO in the post-operative management of infants and children with congenital heart disease. iNO versus placebo and/or conventional management on infants and children with congenital heart disease showed no differences with the use of iNO as compared with control in the majority of outcomes reviewed.

There is still emerging evidence about the treatment and management of bronchopulmonary dysplasia (BPD) related PH. Oxygen is the first line treatment and pulmonary vasodilator for this condition. Evidence is limited but inhaled nitric oxide is the most commonly used second line agent due to the selective pulmonary bed vasodilatory effects. Expert opinion suggests it is reasonable to initiate iNO for acute BPD related PH crisis until patient can be transitioned to enteral agents.

Studies have shown that there is insufficient evidence to support the use of iNO to improve outcomes in children and adults with acute respiratory failure (ARF), hypoxemic respiratory failure (HRF) and acute hypoxemic respiratory failure (AHRF) for the prevention of ischemia-reperfusion injury/acute rejection following lung transplantation, or the treatment of vaso-occlusive crises in patients with sickle cell disease. Studies have shown that iNO produced modest improvements in oxygenation for up to 72 hours, but had no effect on mortality when used for acute hypoxemic respiratory failure (including acute lung injury (ALI), adult respiratory distress syndrome (ARDS), and other diagnoses) in adults and children and appears to increase the risk of renal impairment among adults.

Studies have shown that there is insufficient evidence to support the use of iNO to improve outcomes for acute chest syndrome (ACS) in patients with sickle cell anemia. Lang, et al (2014) conducted a two-center randomized controlled trial to assess the effectiveness of iNO vs. placebo for enhancing allograft function in the immediate post-operative period and reducing longer term complications in 40 liver transplant patients. Subjects were excluded if age was less than 19 years, diagnosed with hepatopulmonary syndrome and/or allograft was being used for split liver transplantation. There were no significant differences between the groups in intensive care and hospital length of stay, or post-operative hepatobiliary complications within the first nine months post-transplantation. There were no reported adverse events due to iNO administration.

Studies have shown that there is insufficient evidence to support the use of iNO to improve outcomes for right heart failure after hemorrhagic shock and trauma pneumonectomy and patients with acute pulmonary embolism.

In patients with bronchiolitis, the study by González de Dios J (2010), was unable to detect a difference in side effects using intermittent high dose iNO or supportive

treatment alone in infants with moderate bronchiolitis. Tal A, Greenberg D, and colleagues (2018) concluded that this study was unable to detect a difference in side effects using intermittent high dose iNO or supportive treatment alone in infants with moderate bronchiolitis. iNO has been trialed to enhance antibiotic treatment in infections of patients with Cystic Fibrosis, however, further studies are needed to define dosing, duration, and long-term clinical outcomes.

Nitric oxide did not reduce mortality in patients with severe Acute Respiratory Distress Syndrome (ARDS) or mild-moderate ARDS. ARDS is the acute onset of pulmonary edema in the absence of volume overload or depressed left ventricular function. There was a statistically significant increase in renal failure in the iNO study groups. There is insufficient evidence to support iNO in any category of critically ill patients with ARDS. Inhaled nitric oxide resulted in a transient improvement in oxygenation but did not reduce mortality and may be harmful, as it seemed to increase renal impairment.

Studies have shown that treating malaria with iNO was associated with reduced risk of fine motor impairment. However, these results need to be validated in a larger study.

iNO has been proposed to be of benefit in the intraoperative management of patients in the setting of right ventricular dysfunction after LVAD insertion. However, data supporting favorable clinical outcomes are lacking. Acute pulmonary embolism is typically a complication secondary to migration of a deep venous clot or thrombi to the lungs and is associated with considerable morbidity and mortality. There is insufficient evidence to support iNO for the treatment of PE.

C. Definitions

- **Corrected Gestational Age** – Gestational age at birth plus the number of weeks old equals corrected gestational age (Eg, 24 weeks gestational age at birth + 10 weeks old = 34 weeks corrected gestational age).
- **Extracorporeal Membrane Oxygenation (ECMO)** – Temporary support of heart and lung function by partial cardiopulmonary bypass (up to 75% of cardiac output). It is used for patients who have reversible cardiopulmonary failure from pulmonary, cardiac, or other disease.
- **Hypoxic Respiratory Failure** – A serious condition that develops when the lungs cannot provide oxygen into the blood to reach the tissues of the body.
- **Nitric Oxide (NO)** – Also called nitrogen monoxide, a colorless lipophilic gas that is formed by the oxidation of nitrogen that performs important chemical signaling functions in humans and other animals and has various applications in medicine.
- **Oxygen Index (OI)** – Used to assess severity of hypoxic respiratory failure (HRF) and persistent pulmonary hypertension of the newborn (PPHN). OI= Mean Airway Pressure x Fio2 x 100/ partial pressure of arterial oxygen.
- **Persistent Pulmonary Hypertension of the Newborn (PPHN)** – Reflects failure of the pulmonary vasculature to relax at birth, which results in increased pulmonary arterial pressure and pulmonary vasculature resistance that leads to shunting of deoxygenated blood into the systemic circulation.

- **Bronchopulmonary dysplasia (BPD)** – Chronic lung disease that generally occurs due to multiple factors in premature infants.

D. Policy

I. TrueCare considers the initiation of iNO therapy medically necessary for treating near-term (≥ 34 weeks corrected gestational age) and term infants with hypoxic respiratory failure or evidence of persistent pulmonary hypertension when **ALL** of the following conditions are present:
   A. Conventional therapies (eg, mechanical ventilation, administration of high concentrations of oxygen (80-100%), high frequency oscillatory ventilation (HFOV), induction of respiratory alkalosis, neuromuscular blockade and sedation) have failed or are expected to fail.
   B. Absence of ductal dependent congenital heart disease.
   C. Evidence of PPHN, such as echocardiographic findings, results of a right heart catheterization or abnormal oxygen index/arterial blood gases that are NOT related to another medical condition.

II. TrueCare considers the use of iNO therapy medically appropriate for **ANY** of the following clinical conditions:
   A. post-operative management of neonates ≥ 34 weeks corrected gestational age after repair of congenital heart disease with evidence of pulmonary hypertension
   B. post-operative management following pediatric heart or lung surgery with evidence of pulmonary hypertension.
   C. management of pulmonary hypertension during a heart catheterization to determine pulmonary vasoreactivity
   D. Management of BPD related pulmonary hypertension during acute crisis (patients with chronic pulmonary hypertension related to BPD should be transitioned to enteral therapy when acute crisis improves).

III. INO therapy for more than 3 days is subject to medical necessity review with medical record documentation to support continued use. (If there is a lack of a positive response to therapy with inability to wean O2 and/or INO after 3 days, then discontinuation of INO therapy should be considered.)

IV. TrueCare considers the use of iNO not medically necessary for the following indications:
   A. congenital diaphragmatic hernia
   B. acute bronchiolitis
   C. bronchopulmonary dysplasia
   D. acute pulmonary embolism
   E. acute respiratory distress syndrome
   F. acute lung injury
   G. lung transplantation
   H. liver transplantation
   I. pulmonary fibrosis

J. hemorrhagic shock
K. pneumonectomy post trauma
L. cystic fibrosis
M. malaria

E. Conditions of Coverage

NA

F. Related Policies/Rules

NA

G. Review/Revision History

	DATE	ACTION
Date Issued	03/12/2025	New policy. Approved at Committee.
Date Revised		
Date Effective	07/01/2025	
Date Archived		

H. References

1. Abman SH, Hansmann G, Archer SL, et al. Pediatric Pulmonary Hypertension: Guidelines From the American Heart Association and American Thoracic Society [published correction appears in Circulation. 2016 Jan 26;133(4):e368. doi: 10.1161/CIR.0000000000000363]. *Circulation*. 2015;132(21):2037-2099. doi:10.1161/CIR.0000000000000329
2. Adhikari N, Granton JT. Inhaled nitric oxide for acute lung injury: no place for NO? *JAMA*. 2004;291(13):1629-1631. doi:10.1001/jama.291.13.1629
3. Adhikari NK, Burns KE, Friedrich JO, et al. Effect of nitric oxide on oxygenation and mortality in acute lung injury: systematic review and meta-analysis. *BMJ*. 2007;334:779. doi:10.1136/bmj.39139.716794.55
4. Adhikari NKJ, Dellinger RP, Lundin S, et al. Inhaled nitric oxide does not reduce mortality in patients with acute respiratory distress syndrome regardless of severity: systematic review and meta-analysis. *Crit Care Med*. 2014;42(2):404-412. doi:10.1097/CCM.0b013e3182a27909
5. Afshari A, Brok J, Moller AM, Wetterslev J. Inhaled nitric oxide for acute respiratory distress syndrome (ARDS) in children and adults. *Cochrane Database Syst Rev*. 2016;(6):CD002787. doi:10.1002/14651858.CD002787.pub3
6. Al Hajeri A, Serjeant GR, Fedorowicz Z. Inhaled nitric oxide for acute chest syndrome in people with sickle cell disease. *Cochrane Database Syst Rev*. 2008;(1):CD006957. doi:10.1002/14651858.CD006957
7. Allen MC, Donohue P, Gilmore M, et al. *Evidence Report/Technology Assessment No. 195: Inhaled Nitric Oxide in Preterm Infants*. Agency for Healthcare Research and Quality; 2010. AHRQ publication no. 11-E001. Accessed December 16, 2024. www.ahrq.gov

8. Arul N, Konduri GG. Inhaled nitric oxide for preterm neonates. *Clin Perinatol*. 2009;36(1):43-61. doi:10.1016/j.clp.2008.09.002
9. Ballard RA, Truog WE, Cnaan A, et al; NO CLD Study Group. Inhaled nitric oxide in preterm infants undergoing mechanical ventilation. *N Engl J Med*. 2006;355(4):343-353. doi:10.1056/NEJMoa061088
10. Barrington KJ, Finer NN, Pennaforte T, Altit G. Nitric oxide for respiratory failure in infants born at or near term. *Cochrane Database Syst Rev*. 2017;1:CD000399. doi:10.1002/14651858.CD000399.pub3
11. Barrington KJ, Finer NN, Pennaforte T, Altit G. Inhaled nitric oxide for respiratory failure in preterm infants. *Cochrane Database Syst Rev*. 2017;1:CD000509. doi:10.1002/14651858.CD000509.pub5
12. Berger JT, Maddux AB, Reeder RW, et al; Eunice Kennedy Shriver National Institute of Child Health and Human Development Collaborative Pediatric Critical Care Research Network. Inhaled nitric oxide use in pediatric hypoxemic respiratory failure. *Pediatr Crit Care Med*. 2020;21(8):708-719. doi:10.1097/PCC.0000000000002310
13. Bhat T, Neuman A, Tantary M, et al. Inhaled nitric oxide in acute pulmonary embolism: a systematic review. *Rev Cardiovasc Med*. 2015;16(1):1-8. doi:10.3909/ricm0718
14. 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. doi:10.1002/14651858.CD005055.pub3
15. British Cardiac Society Guidelines and Medical Practice Committee; British Thoracic Society; British Society of Rheumatology. Recommendations on the management of pulmonary hypertension in clinical practice. *Heart*. 2001;86(Suppl 1):i1-i13. Accessed December 16, 2024. www.ncbi.nlm.nih.gov
16. Brunner N, de Jesus Perez VA, Richter A, et al. Perioperative pharmacological management of pulmonary hypertensive crisis during congenital heart surgery. *Pulm Circ*. 2014;4(1):10-24. doi:10.1086/674885
17. Canadian Congenital Diaphragmatic Hernia Collaborative; Puligandla PS, Skarsgard ED, Offringa M, et al. Diagnosis and management of congenital diaphragmatic hernia: a clinical practice guideline. *CMAJ*. 2018;190(4):E103-E112. doi:10.1503/cmaj.170206
18. Carey WA, Weaver AL, Mara KC, Clark RH. Inhaled nitric oxide in extremely premature neonates with respiratory distress syndrome. *Pediatrics*. 2018;141(3):e20173108. doi:10.1542/peds.2017-3108
19. Clark RH, Kueser TJ, Walker MW, et al; Clinical Inhaled Nitric Oxide Research Group. Low-dose nitric oxide therapy for persistent pulmonary hypertension of the newborn. *N Engl J Med*. 2000;342(7):469-474. doi:10.1056/NEJM200002173420704
20. Cole FS, Alleyne C, Barks JD, et al. NIH Consensus Development Conference statement: inhaled nitric-oxide therapy for premature infants. *Pediatrics*. 2011;127(2):363-369. doi:10.1542/peds.2010-350721
21. Corrected age for preemies. American Academy of Pediatrics. Updated December 10, 2018. Accessed December 16, 2024. www.healthychildren.org

22. Dani C, Corsini I, Cangemi J, Vangi V, Pratesi S. Nitric oxide for the treatment of preterm infants with severe RDS and pulmonary hypertension. *Pediatr Pulmonol*. 2017;52(11):1461-1468. doi:10.1002/ppul.23843
23. Dzierba AL, Abel EE, Buckley MS, Lat I. A review of inhaled nitric oxide and aerosolized epoprostenol in acute lung injury or acute respiratory distress syndrome. *Pharmacotherapy*. 2014;34(3):279-290. doi:10.1002/phar.1365
24. El-Saie A, Varghese NP, Webb MK, et al. Bronchopulmonary dysplasia - associated pulmonary hypertension: An updated review. Semin Perinatol. 2023;47(6):151817. doi:10.1016/j.semperi.2023.151817
25. Gildea TR, Arroliga AC, Minai OA. Treatment and strategies to optimize the comprehensive management of patients with pulmonary arterial hypertension. *Cleve Clin J Med*. 2003;70(Suppl 1):S18-S27. doi:10.3949/ccjm.70.suppl_1.s18
26. Gladwin MT, Kato GJ, Weiner D, et al; DeNOVO Investigators. Nitric oxide for inhalation in the acute treatment of sickle cell pain crisis: a randomized controlled trial. *JAMA*. 2011;305(9):893-902. doi:10.1001/jama.2011.235
27. Gorenflo M, Gu H, Xu Z. Peri-operative pulmonary hypertension in paediatric patients: current strategies in children with congenital heart disease. *Cardiology*. 2010;116(1):10-17. doi:10.1159/000313864
28. Hajeri AA, Serjeant GR, Fedorowicz Z. Inhaled nitric oxide for acute chest syndrome in people with sickle cell disease. *Cochrane Database Syst Rev.* 2008;(1):CD006957. doi:10.1002/14651858.CD006957
29. Hedrick HL, Adzick NS. Congenital diaphragmatic hernia in the neonate. UpToDate. Updated July 19, 2023. Accessed December 16, 2024. www.uptodate.com
30. Karam O, Gebistorf F, Wetterslev J, Afshari A. The effect of inhaled nitric oxide in acute respiratory distress syndrome in children and adults: a Cochrane Systematic Review with trial sequential analysis. *Anaesthesia*. 2017;72(1):106-117. doi:10.1111/anae.13628
31. Kato GJ, Gladwin MT. Evolution of novel small-molecule therapeutics targeting sickle cell vasculopathy. *JAMA*. 2008;300(22):2638-2646. doi:10.1001/jama.2008.598
32. Kinsella JP, Cutter GR, Walsh WF, et al. Early inhaled nitric oxide therapy in premature newborns with respiratory failure. *N Engl J Med*. 2006;355(4):354-364. doi:10.1056/NEJMoa060442
33. Kinsella JP, Cutter GR, Steinhorn RH, et al. Noninvasive inhaled nitric oxide does not prevent bronchopulmonary dysplasia in premature newborns. *J Pediatr*. 2014;165(6):1104-1108. doi:10.1016/j.jpeds.2014.06.018
34. Kumar P; Committee on Fetus and Newborn. Use of inhaled nitric oxide in preterm infants. *Pediatrics*. 2014;133(1):164-170. doi:10.1542/peds.2013-3444
35. Loukanov T, Bucsenez D, Springer W, et al. Comparison of inhaled nitric oxide with aerosolized iloprost for treatment of pulmonary hypertension in children after cardiopulmonary bypass surgery. *Clin Res Cardiol*. 2011;100(7):595-602. doi:10.1007/s00392-011-0284-5
36. Mercier JC, Hummler H, Durrmeyer X, et al; EUNO Study Group. Inhaled nitric oxide for prevention of bronchopulmonary dysplasia in premature babies (EUNO): a randomised controlled trial. *Lancet*. 2010;376(9738):346-354. doi:10.1016/S0140-6736(10)60664-2

37. Porta NFM, Steinhorn RH. Inhaled NO in the experimental setting. *Early Hum Dev*. 2008;84(11):717-723. doi:10.1016/j.earlhumdev.2008.08.004
38. Putnam LR, Tsao K, Morini F, et al; Congenital Diaphragmatic Hernia Study Group. Evaluation of variability in inhaled nitric oxide use and pulmonary hypertension in patients with congenital diaphragmatic hernia. *JAMA Pediatr*. 2016;170(12):1188-1194. doi:10.1001/jamapediatrics.2016.2023
39. Recommendations for the Use of Inhaled Nitric Oxide Therapy in Premature Newborns with Severe Pulmonary Hypertension Kinsella, John P. et al. The Journal of Pediatrics, Volume 170, 312 - 314
40. Sokol J, Jacobs SE, Bohn D. Inhaled nitric oxide for acute hypoxic respiratory failure in children and adults: a meta-analysis. *Anesth Analg*. 2003;97(4):989-998. doi:10.1213/01.ANE.0000078819.48523.26
41. Soll RF. Inhaled nitric oxide in the neonate. *J Perinatol*. 2009;29(Suppl 2):S63-S67. doi:10.1038/jp.2009.40
42. Stark AR. Inhaled NO for preterm infants- getting to yes? *N Engl J Med*. 2006;355(4):404-406. doi:10.1056/NEJMe068129
43. Stark AR, Eichenwald EC. Bronchopulmonary dysplasia (BPD): prevention. UpToDate. Updated November 13, 2023. Accessed December 16, 2024. www.uptodate.com
44. Tal A, Greenberg D, Av-Gay Y, et al. Nitric oxide inhalations in bronchiolitis: a pilot, randomized, double-blinded, controlled trial. *Pediatr Pulmonol*. 2018;53(1):95-102. doi:10.1002/ppul.23905
Van Meurs KP, Wright LL, Ehrenkranz RA, et al; Preemie Inhaled Nitric Oxide Study. Inhaled nitric oxide for premature infants with severe respiratory failure. *N Engl J Med*. 2005;353(1):13-22. doi:10.1056/NEJMoa043927

Independent medical review – 6/29/2020