Medical Policy

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(See policy history boxes for previous effective dates)

Title: Inhaled Nitric Oxide (iNO)

Description/Background

Inhaled nitric oxide is a treatment for neonates with hypoxic respiratory failure that is intended to improve oxygenation, reduce mortality rates and reduce the need for invasive extracorporeal membrane oxygenation (ECMO). It is also proposed as a treatment for premature infants, critically ill children and adults with respiratory failure, and in the postoperative management of children undergoing repair of congenital heart disease and in lung transplantation to prevent or reduce reperfusion injury.

HYPOXIC RESPIRATORY FAILURE

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

Treatment

Its treatment typically includes oxygen support, mechanical ventilation and induction of alkalosis, neuromuscular blockade or sedation.

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

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

Regulatory Status

In 1999, INOmax™ (Ikaria®, Clinton, NJ) was approved by the U.S. Food and Drug Administration (FDA) through the 510(k) process for the following indication: “INOmax, in conjunction with randomized support and other appropriate agents, is indicated for the treatment of term and near-term (greater than 34 weeks) neonates with hypoxic respiratory failure associated with clinical or echocardiographic evidence of pulmonary hypertension.” In 2015, Mallinckrodt (Dublin, Ireland) acquired Ikaria. FDA product code: MRN

In 2014, Advanced Inhalation Therapies received orphan drug designation for its proprietary formulation of nitric oxide as an adjunctive treatment of cystic fibrosis.

In 2019, Genosyl® (nitric oxide for inhalation; Vero Biotech, LLC) received FDA approval to "improve oxygenation and reduce the need for extracorporeal membrane oxygenation in term and near-term (>34 weeks gestation) neonates with hypoxic respiratory failure associated with clinical or echocardiographic evidence of pulmonary hypertension." In April 2021, the GENOSYL DS Nitric Oxide Delivery System was recalled due to a software issue that leads to errors in the delivery of nitric oxide. For impacted devices, the issue was corrected with the release of Software 2.2.4.[1]

In 2020, FDA granted emergency expanded access for INOpulse (Bellerophon Therapeutics) inhaled nitric oxide delivery system for treating COVID-19.

Medical Policy Statement

The safety and effectiveness of the use of inhaled nitric oxide have been established. It may be considered a useful therapeutic option for patients meeting specific patient selection criteria.

Inclusionary and Exclusionary Guidelines

Inclusions:
The following individuals may be considered appropriate candidates for inhaled nitric oxide (iNO) therapy:

- When used as a component of treatment of hypoxic respiratory failure* in neonates at or greater than 34 weeks of gestation.
- iNO therapy for post-operative management of pulmonary hypertensive crisis in infants and children with congenital heart disease.
- iNO therapy as a method of assessing pulmonary vaso-reactivity in persons with pulmonary hypertension.

Exclusions
Other indications for inhaled nitric oxide are experimental/investigational including but not limited to its use in:

- Premature neonates less than or equal to 34 weeks of gestation
- Adults and children with acute respiratory distress syndrome (ARDS)/acute hypoxemic respiratory failure
- Patients with sickle cell disease
- Patients following elective LVAD insertion surgery.
- In lung transplantation, during and/or after graft reperfusion.
- Treatment beyond 2 weeks.
- Combined ECMO and iNO treatment.
- In neonates with a diaphragmatic hernia without persistent pulmonary hypertension of the newborn (PPHN).

For the above conditions, iNO has not been scientifically demonstrated to be as safe and effective as conventional treatment.

* Hypoxic respiratory failure is defined as an oxygenation index (OI) of at least 25 on 2 measurements done 15 minutes apart.

Note:
- The oxygenation index [OI] is calculated as the mean airway pressure times the fraction of inspired oxygen divided by the partial pressure of arterial oxygen times 100. An OI of 25 is associated with a 50% risk of requiring extracorporeal membrane oxygenation [ECMO] or dying. An OI of 40 is often used as a criterion to initiate ECMO therapy. It is used in iNO research trials to identify study participants with severe hypoxic respiratory failure.
- In clinical practice, an OI may not be available in neonates due to lack of arterial access. Alternative non-invasive measures such as pulse oximetry, ventilator data, transcutaneous CO^2 monitoring, and echocardiograms are often used to define respiratory failure and pulmonary hypertension to avoid multiple invasive arterial blood draws.

CPT/HCPCS Level II Codes *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure.)*

Established codes:

94799

Other codes (investigational, not medically necessary, etc.):

N/A

Rationale

Evidence reviews assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are length of life, quality of life, and ability to function—including benefits and harms. Every clinical condition has specific outcomes that are important to patients and to managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of a technology, 2 domains are examined: the relevance and the quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

HYPOXIC RESPIRATORY FAILURE IN TERM OR LATE PRETERM NEONATES

Clinical Context and Therapy Purpose

The purpose of inhaled nitric oxide (iNO) is to provide a treatment option that is an alternative to or an improvement on existing therapies in individuals who are neonates, are term or late preterm at birth, and have hypoxic respiratory failure.

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest are individuals who are neonates, are term or late preterm at birth, and have hypoxic respiratory failure.

Interventions

The therapy being considered is iNO. iNO is a natural vasodilator and has been studied for a variety of types of respiratory failure. Most commonly, it is used as an initial treatment for neonates with hypoxic respiratory failure to improve oxygenation and reduce the need for invasive extracorporeal membrane oxygenation (ECMO). In late preterm neonates, iNO primarily functions as a vasodilator to treat pulmonary hypertension, often due to meconium aspiration or bacterial pneumonia. However, in earlier preterm neonates with respiratory failure, pulmonary hypertension with shunting is less of a risk. Therefore, these two groups of neonates represent distinct clinical issues, and the results of iNO in late preterm neonates cannot be extrapolated to preterm neonates. Also, the risk of intraventricular hemorrhage associated with INO is higher in premature infants.

Comparators

The following practice is currently being used to treat hypoxic respiratory failure in term or late preterm neonates: standard neonatal specialty care without INO managed by neonatologists and pulmonologists in an inpatient clinical setting.

Outcomes

The general outcomes of interest are overall survival (OS), hospitalizations, resource utilization, and treatment-related morbidity (Table 1).

Table 1. Outcomes of Interest

Outcomes	Details	Timing
Resource utilization	Evaluated through outcomes such as requirement for ECMO before hospital discharge	1 week to 6 months
Treatment-related morbidity	Evaluated through outcomes such as rates of adverse events including bronchopulmonary dysplasia and severe intracranial hemorrhage	1 week to 6 months

BPD: bronchopulmonary dysplasia; ECMO: extracorporeal membrane oxygenation.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence

Systematic Reviews

A number of randomized controlled trials (RCTs) and a Cochrane review of RCT data on inhaled nitric oxide (iNO) in infants with hypoxia born at or near-term (>34 weeks' gestation) have been published. The Cochrane review, last updated in 2017, identified 17 trials.[2] Ten trials compared iNO with control (placebo or standard neonatal intensive care without iNO) in infants with moderate severity of illness scores. Another of these allowed backup treatment with iNO and 2 enrolled only infants with diaphragmatic hernia. Another six trials included infants with moderately severe disease and compared immediate iNO with iNO only when infants' conditions deteriorated to a more severe level of illness. The remaining trial compared iNO with high-frequency ventilation. In all of the studies, hypoxemic respiratory failure was required for study entry, and most also required echocardiographic evidence of persistent pulmonary hypertension. The main findings of the meta-analysis are provided in Table 2. Only findings in studies that did not allow backup iNO and that were not limited to patients with diaphragmatic hernia are presented; there were too few studies on other subgroups to allow meaningful meta-analysis.

Table 2. Main Cochrane Findings on iNO in Term or Near Term Infants

Trials	N	Outcome/End Point	RR	95% CI	P	I^2	Quality of Evidence (Grade)
8	860	Death before hosp D/C	0.89	0.60 to 1.31	0.55	0%	High

7	815	ECMO before hosp D/C	0.60	0.50 to 0.71	<0.001	0%	High
8	859	Death or requirement of ECMO	0.66	0.57 to 0.77	<0.001	0%	High

Adapted from Barrington et al (2017)
CI: confidence interval; ECMO: Extracorporeal membrane oxygenation; INO: inhaled nitric oxide
[a] QOE assessed using the GRADE tool

Reviewers found that iNO in hypoxic infants reduced the incidence of the combined end point of death or need for ECMO compared with controls, in studies that did not allow iNO backup in controls. iNO did not have a statistically significant effect on mortality as a sole outcome measure; however, there was a significant effect of iNO on the need for ECMO only. The analysis of mortality alone may have been underpowered.

Section Summary: Hypoxic Respiratory Failure in Term or Late Pre-Term Neonates
Evidence from RCTs and a meta-analysis of RCTs support the use of iNO in term or near-term infants to improve the net health outcome. Pooled analyses of RCT data have found that iNO leads to a significant reduction in the need for ECMO or death and a significant reduction of ECMO use before hospital discharge.

HYPOXIC RESPIRATORY FAILURE IN PREMATURE NEONATES

Clinical Context and Therapy Purpose
The purpose of iNO is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients who are neonates, are premature at birth, and have hypoxic respiratory failure.

The following PICO was used to select literature to inform this review.

Populations
The relevant population of interest is individuals who are neonates, are premature at birth, and have hypoxic respiratory failure.

Interventions
The therapy being considered is iNO. iNO is a natural vasodilator and has been studied for a variety of types of respiratory failure. Most commonly, it is used as an initial treatment for neonates with hypoxic respiratory failure to improve oxygenation and reduce the need for invasive ECMO.

Comparators
The following practice is currently being used to treat hypoxic respiratory failure in premature neonates: standard neonatal intensive care without INO. Patients who are neonates, are premature at birth, and have hypoxic respiratory failure are actively managed by neonatologists and pulmonologists in an inpatient clinical setting.

Outcomes
The general outcomes of interest are OS, hospitalizations, resource utilization, and treatment-related morbidity (Table 3).

Table 3. Outcomes of Interest

Outcomes	Details	Timing

Resource utilization	Evaluated through outcomes such as utilization of ECMO before hospital discharge	1 week to 6 months
Treatment-related morbidity	Evaluated through outcomes such as rates of adverse events including bronchopulmonary dysplasia and severe intracranial hemorrhage	1 week to 6 months

BPD: bronchopulmonary dysplasia; ECMO: Extracorporeal membrane oxygenation

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence

Systematic Reviews

Numerous RCTs and several systematic reviews on iNO for treating hypoxic respiratory failure in preterm neonates have been published. Most recently, a 2017 Cochrane review by Barrington et al, identified 17 RCTs on the efficacy of iNO for treating premature infants (i.e., <35 weeks of gestation) with respiratory disease.[3] The main findings of the meta-analysis are provided in Table 4. Results are reported separately for studies with entry before 3 days based on oxygenation, studies with entry after 3 days based on and bronchopulmonary dysplasia (BPD) risk and studies of routine use of iNO in premature infants on respiratory support. Pooled analyses of 3 or more studies are shown.

Table 4. Main Findings on INO in Preterm Infants

Trials	N	Outcome/End Point	RR	95% CI	P	I^2	Quality of Evidence[a] (Grade)
Death Before Hosp Discharge							
10	1066	Studies with entry before 3 days	1.02	0.89 to 1.18	0.75	3%	High
3	1075	Studies with entry after 3 days	1.18	0.81 to 1.71	0.39	0%	High
4	1924	Studies of routine use	0.90	0.74 to 1.10	0.32	50%	Moderate
BPD at 36 weeks of gestation							
8	681	Studies with entry before 3 days	0.89	0.76 to 1.04	0.13	29%	NR
3	990	Studies with entry after 3 days	0.91	0.83 to 1.01	0.068	11%	NR
4	1782	Studies of routine use	0.95	0.85 to 1.05	0.32	10%	NR
BPD or Death at 36 weeks of gestation							
8	957	Studies with entry before 3 days	0.94	0.87 to 1.01	0.084	26%	High
3	1075	Studies with entry after 3 days	0.92	0.85 to 1.01	0.079	51%	High
4	1924	Studies of routine use	0.94	0.87 to 1.02	0.12	11%	High

Adapted from Barrington et al (2017)[3]
BPD: bronchopulmonary dysplasia; CI: confidence interval; INO: inhaled nitric oxide; NR: not reported; QOE: quality of evidence.
[a] QOE assessed using the GRADE tool

Reviewers found that iNO in premature infants with respiratory failure did not significantly improve outcomes (e.g. death before hospital discharge, BPD at 36 weeks' postmenstrual age) or the combined outcome of BPD or death at 36 weeks' postmenstrual age. Findings were not statistically significant in subgroups of studies that enrolled patients before three days old, enrolled patients after 3 days and that used INO routinely. A fourth primary outcome, intraventricular hemorrhage was only pooled in studies with entry before 3 days and did not find a significant benefit of iNO versus control (RR: 0.94, 95% CI: 0.69 to 1.28).

A 2016 meta-analysis by Yang et al identified 22 trials comparing iNO to a control intervention in preterm infants.[4] Reviewers did not report a definition of "preterm" for identifying studies beyond use of the keyword in literature searches. A pooled analysis of all 22 studies did not find a significant difference between groups in mortality (RR: 1.00, 95% CI 0.92 to 1.09). There was also no significant difference between iNO and control in the rate of severe intracranial hemorrhage in a pooled analysis of 17 studies (RR: 0.99, 95% CI: 0.83 to 1.16). However, a pooled analysis of 20 studies found a significantly lower rate of BPD in the iNO compared with control groups (RR: 0.88, 95% CI: 0.82 to 0.95). The authors noted that their findings on BPD differed from those in other meta-analyses and stated that the difference may be due to their inclusion of Chinese language studies.

Previously, in 2011, an Agency for Healthcare Research and Quality (AHRQ)-sponsored systematic review of randomized trials on iNO for premature infants (less than 35 weeks' gestation) was published.[5] Thirty-one articles were initially selected; these included 14 unique RCTs. Studies had sample sizes ranging from 29 to 800, and data from 3,461 infants were available for the review. The primary outcomes of the AHRQ analysis were survival and bronchopulmonary dysplasia (BPD). Regardless of how mortality was reported or defined (e.g., death within 7 days or 28 days, or death in the neonatal intensive care unit), there was no statistically significant difference between the iNO group and control group in any of the 14 RCTs, or in pooled analyses of RCTs. For example, in a pooled analysis of 11 trials that reported death by 36 weeks' postmenstrual age or in the neonatal intensive care unit, the RR was 0.97 (95% CI, 0.82 to 1.15). Twelve trials reported data on BPD at 36 weeks' postmenstrual age, and despite variations in reporting of BPD, there was no significant benefit of iNO treatment in any trial. A pooled analysis of data from 8 trials reporting BPD at 36 weeks' postmenstrual age among survivors resulted in a RR of 0.93 (95% CI, 0.86 to 1.00).

Randomized Controlled Trials

The largest trial to date was published in 2010 by Mercier et al.[6] This was a multicenter industry-sponsored study known as the European Union Nitric Oxide trial and it evaluated low-dose iNO therapy. Of 800 patients, 792 (99%) received their assigned treatment, and all 800 were included in the intention-to-treat analysis. Primary outcomes were survival without BPD at 36 weeks of postmenstrual age, OS at 36 weeks of postmenstrual age, and BPD at 36 weeks of postmenstrual age. The number of patients with BPD at 36 weeks of postmenstrual age was 81 (24%) in the INO group and 96 (27%) in the control group (RR, 0.83; 95% CI, 0.58 to 1.17; p=.29). The secondary endpoint (survival without brain injury at gestational age 36 weeks) also did not differ significantly between groups (RR, 0.78; 95% CI, 0.53 to 1.17; p=.23). This endpoint was attained by 181 (69%) patients in the INO group and 188 (76%) patients in the placebo group. The most common adverse event was intracranial hemorrhage, which affected 114 (29%) in the INO group and 91 (23%) in the control group (p value not reported). Durrmeyer et al (2013) published 2-year outcomes of the EUNO trial.[7] Of the original 800 patients, 737 (92%) were evaluable at this time point. There were also no statistically significant differences between groups in other outcomes (e.g., hospitalization rates, use of

respiratory medications, growth). At 7 years of follow-up, 305 patients were available for evaluation, with no deaths reported from the end of the 2-year follow-up to the 7-year follow-up and no significant differences in any questionnaire-documented health outcomes between groups.[7] Tables 5 and 6 summarize the key characteristics and results of the EUNO trial and its 2- and 7-year follow-ups.

Table 5. Summary of Key RCT Characteristics

Study; Trial	Countries	Sites	Dates	Participants	Interventions	
					Active	Comparator
Mercier (2010); EUNO[5]	EU	35	2005-2008	Preterm infants (between 24 and 28 weeks gestational age) weighing ≥500 g and requiring surfactant within 24 hours of birth	INO 5 ppm (n=399)	Placebo-equivalent nitrogen gas (n=401)
Durrmeyer (2013); EUNO[6]	EU	35	2005-2008	Infants born at <29 weeks gestational age with moderate respiratory failure	INO 5 ppm (n=306)	Placebo-equivalent nitrogen gas (n=324)
Greenough (2021); EUNO[7]	EU	24	2005-2008	Preterm infants (between 24 and 28 weeks gestational age) weighing ≥500 g and requiring surfactant within 24 hours of birth	INO 5 ppm (n=152)	Placebo-equivalent nitrogen gas (n=153)

EU: European Union; EUNO: European Union Nitric Oxide trial; INO: inhaled nitric oxide; RCT: randomized controlled trial.

Table 6. Summary of Key RCT Results

Study	Survival Outcomes	Adverse Events
Mercier (2010); EUNO[5]	OS at 36 weeks postmenstrual age	Serious adverse events[a]
INO	343 (86%)	158 (40%)
Placebo	359 (90%)	164 (41%)
RR; 95% CI; p-value	0.74; 0.48 to 1.15;.21	NR; NR;.72
	Survival without BPD at 36 weeks postmenstrual age	
INO	258 (65%)	
Placebo	262 (66%)	
RR; 95% CI; p-value	1.05; 0.78 to 1.43;.73	
Durrmeyer (2013); EUNO[6]	OS between 36 weeks postmenstrual age and 2 years	
INO	391 (99%)	
Placebo	390 (98.2%)	
RR; 95% CI; p-value	NR; NR; NR	
	Survival without severe or moderate disability at 2 years	

INO	244 (79.7%)	
Placebo	270 (83.3%)	
RR; 95% CI; P-value	NR; NR;.29	
Greenough (2021); EUNO[7]	Hospitalization rates - end of 2 years to the 7-year follow-up	
INO	44 (28.9%)	
Placebo	53 (34.6%)	
p-value	.29	
	Proportion of patients using respiratory medications at 7 years	
INO	10 (6.6%)	
Placebo	14 (9.2%)	
p-value	.40	

AEs: adverse events; BPD: bronchopulmonary dysplasia; CI: confidence interval; EUNO: European Union Nitric Oxide trial; INO: inhaled nitric oxide; NR: not reported; OS: overall survival; RCT: randomized controlled trial; RR: risk ratio.
[a] Serious AEs included intraventricular hemorrhage, periventricular leukomalacia, patient ductus arteriosus, pneumothorax, pulmonary hemorrhage, necrotizing enterocolitis, and sepsis.

The purpose of the study design and conduct limitation table (see Table 7) is to display notable limitations identified in each study. This information is synthesized as a summary of the body of evidence following each table and provides the conclusions on the sufficiency of evidence supporting the position statement. No relevance limitations were noted from these trials.

Table 7. Study Design and Conduct Limitations

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
Mercier (2010); EUNO[5]	3. Allocation concealment unclear					
Durrmeyer (2013); EUNO[6]	3. Allocation concealment unclear					3. Confidence intervals not reported for all outcomes
Greenough (2021); EUNO[7]	3. Allocation concealment unclear					3. Confidence intervals not reported

EUNO: European Union Nitric Oxide trial.
The evidence limitations stated in this table are those notable in the current review; this is not a comprehensive limitations assessment.
[a] Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.
[b] Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.
[c] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
[d] Follow-Up key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials).
[e] Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.
[f] Statistical key: 1. Intervention is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Intervention is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4.Comparative treatment effects not calculated.

Section Summary: Hypoxic Respiratory Failure in Premature Neonates
A large number of RCTs evaluate iNO for premature neonates, with most of the trials reporting no difference on the primary endpoints such as mortality and BPD. Meta-analyses of these RCTs have not found better survival rates in patients who receive iNO compared with a control intervention. Most meta-analyses did not find other outcomes (e.g., BPD and intracranial hemorrhage) were improved by iNO.

ACUTE HYPOXEMIC RESPIRATORY FAILURE IN ADULTS AND CHILDREN

Clinical Context and Therapy Purpose
The purpose of iNO is to provide a treatment option that is an alternative to or an improvement on existing therapies in individuals who are adults or children in acute hypoxemic respiratory failure.

The following PICO was used to select literature to inform this review.

Populations
The relevant population of interest is individuals who are adults or children in acute hypoxemic respiratory failure.

Interventions
The therapy being considered is INO. INO is a natural vasodilator and has been studied for a variety of types of respiratory failure.

Comparators
The following practice is currently being used to treat acute hypoxemic respiratory failure in adults and children: standard medical intensive care without INO. This is managed by pulmonologists and primary care providers in an inpatient clinical setting.

Outcomes
The general outcomes of interest are OS, hospitalizations, resource utilization, and treatment-related morbidity.

Table 8. Outcomes of Interest

Outcomes	Details	Timing
Treatment-related morbidity	Evaluated through outcomes such as rates of adverse events including renal dysfunction	1 week-6 months

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.

- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence

Systematic Reviews

Several meta-analyses and RCTs have evaluated the efficacy of iNO for treating acute respiratory distress syndrome (ARDS) and acute lung injury (together known as acute hypoxemic respiratory failure [AHRF]). A Cochrane review by Gebistorf et al (2016) identified 14 RCTs comparing iNO with control in adults and children with ARDS.[9] The primary objective of the review was to evaluate the effects of iNO on mortality, which was measured in several ways. The main findings of the meta-analysis are provided in Table 9.

Table 9. Main Cochrane Findings on INO in Patients with ARDS

Trials	N	Outcome/End Point	RR	95% CI	p	I^2	QOE[a]
11	1243	Overall mortality	1.04	0.90 to 1.19	0.63	0%	Moderate
9	1105	Mortality at 28 to 30 days	1.08	0.92 to 1.27	0.36	0%	Moderate
		Overall mortality stratified by age group					
3	185	Pediatric	0.78	0.51 to 1.18	0.24	22%	Moderate
10	1085	Adult	1.09	0.93 to 1.25	0.32	0%	NR

Adapted from Gebistorf et al (2016)[8]
ARDS: acute respiratory distress syndrome: CI: confidence interval; INO: inhaled nitric oxide; NR: not reported; QOE: quality of evidence.a QOE assessed using the GRADE tool.
[a]QOE assessed using the GRADE tool.

iNO was not found to significantly improve mortality when used to treat ARDS. Other outcomes (e.g., mean number of ventilator days and duration of mechanical ventilation) also did not differ significantly between groups. In terms of potential harms associated with iNO use in this population, a pooled analysis of 4 trials found a significantly higher rate of renal impairment in groups treated with iNO versus control (RR: 1.59, 95% CI: 1.17 to 2.16).

Other systematic reviews and meta-analyses had similar findings on mortality.[10, 11] For example, a 2014 meta-analysis by Adhikari et al identified 9 RCTs conducted with adults or children (other than neonates) in which at least 80% of patients, or a separately reported subgroup, had ARDS.[10] Moreover, the trials included in the review compared iNO with placebo or no gas, used iNO as a treatment of ARDS (i.e., not a preventive measure), and had less than 50% crossover between groups. Findings were not stratified by adult and pediatric populations. A pooled analysis of data from the 9 trials (total N=1142 patients) found no statistically significant benefit of iNO on mortality (RR=1.10; 95% CI, 0.94 to 1.29; p=0.24). In a preplanned subgroup analysis, iNO did not reduce mortality in patients with severe ARDS (baseline partial pressure of oxygen, arterial [PaO^2]/fraction of expired oxygen [FIO^2] ≤100 mm Hg) or in patients with mild-to-moderate ARDS (baseline PaO_2/FIO_2 >100 mg Hg).

A systematic review by Prakash et al (2021) reviewed the impact of INO compared to standard of care in the treatment of severe ARDS in the context of the 2019 Coronavirus disease (COVID-19).[12] The review included 14 retrospective or prospective studies including

423patients (range, 5 to 169). Racial and ethnic demographics of patients included in these studies were not described. Across these studies, INO demonstrated a slight increase in oxygenation, but appeared to have no impact on mortality.

Adverse Events

A 2016 cohort study by Ruan et al evaluated the risk of renal dysfunction in patients with ARDS treated with iNO.[13] Using electronic medical record data from a teaching hospital, 547 patients with ARDS were identified. Among these patients, 216 had been treated with iNO and 331 had not received iNO. The 30-day incidence of renal replacement therapy (RRT) was 34% in the iNO group and 23% in the non-iNO group. In the final propensity-matched analysis, there was a significantly higher risk of need for RRT in the iNO versus the non-iNO group (hazard ratio [HR]: 1.59 (95% CI: 1.08 to 2.34, p=0.02). Similarly, in a meta-analysis of 15 RCTs involving 1853 patients, INO therapy was associated with a significant increase in the risk of acute kidney injury in patients with ARDS (RR, 1.55; 95% CI, 1.15 to 2.10; p=.004).[13]

Section Summary: Acute Hypoxemic Respiratory Failure in Adults and Children

A large number of RCTs have evaluated iNO for treatment of acute hypoxemic respiratory failure. Meta-analyses of these RCTs have not found that iNO significant reduces mortality or shortens the duration of mechanical ventilation. Moreover, a subanalysis by age group in a 2016 Cochrane review did not find a significant benefit of iNO on mortality in either pediatric or adult studies. There is evidence from a meta-analysis of 4 RCTs included in the Cochrane review and from a cohort study that iNO increases the risk of renal impairment in patients with ARDS.

ADULTS AND CHILDREN WITH CONGENITAL HEART DISEASE WHO HAVE HAD HEART SURGERY

Clinical Context and Therapy Purpose

The purpose of iNO is to provide a treatment option that is an alternative to or an improvement on existing therapies in individuals who are adults and children with congenital heart disease who have had heart surgery.

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is individuals who are adults and children with congenital heart disease who have had heart surgery.

Interventions

The therapy being considered is iNO. iNO is a natural vasodilator and has been studied for a variety of types of respiratory failure.

Comparators

The following practice is currently being used to treat adults and children with congenital heart disease who have had heart surgery: standard medical care without INO.

Outcomes

The general outcomes of interest are OS, hospitalizations, resource utilization, and treatment-related morbidity (Table 10).

Table 10. Outcomes of Interest

Outcomes	Details	Timing
Treatment-related morbidity	Evaluated through outcomes such as right ventricular dysfunction, pulmonary arterial hypertension, mean arterial pressure, and neurodevelopmental disability	1 week-6 months
Resource utilization	Evaluated through outcomes such as mean number of days on mechanical ventilation, length of stay in intensive care unit or hospital	1-6 weeks

RVD: right ventricular dysfunction.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence

Adults

A 2011 trial by Potapov et al evaluated the prophylactic use of inhaled NO in adult patients undergoing left ventricular-assist device (LVAD) implantation for congestive heart failure.[15] This double-blind trial was conducted at eight centers in the United States and Germany. Patients were randomized to receive inhaled nitric oxide (40 ppm) (n=74) or placebo (n=77) beginning at least 5 minutes before the first weaning attempt from mechanical ventilation. The primary study outcome was right ventricular dysfunction (RVD). Patients continued use of inhaled NO or placebo until they were extubated, reached the study criteria for RVD or were treated for 48 hours, whichever occurred first. Patients were permitted to crossover to open-label inhaled NO if they failed to wean from mechanical ventilation, still required pulmonary vasodilator support at 48 hours, or met criteria for RVD. Thirteen of 150 randomized patients (9%) did not receive the study treatment. In addition, crossover to inhaled NO occurred in 15 of 73 patients (21%) in the inhaled NO group and 20 of 77 (26%) in the placebo group. In an intention-to-treat (ITT) analysis, the RVD criteria were met by 7 of 73 (9.6%) patients in the inhaled NO group and 12 of 77 (15.6%) patients in the placebo group; this difference was not statistically significant (p=0.33). Other outcomes also did not differ significantly between groups. For example, the mean number of days on mechanical ventilation, 5.4 in the inhaled NO group and 11.1 in the placebo group (p=0.77), and the mean number of days in the hospital, 41 in each group.

Children

Systematic Reviews

A 2014 Cochrane review by Bizzarro et al identified four RCTs comparing postoperative INO versus placebo or usual care in the management of children with congenital heart disease.[16] All of the trials included participants who were identified as having pulmonary hypertension in the preoperative or postoperative period. Studies included a total of 210 participants. Three trials were parallel group trials, and 3 was a crossover trial. Mortality was the primary outcome

of the Cochrane meta-analysis. Two trials with a total of 162 patients reported mortality before discharge. A pooled analysis of findings from these 2 trials did not find a significant difference in mortality between the group receiving INO compared with the control group (OR=1.67; 95% CI, 0.38 to 7.30). Among secondary outcomes, a pooled analysis of 2 studies did not find a significant between-group difference in mean pulmonary arterial hypertension (pooled treatment effect, -2.94 mm Hg; 95% CI, -9.28 to 3.40), and a pooled analysis of 3 studies did not find a significant difference between groups in mean arterial pressure (pooled treatment effect, -3.55 mm Hg; 95% CI, -11.86 to 4.76). Insufficient data were available for pooled analyses of other outcomes. The authors noted the lack of data on long-term mortality, length of stay in an intensive care unit or hospital, and neurodevelopmental disability, and also had concerns about methodologic quality of studies, sample size, and heterogeneity between studies. These results do not support a benefit for NO treatment for this patient group. Wide Cis around the pooled treatment effects reflect the relatively small amount of data available on each outcome.

Randomized Controlled Trials

The RCT with the largest sample size was published by Miller et al in Australia in 2000.[17] The study included 124 infants (median age 3 months) who were candidates for corrective heart surgery. Eligibility requirements included presence of congenital heart lesions, high pulmonary flow, pressure or both, and objective evidence of pulmonary hypertension in the immediate preoperative period. Participants were randomized to receive inhaled NO gas 10 ppm (n=63) or placebo nitrogen gas (n=61) after surgery until just before extubation. Randomization was stratified by presence (45/124, 36%) or absence (79/124, 64%) of Down's syndrome. The primary outcome was reduction of pulmonary hypertensive crisis (PHTC) episodes, defined as a pulmonary/systemic artery pressure ratio more than 0.75. Episodes were classified as major if there was a fall in systemic artery pressure of at least 20% and/or a fall in transcutaneous oxygen saturation to less than 90%. Episodes were classified as minor if the systemic artery pressure and transcutaneous oxygen saturation remained stable. The study found that infants who received inhaled NO after surgery had significantly fewer PHTC (median=4) than those receiving placebo (median=7); unadjusted relative risk: 0.66; 95% CI: 0.59 to 0.74, p<.001. Among secondary outcomes, the median time until eligibility for extubation was significantly shorter in the inhaled NO than placebo group, 80 versus 112 hours, respectively, p=.019. There were 5 deaths in the inhaled NO group and 3 deaths in the placebo group; this difference was not statistically significant, p=.49. Similarly, there was not a significant difference in median time to discharge from intensive care, 138 hours in the NO group and 162 hours in the placebo group, p>.05. This trial does report a reduction in pulmonary hypertensive crisis episodes, but the changes in this physiologic outcome did not result in improvements in survival or other clinical outcomes. The study was likely to have been underpowered to detect differences in these more clinically relevant secondary outcomes.

Section Summary: Adults and Children With Congenital Heart Disease Who Have Had Heart Surgery

Evidence from a number of small RCTs and a systematic review of these trials did not find a significant benefit for INO on mortality and other health outcomes in the postoperative management of children with congenital heart disease. There is less evidence on the use of iNO for adults with congenital heart disease. One RCT did not find a significant effect of iNO treatment on the improvement of postoperative outcomes in adults with congestive heart failure who had left ventricular assist device surgery. However, practicing standards have evolved possibly beyond the available evidence. So, consideration of specialty society guidelines and subject matter expert input have led to acknowledgement that iNO therapy can

be effective for post-operative management of pulmonary hypertensive crisis in infants and children with congenital heart disease. Another established use for iNO in clinical practice is for acute vasoreactivity testing for pulmonary arterial hypertension. It is performed during right heart catheterization procedures to determine how much the pulmonary blood vessels can relax over a period of time and helps to identify individuals who might respond favorably to calcium channel blockers.

LUNG TRANSPLANTATION

Clinical Context and Therapy Purpose

The purpose of iNO is to provide a treatment option that is an alternative to or an improvement on existing therapies in individuals with lung transplant.

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is individuals with lung transplant.

Interventions

The therapy being considered is iNO. iNO is a natural vasodilator and has been studied for a variety of types of respiratory failure.

Comparators

The following practice is currently being used to treat patients with a lung transplant: standard post-transplant care without iNO. This is managed by transplant surgeons, pulmonologists, and primary care providers in an inpatient clinical setting.

Outcomes

The general outcomes of interest are OS, hospitalizations, resource utilization, and treatment-related morbidity (Table 11).

Table 11. Outcomes of Interest

Outcomes	Details	Timing
Resource utilization	Evaluated through outcomes such as length of hospital or ICU stay	1 to 6 weeks
Treatment-related morbidity	Evaluated through outcomes such as time to extubation, duration of ventilation, fluid balance during 24 hours after ICU admission, development of grade II to III primary graft dysfunction or gas exchange	1 week to 6 months

ICU: intensive care unit

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence

Systematic Reviews

Tavare and Tsakok (2011) reviewed the literature on whether prophylactic iNO in patients undergoing a lung transplant reduces morbidity and mortality.[18] They identified six relevant studies, 2 RCTs [Meade et al,[19] Perrin et al[20]] and four uncontrolled cohort studies. They also identified a third RCT [Botha et al[21]], which they excluded from the review because they did not view the outcomes in that study as clinically useful. The reviewers observed that there are few controlled studies and all published studies, including the RCTs, had small sample sizes. Moreover, they noted that no RCTs found that iNO reduced mortality or morbidity (e.g., time to extubation, length of hospital stay) and thus concluded, "it is difficult to currently recommend the routine use of prophylactic iNO in lung transplant surgery." Published RCTs are summarized in Table 12.

Table 12. Summary of RCTs Evaluating INO After Lung Transplantation

Author (Year)	N	Interventions	Primary End Points	Synopsis of Findings
Meade et al (2003)[19]	84	iNO 20 ppm 10 min after reperfusion vs. placebo gas mixture	Duration of mechanical ventilation from admission to ICU to first successful extubation	No statistically significant difference in time to successful extubation (mean, 25.7 h in iNO group vs. 27.3 h in control group; p=0.76). No statistically significant differences in secondary outcomes (e.g., severe reperfusion injury, time to hospital discharge, hospital mortality, 30-d mortality
Perrin et al (2006)[20]	30	iNO 20 ppm at reperfusion for 12 h vs. no intervention	Not specific	No statistically significant differences between groups on outcomes (e.g., ICU length of stay, duration of ventilation, fluid balance during 24 h after ICU admission)
Botha et al (2007)[21]	20	Prophylactic iNO 20 ppm vs. standard gas mixture during 30 min of reperfusion	Not specific	No statistically significant differences between groups in development of grade II-III primary graft dysfunction or gas exchange

ICU: intensive care unit; INO: inhaled nitric oxide; RCT: randomized controlled trial.

Section Summary: Lung Transplantation

Three small RCTs have evaluated iNO after lung transplantation and none found statistically significant improvements in health outcomes. A systematic review of RCTs and observational studies concluded that there is insufficient evidence to support routine use of iNO after lung transplant.

SUMMARY OF EVIDENCE

For individuals who are neonates and are term or late pre-term at birth and have hypoxic respiratory failure who receive inhaled nitric oxide (iNO), the evidence includes randomized controlled trials (RCTs) and a systematic review. Relevant outcomes are overall survival (OS), hospitalizations, resource utilization, and treatment-related morbidity. Evidence from RCTs and

a meta-analysis support the use of iNO in term or near-term infants. Pooled analyses of RCT data have found that iNO leads to a significant reduction in the need for extracorporeal membrane oxygenation (ECMO) and in the combined outcome of ECMO or death. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who are neonates, are premature at birth, and have hypoxic respiratory failure who receive iNO, the evidence consists of RCTs and systematic reviews. Relevant outcomes are overall survival, hospitalizations, resource utilization, and treatment-related morbidity. A large number of RCTs have evaluated iNO for premature neonates, and most trials have reported no significant difference on primary end points such as mortality and bronchopulmonary dysplasia (BPD). Meta-analyses of these RCTs have not found better survival rates in patients who receive iNO compared to a control intervention. Most meta-analyses did not find other outcomes e.g., BPD and intracranial hemorrhage were improved by iNO. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who are adults and children in acute hypoxemic respiratory failure (non-neonates) who receive iNO, the evidence consists of RCTs and systematic reviews. Relevant outcomes are overall survival, hospitalizations, resource utilization, and treatment-related morbidity. Several systematic reviews of RCTs have not found that this significantly influences mortality or duration of mechanical ventilation in adults or children with acute hypoxic respiratory failure. Meta-analyses of these RCTs have not found that iNO significant reduces mortality or shortens the duration of mechanical ventilation. There is some evidence from a meta-analysis of 4 RCTs and from a cohort study that iNO may be associated with an increased risk of renal impairment in patients with acute respiratory distress syndrome (ARDS). The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.
For individuals who are adults and children with congenital heart disease who have had heart surgery who receive iNO, the evidence consists of RCTs and a systematic review. Relevant outcomes are overall survival, hospitalizations, resource utilization, and treatment-related morbidity. Evidence from two retrospective reviews found that the use of iNO therapy for children with congenital heart disease after cardiac surgery in the described range of 5-40 ppm, resulting in a maximum of 4% methemoglobin blood level, is feasible and safe. In addition, Implementation of standardized iNO initiation and weaning guidelines successfully reduced mean iNO usage per event and variation in iNO usage without affecting the quality of care provided to the patients.

For individuals who are adults and children who have received iNO as a method of risk stratification for pulmonary hypertension, the evidence consists of one review and one case series. Vasodilator responsiveness to iNO is shown to be an important method of risk stratifying pulmonary hypertension patients. Although a number of vasodilators have been used for diagnostic testing during cardiac catheterization, iNO safely and effectively assesses the capacity for pulmonary vasodilation in pediatric and adult patients with pulmonary hypertension without causing systemic side effects that vasodilators such as prostacyclin and calcium channel blockers may cause.

For individuals who have lung transplant who receive iNO, the evidence consists of RCTs and a systematic review. Relevant outcomes are overall survival, hospitalizations, resource utilization, and treatment-related morbidity. Several small RCTs have evaluated iNO after lung

transplantation and have not found statistically significant improvement in health outcomes. A systematic review of RCTs and observational studies concluded that there is insufficient evidence to support routine use of iNO after lung transplant. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

SUPPLEMENTAL INFORMATION

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

Clinical Input Received Through Physician Specialty Societies and Academic Medical Centers:

While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

2021 Input

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

2012 Input

Input was received through two physician specialty societies and nine academic medical centers. There was consensus agreement that iNO may be considered medically necessary as a component of treatment of hypoxic respiratory failure in neonates born at more than 34 weeks of gestation. There was general agreement with the criterion in the Policy Guidelines section for hypoxic respiratory failure, i.e., an oxygenation index of at least 25 on 2 measurements made at least 15 minutes apart. In addition, input was mixed on whether other indications for iNO should be considered investigational. Several reviewers stated that they thought iNO is clinically useful for the postoperative treatment of selected patients with congenital heart disease.

Also, clinician reviewers generally agreed that iNO should be discontinued when ECMO is initiated. There was near-consensus agreement that prolonged use of iNO (e.g., beyond a week or 2 in near-term neonates) does not improve outcomes i.e., beyond a transient improvement in oxygenation. However, there was a wide range of responses to the question on how long iNO should be continued once it is initiated, with the majority of reviewers who responded citing an upper limit of not more than 2 weeks.

2010 Input

Input was received through four Physician Specialty Societies and five Academic Medical Centers. The clinical input was consistent in its agreement with the policy statements on treatment of hypoxic respiratory failure in neonates born at 34 or more weeks of gestation and adults with acute respiratory distress syndrome and was mixed for the statement on premature

neonates born at less than 34 weeks' gestation. There was no consensus or near-consensus among reviewers on potential additional medically necessary indications for iNO therapy.

PRACTICE GUIDELINES AND POSITION STATEMENTS

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

Pediatric Academic Society

In April 2019, the Pediatric Academic Society convened a workshop regarding the role of INO in infants born preterm.[21] The controversy surrounding its use in this patient population was reviewed by established experts in the field. The experts at the workshop concluded that the "rate of INO use in the infant born preterm is not declining, despite the publication of RCTs and related consensus statements that discourage its routine use due to lack of evidence for bronchopulmonary dysplasia prevention." These experts stated that "none of these studies or recommendations are based on its role in the management of persistent primary hypertension of the newborn in infants born preterm." In this setting, "extensive case series, guidelines, and others recommend the selective use of INO in infants born preterm with documented persistent primary hypertension of the newborn physiology as a contributing cause of hypoxemia, as best confirmed by echocardiography."

Pediatric Pulmonary Hypertension Network

In 2016, The Pediatric Pulmonary Hypertension Network (a network of clinicians, researchers, and centers) published recommendations for use of iNO in premature infants with severe pulmonary hypertension.[22] Key recommendations are:

> "(1) iNO therapy should not be used in premature infants for the prevention of BPD [bronchopulmonary dysplasia], as multicenter studies data have failed to consistently demonstrate efficacy for this purpose.
> (2) iNO therapy can be beneficial for preterm infants with severe hypoxemia that is primarily due to PPHN [persistent pulmonary hypertension of the newborn] physiology rather than parenchymal lung disease, particularly if associated with prolonged rupture of membranes and oligohydramnios.
> (3) iNO is preferred over other pulmonary vasodilators in preterm infants based on a strong safety signal from short- and long-term follow-up of large numbers of patients from multicenter randomized clinical trials for BPD prevention…."

National Institutes of Health

The National Institutes of Health (2011) published a consensus development conference statement on INO for premature infants,[23] which was based on the Agency for Healthcare Research and Quality–sponsored systematic review of the literature, previously described.[4] Conclusions included:

- “Taken as a whole, the available evidence does not support use of iNO (inhaled NO) in early-routine, early-rescue, or later-rescue regimens in the care of premature infants of <34 weeks’ gestation who require respiratory support.”
- “There are rare clinical situations, including pulmonary hypertension or hypoplasia, that have been inadequately studied in which iNO may have benefit in infants of <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.”

The National Institutes for Health guidelines for COVID-19 treatment recommended against the routine use of INO in pediatric or adult patients who are mechanically ventilated; however, they suggest that INO may be used after other options have failed.[26]

American Heart Association/American Thoracic Society

The American Heart Association and American Thoracic Society (2015) published guidelines on the management of pediatric pulmonary hypertension.[24]

Relevant recommendations related to INO included:

- "Inhaled nitric oxide (iNO) is indicated to reduce the need for extracorporeal membrane oxygenation (ECMO)support in term and near-term infants with persistent pulmonary hypertension of the newborn (PPHN) or hypoxemic respiratory failure who have an oxygenation index that exceeds 25 (Class I; Level of evidence A)."
- "iNO can be beneficial for preterm infants with severe hypoxemia that is due primarily to PPHN physiology rather than parenchymal lung disease, particularly if associated with prolonged rupture of membranes and oligohydramnios (Class IIa; Level of evidence B)."

American Academy of Pediatrics

In 2014, the American Academy of Pediatrics provided the following recommendations on the use of INO in premature infants (see Table 13).[25]

Table 13. Guidelines on Use of INO for Premature Infants

Recommendation	QOE	GOR
“Neither rescue nor routine use of iNO improves survival in preterm infants with respiratory failure.”	A	Strong
“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.”	A	Strong
“The incidence of cerebral palsy, neurodevelopmental impairment, or cognitive impairment in preterm infants treated within iNO is similar to that of control infants.”	A	NR

BPD: bronchopulmonary dysplasia; GOR: grade of recommendation; INO: inhaled nitric oxide; NR: not reported; QOE: quality of evidence

National Institute for Health and Care Excellence

In April 2019, NICE issued a guidance on specialist neonatal respiratory care for preterm infants.[26] The guidance recommends against the routine use of INO for preterm infants who need respiratory support for respiratory distress syndrome, unless there are other indications such as pulmonary hypoplasia or pulmonary hypertension.

Ongoing and Unpublished Clinical Trials

Some currently unpublished trials that might influence this review are listed in Table 14.

Table 14. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT05757557	Perioperative Nitric oxiDE-conditioning, Produced by Plasma-chemical Synthesis Technology, For prevEnt Acute kidNey Injury During carDiac surgEry in Patients With chRonic Kidney Disease (DEFENDER-trial)	136	Jan 2025
NCT04305457	Nitric oxide gas inhalation therapy in spontaneous breathing patients with mild/moderate COVID-19: a RCT	70	Apr 2025
Unpublished			
NCT00515281	Inhaled nitric oxide and neuroprotection in premature infants Results pending changes by sponsor or investigator	484	Jun 2023
NCT03661385	A Randomised Controlled Trial of Nitric Oxide Administration DuringCardiopulmonary Bypass in Infants Undergoing Arterial Switch Operation for Repair of Transposition of the Great Arteries (no results posted)	300	Apr 2023
NCT02836899	Prevention of acute kidney injury by nitric oxide in prolonged cardiopulmonary bypass. A double blind controlled randomized trial in cardiac surgical patients with endothelial dysfunction (no results posted)	250	Nov 2023
NCT04306393	Nitric oxide gas inhalation therapy for mechanically ventilated patients with severe acute respiratory syndrome caused by SARS-CoV2: a RCT (no results posted)	200	Jan 2022

NCT: national clinical trial.

Government Regulations
National/Local:

Medicare does not have a specific policy on inhaled nitric oxide. There is no HCPCS code to describe iNO treatments.

(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)

Related Policies

Extracorporeal Membrane Oxygenation

References

1. U.S. Food and Drug Administration (FDA). Medical Device Recalls: Vero Biotech Recalls GENOSYL DS; Nitric Oxide Delivery System Due to Software Error. 2021; https://www.fda.gov/medical-devices/medical-device-recalls/vero-biotech-recalls-genosyl-ds-nitric-oxide-delivery-system-due-software-error. Accessed

2. Barrington KJ, Finer N, Pennaforte T, et al. Nitric oxide for respiratory failure in infants born at or near term. Cochrane Database Syst Rev. Jan 05 2017; 1: CD000399. PMID 28056166
3. Barrington KJ, Finer N, Pennaforte T. Inhaled nitric oxide for respiratory failure in preterm infants. Cochrane Database Syst Rev. Jan 03 2017; 1: CD000509. PMID 28045472
4. Yang Y, Feng Y, Zhou XG, et al. Inhaled nitric oxide in preterm infants: An updated meta-analysis. J Res Med Sci.2016; 21: 41. PMID 27904587
5. Donohue PK, Gilmore MM, Cristofalo E, et al. Inhaled nitric oxide in preterm infants: a systematic review. Pediatrics. Feb 2011; 127(2): e414-22. PMID 21220391
6. Mercier JC, Hummler H, Durrmeyer X, et al. Inhaled nitric oxide for prevention of bronchopulmonary dysplasia in premature babies (EUNO): a randomised controlled trial. Lancet. Jul 31 2010; 376(9738): 346-54. PMID 20655106
7. Durrmeyer X, Hummler H, Sanchez-Luna M, et al. Two-year outcomes of a randomized controlled trial of inhaled nitric oxide in premature infants. Pediatrics. Sep 2013; 132(3): e695-703. PMID 23940237
8. 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. Sep 07 2020; 49(1): 104-110. PMID 32892178
9. Gebistorf F, Karam O, Wetterslev J, et al. Inhaled nitric oxide for acute respiratory distress syndrome (ARDS) in children and adults. Cochrane Database Syst Rev. Jun 27 2016; (6): CD002787. PMID 27347773
10. Adhikari NK, 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. Feb2014; 42(2): 404-12. PMID 24132038
11. Afshari A, Brok J, Moller AM, et al. Inhaled nitric oxide for acute respiratory distress syndrome and acute lung injury in adults and children: a systematic review with meta-analysis and trial sequential analysis. Anesth Analg.Jun 2011; 112(6): 1411-21. PMID 21372277
12. Prakash A, Kaur S, Kaur C, et al. Efficacy and safety of inhaled nitric oxide in the treatment of severe/criticalCOVID-19 patients: A systematic review. Indian J Pharmacol. May-Jun 2021; 53(3): 236-243. PMID 34169911
13. Ruan SY, Wu HY, Lin HH, et al. Inhaled nitric oxide and the risk of renal dysfunction in patients with acute respiratory distress syndrome: a propensity-matched cohort study. Crit Care. Nov 30 2016; 20(1): 389. PMID27903300
14. Wang J, Cong X, Miao M, et al. Inhaled nitric oxide and acute kidney injury risk: a meta-analysis of randomized controlled trials. Ren Fail. Dec 2021; 43(1): 281-290. PMID 33494652
15. Potapov E, Meyer D, Swaminathan M, et al. Inhaled nitric oxide after left ventricular assist device implantation: a prospective, randomized, double-blind, multicenter, placebo-controlled trial. J Heart Lung Transplant. Aug 2011;30(8): 870-8. PMID 21530317
16. 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. Jul 03 2014; (7): CD005055.PMID 24991723
17. Miller OI, Tang SF, Keech A, et al. Inhaled nitric oxide and prevention of pulmonary hypertension after congenital heart surgery: a randomised double-blind study. Lancet. Oct 28 2000; 356(9240): 1464-9. PMID 11081528

18. Tavare AN, Tsakok T. Does prophylactic inhaled nitric oxide reduce morbidity and mortality after lung transplantation?. Interact Cardiovasc Thorac Surg. Nov 2011; 13(5): 516-20. PMID 21791520
19. Meade MO, Granton JT, Matte-Martyn A, et al. A randomized trial of inhaled nitric oxide to prevent ischemia-reperfusion injury after lung transplantation. Am J Respir Crit Care Med. Jun 01 2003; 167(11): 1483-9. PMID12770854
20. Perrin G, Roch A, Michelet P, et al. Inhaled nitric oxide does not prevent pulmonary edema after lung transplantation measured by lung water content: a randomized clinical study. Chest. Apr 2006; 129(4): 1024-30.PMID 16608953
21. Botha P, Jeyakanthan M, Rao JN, et al. Inhaled nitric oxide for modulation of ischemia-reperfusion injury in lung transplantation. J Heart Lung Transplant. Nov 2007; 26(11): 1199-205. PMID 18022088
22. Lakshminrusimha S, Kinsella JP, Krishnan US, et al. Just Say No to iNO in Preterms-Really?. J Pediatr. Mar 2020;218: 243-252. PMID 31810629
23. 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. Mar 2016; 170: 312-4. PMID 26703869
24. Cole FS, Alleyne C, Barks JD, et al. NIH Consensus Development Conference statement: inhaled nitric-oxide therapy for premature infants. Pediatrics. Feb 2011; 127(2): 363-9. PMID 21220405
25. Abman SH, Hansmann G, Archer SL, et al. Pediatric Pulmonary Hypertension: Guidelines From the American Heart Association and American Thoracic Society. Circulation. Nov 24 2015; 132(21): 2037-99. PMID 26534956
26. Kumar P, Papile LA, Polin RA, et al. Use of inhaled nitric oxide in preterm infants. Pediatrics. Jan 2014; 133(1):164-70. PMID 24379225
27. National Institute for Health and Care Excellence (NICE). NICE guideline: Specialist neonatal respiratory care for babies born preterm [NG124]. April 2019; https://www.nice.org.uk/guidance/ng124 Accessed May 30, 2024.
28. National Institutes of Health. COVID-19 Treatment Guidelines. https://www.covid19treatmentguidelines.nih.gov/management/critical-care-for-children/oxygenation-and-ventilation-for-children/. Updated February 29, 2024. Accessed May 30, 2024.
29. Blue Cross Blue Shield Association. Inhaled Nitric Oxide. Medical Policy Reference Manual. Policy #8.01.37, original policy date 8/18/00, last review date June 2024.

The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through May 30, 2024, the date the research was completed.

Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
4/24/02	4/24/02	4/24/02	Joint medical policy established
11/18/03	N/A	N/A	Policy retired
7/26/05	7/26/05	5/21/05	Policy updated per provider request
9/1/06	7/10/06	7/5/06	Medical policy statement clarified. Policy retired.
7/1/09	N/A	N/A	Taken out of retirement to discuss treatment of respiratory distress syndrome in patients other than neonates. Case elevated to CMOs due to anticipated divergence in status
11/1/11	8/16/11	9/8/11	Routine maintenance. Policy reformatted to match BCBSA policy. Mirrors BCBSA policy status.
3/1/14	12/10/13	1/6/14	Routine maintenance. Addition of references, rationale updated.
1/1/16	10/13/15	10/27/15	Routine maintenance. Added references. No change in policy status.
1/1/17	10/11/16	10/11/16	Routine policy maintenance. Updated references and rationale.
1/1/17	10/19/17	10/19/17	Updated rationale section, added references 1-3, 7 and 10. Policy status remains unchanged.
1/1/19	12/13/18	11/7/18	Routine policy maintenance, added reference #21. Added coverage for post-operative management of pulmonary hypertensive crisis in infants and children with congenital heart disease Add coverage for diagnostic use of iNO as a method of assessing pulmonary vaso-reactivity in persons with pulmonary hypertension. No change in policy status.
11/1/19	8/20/19		Routine policy maintenance, no change in policy status.
11/1/20	8/18/20		Routine policy maintenance, removed old references 11-13. No change in policy status.
11/1/21	8/17/21		Routine policy maintenance, no change in policy status.
11/1/22	8/16/22		Routine maintenance; no change to policy status
11/1/23	8/15/23		Routine maintenance; no change to policy status. Vendor: N/A (ky)
11/1/24	8/20/24		Routine maintenance

			On 11.21.23 we received local input from Michigan Medicine (MM): they recommended that we clarify what gestational age neonates could receive iNO treatment and they recommended the utility of the oxygenation index (OI) be clarified. OI was removed as criteria but we left a note explaining the utility of the OI. Other changes were related to standard policy formatting. Vendor: N/A (ky)

Next review: 3rd Qtr. 2025

Pre-Consolidation Medical Policy History

Original Policy Date	Comments
BCN: N/A	Revised: N/A
BCBSM: 1/12/02	Revised: N/A

BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: INHALED NITRIC OXIDE (iNO)

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	Covered; criteria applies
BCNA (Medicare Advantage)	See government section.
BCN65 (Medicare Complementary)	Coinsurance covered if primary Medicare covers the service.

II. Administrative Guidelines:

- The member's contract must be active at the time the service is rendered.
- Coverage is based on each member's certificate and is not guaranteed. Please consult the individual member's certificate for details. Additional information regarding coverage or benefits may also be obtained through customer or provider inquiry services at BCN.
- The service must be authorized by the member's PCP except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Services must be performed by a BCN-contracted provider, if available, except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Payment is based on BCN payment rules, individual certificate and certificate riders.
- Appropriate copayments will apply. Refer to certificate and applicable riders for detailed information.
- CPT - HCPCS codes are used for descriptive purposes only and are not a guarantee of coverage.