Prior Authorization Review Panel
MCO Policy Submission

A separate copy of this form must accompany each policy submitted for review.
Policies submitted without this form will not be considered for review.

Plan: Keystone First Community Health Choices	**Submission Date**: 04/27/2022
Policy Number: CCP.1086	**Effective Date:** 06/2014 **Revision Date:** April 5, 2022
Policy Name: Inhaled nitric oxide	
Type of Submission – Check all that apply: ☑ **New Policy** ☐ **Revised Policy*** ☐ **Annual Review – No Revisions** ☐ **Statewide PDL**	
***All revisions to the policy must be highlighted using track changes throughout the document.** **Please provide any clarifying information for the policy below:** This is a new policy.	
Name of Authorized Individual (Please type or print): Akintayo Akinlawon, MD	**Signature of Authorized Individual:** 

Inhaled nitric oxide

Clinical Policy ID: CCP.1086

Recent review date: 4/2022

Next review date: 8/2023

Policy contains: Inhaled nitric oxide; pediatric pulmonary hypertension; respiratory distress.

Keystone First Community HealthChoices has developed clinical policies to assist with making coverage determinations. Keystone First Community HealthChoices' clinical policies are based on guidelines from established industry sources, such as the Centers for Medicare & Medicaid Services (CMS), state regulatory agencies, the American Medical Association (AMA), medical specialty professional societies, and peer-reviewed professional literature. These clinical policies along with other sources, such as plan benefits and state and federal laws and regulatory requirements, including any state- or plan-specific definition of "medically necessary," and the specific facts of the particular situation are considered by Keystone First Community HealthChoices when making coverage determinations. In the event of conflict between this clinical policy and plan benefits and/or state or federal laws and/or regulatory requirements, the plan benefits and/or state and federal laws and/or regulatory requirements shall control. Keystone First Community HealthChoices' clinical policies are for informational purposes only and not intended as medical advice or to direct treatment. Physicians and other health care providers are solely responsible for the treatment decisions for their patients. Keystone First Community HealthChoices' clinical policies are reflective of evidence-based medicine at the time of review. As medical science evolves, Keystone First Community HealthChoices will update its clinical policies as necessary. Keystone First Community HealthChoices' clinical policies are not guarantees of payment.

Coverage policy

Inhaled nitric oxide is clinically proven and, therefore, medically necessary for the management of at- or near-term infants at risk for pulmonary hypertension when all of the following criteria are met (Abman, 2015; DiBlasi, 2010; Hansmann, 2016; Kinsella, 2016; U.S. Food and Drug Administration, 1999):

- Inhaled nitric oxide is a component treatment of respiratory failure associated with pulmonary hypertension.
- Infants are ≥ 35 weeks of gestation.
- There is no presence of congenital diaphragmatic hernia.
- Inhaled nitric oxide is performed in centers with Level 3 or Level 4 neonatal intensive care units and referral access to extracorporeal membrane oxygenation.

Inhaled nitric oxide is investigational and, therefore, not medically necessary for respiratory distress in infants less than 35 weeks of gestation (Cole, 2011; Kumar, 2014).

Limitations

All other uses of inhaled nitric oxide are not medically necessary (Gebistorf, 2016).

Alternative covered services

Standard medical care as found in the peer-reviewed medical journals for the treatment of asthma, respiratory distress, chronic lung disease, and pulmonary disease in infants and newborns.

Background

Persistent pulmonary hypertension in newborns results from failure of successful postnatal transition of fetal pulmonary circulation Theh incidence of the condition ranges from 0.4 to 2.0 cases per 1000 live births, with a mortality rate of 11% (Shivanna, 2019).

Nitric oxide is a free radical gas serving formed from the actions of nitric oxide synthease catalyzing the abduction of guanidine nitrogen from arginine, raising intracellular levels of cyclic-guanosine 3', 5'-monophosphate and yielding nitric oxide and water (Wang, 2019). The nitric oxide synthease isoenzymes are expressed in the epithelium of the airways in both normal and asthmatic subjects. Physiologically, nitric oxide causes vasodilatation and relaxation of airway smooth muscles. It inhibits platelet aggregation, induces disaggregation of aggregated platelets, and inhibits platelet adhesion to the vascular endothelium. In the face of inflammatory processes, more nitric oxide is produced and, in turn, is reduced in the face of glucocorticosteroids. Studies indicate that inhaled nitric oxide treatment is generally safe; potential side effects, including methemoglobinemia, inhibition of platelet aggregation and systemic vasodilatation, are often clinically insignificant (Ruan, 2015).

Inhaled nitric oxide has been proposed as a treatment option for pulmonary hypertension and hypoxemic respiratory failure. The U.S. Food and Drug Administration (1999) approved inhaled nitric oxide (marketed as INOmax gas, Mallinckrodt Hospital Products IP Limited, Hampton, New Jersey) as a vasodilator to improve oxygenation and reduce the need for extracorporeal membrane oxygenation in term and near-term (> 34 weeks of gestation) neonates with hypoxic respiratory failure associated with clinical or echocardiographic evidence of pulmonary hypertension, in conjunction with ventilatory support and other appropriate agents. The U.S. Food and Drug Administration (2004) warns of rebound pulmonary hypertension syndrome following abrupt discontinuation from inhaled nitric oxide, methemoglobinemia, airway injury, and heart failure as a result of nitric oxide. Off-label use is widespread (Keszler, 2012).

Findings

An Agency for Healthcare Research and Quality-funded evidence report on inhaled nitric oxide in preterm infants found a 7% reduction in the composite outcome of death or bronchopulmonary dysplasia at 36 weeks compared to control; however, there was insufficient evidence to support the use of inhaled nitric oxide outside of rigorous randomized controlled trials (Allen, 2010).

A consensus panel from the American Association for Respiratory Care recommended: (1) a trial of inhaled nitric oxide in newborns ≥ 34 weeks of gestation with oxygen tension < 100 mm Hg on 100% oxygen; (2) using inhaled nitric oxide starting early to reduce duration of mechanical ventilation; and (3) not using inhaled nitric oxide in infants with congenital diaphragmatic hernia, cardiac anomalies with right-to-left shunts, or heart failure (DiBlasi, 2010).

The American Association or Respiratory Care relied on evidence compiled by the Cochrane Neonatal Group, which failed to find evidence to support inhaled nitric oxide as rescue therapy but did find that early use of inhaled nitric oxide in preterm infants with respiratory conditions did not affect brain injury or mortality (Barrington, 2010).

A National Institutes of Health panel did not find evidence supporting the use of inhaled nitric oxide for rescue and care of infants with < 34 weeks of gestation (Cole, 2011). Another meta-analysis of 14 published trials found significant differences in the design of published trials that precluded a determination of the salutary impact of inhaled nitric oxide (Askie, 2011). The American Academy of Pediatrics' literature review found insufficient evidence to support treating preterm infants who have respiratory failure with inhaled nitric oxide and no evidence of a salutary impact on neurodevelopmental processes for infants who received inhaled nitric oxide compared to controls (Kumar, 2014).

As a summary of the findings of the studies, the following points may be made:

- There is evidence to support the use of inhaled nitric oxide in term or late preterm infants with respiratory distress and pulmonary hypertension for its acute favorable impacts as a smooth muscle relaxant on pulmonary vascular system and bronchiolar tree.
- Inhaled nitric oxide should not be used for more than four days because of toxicity, nor should it be used to treat hypoxemia related to congenital diaphragmatic hernia.
- Inhaled nitric oxide for treatment of preterm infants with respiratory distress, bronchopulmonary dysplasia, or pulmonary hypertension has not been standardized, and its impact is not known.
- The effectiveness of inhaled nitric oxide in adults with acute respiratory distress syndrome has not been demonstrated.
- The above recommendations for the use of inhaled nitric oxide are based on controlled clinical trials, except as mentioned in the first bullet.

In 2017, we found three Cochrane reviews (Barrington, 2017a, 2017b [update of 2010]; Gebistorf, 2016) and one consensus statement (Hansmann, 2016) for this policy update. The new evidence found that inhaled nitric oxide is effective at an initial concentration of 20 ppm for term and near-term infants with hypoxic respiratory failure who do not have a diaphragmatic hernia, but it is not an effective treatment for preterm infants (Barrington, 2017a, 2017b). For adults with acute respiratory distress syndrome, inhaled nitric oxide results in a transient improvement in oxygenation but not a reduction in mortality, and may increase renal impairment (Gebistorf, 2016).

The European Paediatric Pulmonary Vascular Disease Network strongly supports inhaled nitric oxide for treating acute pulmonary vascular crisis and/or acute exacerbation of pediatric pulmonary hypertension, but only weakly supports inhaled nitric oxide for treating post-operative pediatric pulmonary hypertension in the intensive care unit (Hansmann, 2016). These results do not change previous findings. Therefore, no policy changes are warranted.

In 2018, we identified one meta-analysis (Askie, 2018) and one multisite randomized controlled trial (Hasan, 2017) that addressed the effects of inhaled nitric oxide on survival without bronchopulmonary dysplasia in high-risk preterm infants. Both studies lacked a standardized approach to treatment and enrollment criteria, and produced conflicting results. These findings are consistent with earlier conclusions, and no policy changes are warranted.

In 2019, we identified no newly published, relevant literature to add to the policy. The policy ID was changed from CP# 11.02.02 to CCP.1086.

In 2020, we added one meta-analysis (Wang, 2019) of nine randomized controlled trials to the policy. The findings are consistent with the current policy, and no policy changes are warranted.

In 2021, we removed one reference and added two guidelines to the policy (Abman, 2015; Kinsella, 2016) to the policy with no policy changes warranted.

In 2022, we added a Cochrane review that described inhaled nitric oxide as the only treatment proven to improve clinical outcomes for persistent pulmonary hypertension in newborns (Shivanna, 2019). We added another Cochrane review that reported a 30% rate of neonatal pulmonary hypertension cases that are refractory to inhaled nitric oxide (Kelly, 2017).

References

On January 25, 2022, we searched PubMed and the databases of the Cochrane Library, the U.K. National Health Services Centre for Reviews and Dissemination, the Agency for Healthcare Research and Quality, and the

Centers for Medicare & Medicaid Services. Search terms were “nitric oxide” (MeSH), “inhaled nitric oxide,” and “respiratory distress.” We included the best available evidence according to established evidence hierarchies (typically systematic reviews, meta-analyses, and full economic analyses, where available) and professional guidelines based on such evidence and clinical expertise.

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Policy updates

2/2014: initial review date and clinical policy effective date: 6/2014

9/2016: Policy ID added.

3/2017: Policy references updated.

3/2018: Policy references updated.

3/2019: Policy references updated. Policy ID changed.

3/2020: Policy references updated.

3/2021: Policy references updated.

4/2022: Policy references updated.