I. POLICY

Inhaled nitric oxide may be considered medically necessary as a component of the treatment of hypoxic respiratory failure in neonates born at more than 34 weeks of gestation.

Other indications for inhaled nitric oxide are considered investigational, including, but not limited to, its use in premature neonates born at less than or equal to 34 weeks of gestation, adults and children with acute hypoxemic respiratory failure. There is insufficient evidence to support a conclusion concerning the health outcomes or benefits associated with this procedure.

POLICY GUIDELINES

Inhaled nitric oxide appears to be of greatest benefit in individuals for whom primary or secondary pulmonary hypertension is a component of hypoxic respiratory failure. The benefit of inhaled nitric oxide appears limited in term or near-term infants whose hypoxic respiratory failure is due to diaphragmatic hernia.

The following criterion for hypoxic respiratory failure has been reported:

- An oxygenation index of at least 25 on 2 measurements made at least 15 minutes apart.  

(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.)

Clinical input from academic medical centers and specialty societies obtained in 2012 indicated that:

- Prolonged use of INO [inhaled NO] beyond 1-2 weeks has not been shown to improve outcomes. Use of INO beyond 2 weeks of treatment is therefore not recommended.
• If ECMO is initiated in near-term neonates, inhaled NO should be discontinued as there is no benefit to combined treatment.

II. PRODUCT VARIATIONS

[N] = No product variation, policy applies as stated
[Y] = Standard product coverage varies from application of this policy, see below

[N] Capital Cares 4 Kids
[N] PPO
[N] HMO
[N] SeniorBlue HMO
[N] SeniorBlue PPO
[N] Indemnity
[N] SpecialCare
[N] POS
[Y] FEP PPO*

*Refer to FEP Medical Policy Manual MP-8.01.37 Inhaled Nitric Oxide. The FEP Medical Policy manual can be found at: [www.fepblue.org](http://www.fepblue.org)

III. DESCRIPTION/BACKGROUND

Inhaled nitric oxide (NO) 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.

Hypoxic respiratory failure may result from respiratory distress syndrome (RDS), persistent pulmonary hypertension, meconium aspiration, pneumonia, or sepsis. 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 (newborns) when other therapies fail. Inhaled nitric oxide (NO) is both a vasodilator and a mediator in many physiologic and pathologic processes.

INOmax, a commercially available inhaled NO product, is FDA-approved for use in term and near-term neonates with hypoxic respiratory failure along with respiratory support and other appropriate treatments. Inhaled NO has also been proposed for use in preterm infants less than 34 weeks’ gestation. Another potential application of inhaled NO is to improve...
Oxygenation in patients with acute hypoxic respiratory failure (AHRF), including acute respiratory distress syndrome (ARDS) and acute lung injury. These conditions are associated with inflammation of the alveolar-capillary membrane which leads to hypoxemia and pulmonary hypertension. In addition, inhaled nitric oxide is proposed for management of 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 post-operative pulmonary hypertension, which can prevent weaning from ventilation and is associated with substantial morbidity and mortality.

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 ventilatory 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.”

IV. Rationale

This policy was created in 2000 with a literature search using MEDLINE and was updated regularly with MEDLINE searches. The most recent literature update was for the period May 2011 through July 2012.

Following is a summary of the key literature published to date:

Term or near-term neonates

In 2006, a Cochrane review of randomized controlled trials (RCTs) on inhaled nitric oxide (NO) in infants with hypoxia born at or near-term (greater than 34 weeks’ gestation) was published. (1) The review identified 14 trials. Eleven trials compared inhaled NO to control (placebo or standard neonatal intensive care) in infants with moderate severity of illness scores; 4 of these trials allowed back-up treatment with NO if infants continued to satisfy the same criteria after a pre-specified period of time. Another 2 trials included infants with moderate severity of disease; they compared immediate NO to NO only when infants’ conditions deteriorated to a more severe level of illness. One of the trials only included infants with diaphragmatic hernia. The remaining trial compared NO to high-frequency ventilation. In all of the studies, hypoxic 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 as follows:
**Combined outcome, death, or ECMO (extracorporeal membrane oxygenation)**

<table>
<thead>
<tr>
<th>No. studies</th>
<th>Inhaled nitric oxide n/N</th>
<th>Control n/N</th>
<th>Risk ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Backup use of nitric oxide not allowed</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>149/418 (36%)</td>
<td>194/335 (58%)</td>
<td>0.65 (0.55-0.76)</td>
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<tr>
<td><strong>Backup use of nitric oxide allowed</strong></td>
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<tr>
<td>3</td>
<td>20/87 (23%)</td>
<td>14/75 (19%)</td>
<td>1.15 (0.67-1.97)</td>
</tr>
<tr>
<td><strong>All studies</strong></td>
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<tr>
<td>9</td>
<td>169/505 (33%)</td>
<td>208/410 (51%)</td>
<td>0.68 (0.59-0.79)</td>
</tr>
</tbody>
</table>

**Death**

<table>
<thead>
<tr>
<th>No. studies</th>
<th>Inhaled nitric oxide n/N</th>
<th>Control n/N</th>
<th>Risk ratio (95% CI)</th>
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</thead>
<tbody>
<tr>
<td><strong>Backup use of nitric oxide not allowed</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>35/417 (8%)</td>
<td>33/337 (10%)</td>
<td>0.92 (0.58-1.48)</td>
</tr>
<tr>
<td><strong>Backup use of nitric oxide allowed</strong></td>
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<tr>
<td>3</td>
<td>9/79 (11%)</td>
<td>12/83 (13%)</td>
<td>0.86 (0.37-1.98)</td>
</tr>
<tr>
<td><strong>All studies</strong></td>
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<tr>
<td>9</td>
<td>44/496 (9%)</td>
<td>45/420 (11%)</td>
<td>0.91 (0.60-1.37)</td>
</tr>
</tbody>
</table>

**ECMO**

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<thead>
<tr>
<th>No. studies</th>
<th>Inhaled nitric oxide n/N</th>
<th>Control n/N</th>
<th>Risk ratio (95% CI)</th>
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[Note: Final page is signature page and is kept on file, but not issued with Policy.]
The investigators found that inhaled NO in hypoxic infants reduced the incidence of the combined endpoint of death or need for extracorporeal membrane oxygenation (ECMO) compared to controls. In a pooled analysis of 8 studies, the risk ratio (RR) was 0.68 (95% confidence interval [CI]: 0.59–0.79). The combined outcome of death or need for ECMO was also significantly reduced in a pooled analysis of the 6 studies in which backup nitric oxide was not allowed (RR: 0.65; 95% CI: 0.55–0.76), but this was not the case in an analysis of the 2 studies in which NO was allowed (RR: 1.15; 95% CI: 0.67–1.97).

Inhaled NO did not have a statistically significant effect on mortality when this was the sole outcome measure. In a pooled analysis of 9 studies, the RR was 0.91 (95% CI: 0.60–1.37). There was, however, a significant effect of inhaled NO on need for ECMO only. When findings of 8 studies were pooled, the risk ratio was 0.63 (95% CI: 0.54-0.75). One trial that was limited to infants with congenital diaphragmatic hernia did not find that inhaled NO improved outcomes. When findings of this trial were combined with data on infants with diaphragmatic hernia from another trial (the only other trial from which this information could be extrapolated), there was not a significant effect on mortality, or the combined outcome, mortality, or requiring ECMO in infants who used NO. However, there was a marginally significant increase in the requirement for ECMO in those receiving NO, although the analysis was based on a small number of infants. Thirty-one of 46 (67%) controls compared to 32 of 38 (84%) infants in the NO group required ECMO (RR: 1.27, 95% CI: 1.00 to 1.62). The authors concluded that, based on the available evidence, it appeared reasonable to use inhaled NO in an initial concentration of 20 ppm for term and near-term infants with hypoxic respiratory failure who do not have a diaphragmatic hernia.

A pooled analysis of data from 3 clinical trials on inhaled NO for treating term and near-term infants (at least 34 weeks’ gestation) with hypoxia was published in 2010 by Golombek and Young. (2) This study was not based on a systematic review of the
literature; all of the trials and the pooled analyses were industry-sponsored. The trials had sample sizes of 235, 155 and 248, respectively. The 3 trials all compared inhaled NO at a starting dose of 20 ppm to a control treatment (100% oxygen, inhaled NO at 0 ppm or nitrogen gas). The primary outcome was change in partial pressure of arterial oxygen (PaO2). A pooled analysis found that patients in the treatment group had a significantly higher mean PaO2 level after 30 minutes than patients in the control group (118.9 vs. 68.3 mm Hg, p<0.001). In addition, after 30 minutes, there was a significantly higher increase from baseline in PaO2 in the inhaled NO group (54.9 mm Hg) than the control group (14.1 mm Hg), p<0.001. Duration of mechanical ventilation in patients who survived without ECMO, a secondary outcome of the analysis, was significantly lower in the inhaled NO group (11 days) than the control group (14 days), p=0.003. The article did not report survival or need for ECMO.

**Conclusions:** Evidence from RCTs and meta-analyses of RCTs support the use of inhaled NO in term or near-term infants to improve the net health outcome. These data have established that the use of inhaled NO leads to a reduction in the need for ECMO but is not sufficient to conclude that there is a reduction in mortality.

**Premature neonates**

In near-term neonates, the role of inhaled NO primarily functions as a vasodilator to treat pulmonary hypertension, often due to meconium aspiration or bacterial pneumonia. However, in preterm neonates with respiratory failure, pulmonary hypertension with shunting is not a clinical problem. Therefore, these 2 groups of neonates represent distinct clinical issues, and the results of inhaled NO in near-term neonates cannot be extrapolated to preterm neonates. In addition, there is concern regarding the possible risk of intraventricular hemorrhage associated with inhaled NO in premature infants.

Numerous RCTs and several systematic reviews have been published. In 2011, an Agency for Healthcare Research and Quality (AHRQ)-sponsored systematic review of randomized trials on inhaled NO for premature infants (less than 35 weeks’ gestation) was published. (3) 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. (Note that 3 trials were published since the 2007 Cochrane review including one study with 800 participants.) 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 inhaled NO group and control group in any of the 14 RCTs. In a pooled analysis of 11 trials that reported death by 36 weeks’ postmenstrual age or in the neonatal intensive care unit, the risk ratio was 0.97 (95% CI: 0.82 to 1.15). Similarly, 9 trials reported survival to between 1 and 5 years of age, and none of these reported a statistically significant difference between the inhaled NO and control groups. A pooled analysis of data from 7
trials reporting mortality between 12 and 30 months of age had a risk ratio of 1.02 (95% CI: 0.86 to 1.20). Twelve trials reported data on BPD at 36 weeks’ postmenstrual age, and despite variations in reporting of BPD, there was no significant benefit of inhaled NO treatment in any trial. A pooled analysis of data from 8 trials reporting BPD at 36 weeks’ postmenstrual age among survivors resulted in a risk ratio of 0.93 (95% CI: 0.86-1.003). Eleven RCTs reported the composite outcome of death or BPD at 36 weeks’ postmenstrual age. Eight of these trials reported no significant difference between groups, and 3 reported significantly lower rates in the inhaled NO group. A pooled analysis of data from all 11 of these trials resulted in a small but statistically significant difference favoring inhaled NO (RR: 0.93; 95% CI: 0.87 to 0.99). A sensitivity analysis by dose of inhaled NO did not affect findings on the composite outcome. The systematic review did not find evidence that inhaled NO increased the rate of adverse effects such as ductus arteriosus or pulmonary hemorrhage. In addition, a meta-analysis of 5 trials that reported a composite outcome of brain injury did not find a significant difference in rates between groups (RR: 0.86, 95% CI: 0.58 to 1.29). The overall conclusions from this systematic review are that the use of NO does not significantly reduce mortality or BPD in this patient group. This evidence does not support the use of inhaled NO in preterm infants with respiratory failure outside of the clinical trial setting.

Askie and colleagues conducted a meta-analysis of individual patient data from RCTs evaluating the efficacy of inhaled NO in preterm infants (less than 37 weeks’ gestation). (4) Data from 12 trials with a total of 3,298 infants were included. The primary endpoints of the analysis were death or severe neurologic events during the trial and chronic lung disease (defined as receipt of supplemental oxygen at 36 weeks’ postmenstrual age). Overall, the rate of mortality or chronic lung disease occurred in 59% of infants treated with inhaled NO and 61% of control infants. The difference between groups was not statistically significant; RR: 0.96; 95% CI: 0.92-1.01, p=0.11. Severe neurologic events occurred in 25% of infants in the inhaled NO group and 23% in control infants; RR: 1.12, 95% CI: 0.98-1.28, p=0.09. Sub-analyses (e.g., by birth weight gestational age, race, etc.) did not find any characteristics significantly associated with a benefit from inhaled NO. The authors concluded that routine use of inhaled NO in preterm infants is not recommended.

In 2007, a Cochrane systematic review of the major RCTs on inhaled NO for preterm infants (less than 35 weeks’ gestation) was published. (5) This review included 11 trials; results of the meta-analyses were stratified on the indications for NO (routine use for intubated infants; during the first 3 days of life for severe respiratory failure; and after the first 3 days of life to prevent bronchopulmonary dysplasia (BPD) based on risk). There was no statistically significant reduction in BPD or death at 36 weeks with inhaled NO in pooled analysis of studies with entry before 3 days based on oxygenation (6 studies) or studies with entry after 3 days based on BPD (3 studies). A pooled analysis of 2 studies found a statistically significant reduction in BPD or death at 36 weeks in studies of...
routine use of inhaled NO in intubated preterm infants. Bronchopulmonary dysplasia among survivors at 36 weeks was not significantly reduced by use of inhaled NO in any of the 3 types of studies. The Cochrane review concluded that early routine use of inhaled NO may improve survival without BPD but that further studies are needed to confirm these findings and evaluate long-term outcomes. The authors also concluded that inhaled NO as rescue therapy in the first 3 days and after 3 days of life to prevent BPD based on risk does not appear to be effective.

The largest trial to date was published in 2010 by Mercier and colleagues. (6) This was a multicenter industry-sponsored randomized trial that evaluated low-dose inhaled NO therapy. The study included 800 preterm infants (gestational age at birth between 24 and 28 weeks 6 days) who weighed at least 500 grams and required surfactant or continuous positive airway pressure for respiratory distress syndrome (RDS) within 24 hours of birth. Patients were randomized to receive treatment with inhaled NO 5 ppm (n=399) or placebo-equivalent nitrogen gas (n=401). Therapy was given for 7 to 21 days (mean duration=16 days). A total of 792 of 800 (99%) of patients were given their assigned treatment, and all 800 were included in the intention-to-treat analysis. The primary outcomes were survival without BPD at 36 weeks’ postmenstrual age, overall survival at 36 weeks’ postmenstrual age, and BPD at 36 weeks’ postmenstrual age.

Survival without BPD at 36 weeks’ postmenstrual age, was attained by 258 (65%) of patients in the inhaled NO group and 262 (66%) of patients in the placebo group, a difference that was not statistically significant (RR: 1.05; 95% CI: 0.78 to 1.43, p=0.73). Overall survived at 36 weeks’ postmenstrual age was attained by 343 (86%) in the inhaled NO group and 359 (90%) in the control group (RR: 0.74; 95% CI: 0.48-1.15, p=0.21). The percent of patients with BPD at 36 weeks’ postmenstrual age was 81 (24%) in the NO group and 96 (27%) in the control group (RR: 0.83; 95% CI: 0.58-1.17, p=0.29). The secondary endpoint of survival without brain injury at gestational age 36 weeks also did not differ significantly between groups (RR: 0.78; 95% CI: 0.53-1.17, p=0.23). This endpoint was attained by 181 (69%) patients in the inhaled NO group and 188 (76%) patients in the placebo group, p=0.23. Rates of serious adverse events (i.e., intraventricular hemorrhage, periventricular leukomalacia, patient ductus arteriosus, pneumothorax, pulmonary hemorrhage, necrotizing enterocolitis and sepsis) were 158/395 (40%) in the inhaled NO group and 164/397 (41%) in the control group, p=0.72. The most common adverse effect was intracranial hemorrhage, which affected 114 (29%) in the inhaled NO group and 91 (23%) in the control group (exact p value not reported).

Conclusions: A large number of RCTs evaluate inhaled NO for premature neonates, with most of the trials reporting no difference on the primary endpoints. Meta-analyses of these RCTs have not found better outcomes with inhaled NO in premature neonates. This evidence does not support the routine use of inhaled NO in preterm infants.

**Adults and children with acute hypoxemic respiratory failure**
In 2011, Afshari and colleagues published a systematic review and meta-analysis of RCTs evaluating the efficacy of acute respiratory distress syndrome (ARDS) and acute lung injury (together known as acute hypoxic respiratory failure). (7) Studies of neonates were excluded. The authors identified a total of 24 papers that underwent full review. They excluded 8 trials, leaving 16 reports of 14 trials. Most trials included adults with a mixture of ARDS and acute lung injury; 3 trials included pediatric populations, and 1 trial included mainly adults and some children. Sample size in individual trials varied from 14 to 385 participants. The primary outcome was all-cause mortality. A pooled analysis of data from all 14 trials on mortality at longest follow-up reported 265/660 (40.2%) deaths in the group receiving inhaled NO and 228/590 (38.6%) deaths in the control group. The difference between groups was not statistically significant (RR: 1.06; 95% CI: 0.93 to 1.22). Findings were similar for analyses of mortality after 1 month and for the subgroups of adults and children. In other pooled analyses, inhaled NO was not found to have a beneficial effect on the number of ventilator-free days or the duration of mechanical ventilation. Regarding adverse effects, a meta-analysis did not find a significant difference in bleeding rates between groups. However, a pooled analysis of 4 trials with data on renal impairment found a significant increase in events in the group receiving inhaled NO. There were 91/503 (18.1%) events in the inhaled NO group and 51/442 (11.5%) events in the control group (RR: 1.59; 95% CI: 1.17 to 2.16). Exact numbers of events were not reported for most secondary or sub-group analyses. The results of this analysis do not support a benefit for inhaled NO in children and adults with hypoxic respiratory failure.

A 2003 Cochrane systematic review identified 5 RCTs comparing inhaled NO and placebo for acute hypoxic respiratory failure (8). All of these trials were included in the 2011 Afshari et al. meta-analysis. The Cochrane authors conducted only 1 pooled analysis, and it combined findings from 2 studies. The meta-analysis did not find a significant impact of inhaled NO on mortality in studies without crossover of failures to treatment with inhaled NO (pooled RR: 0.98; 95% CI: 0.66 to 1.44). Insufficient data from no more than one trial each were available on other outcomes including length of stay in the intensive care unit and duration of hospital stay. Two trials reported on ventilator-free days after 1 month, but the data could not be pooled due to differences in the outcome variable; 1 trial reported number of ventilator-free days, and the other reported the percentage of patients alive and extubated at 30 days. Individually, neither of these 2 studies found a significant difference in outcome between the inhaled NO and control groups.

The largest individual trial was published by Taylor and colleagues in 2004 and did not report improvements for patients treated with inhaled NO. (9) The investigators randomly assigned 385 patients with acute lung injury to receive either low-dose inhaled NO or placebo. Patient selection criteria included no more than 72 hours from the onset of lung injury and absence of sepsis or non-pulmonary organ system dysfunction. The authors
reported that inhaled NO was not associated with an improvement in number of days alive or days off ventilation. A follow-up, a priori analysis of long-term pulmonary function, was published in 2012. (10) A total of 92 of 385 (24%) randomized patients participated in the 6-month follow-up, 55 in the inhaled NO group and 41 in the placebo group. Of 14 pulmonary function measures reported, 5 differed significantly between groups at the p<0.05 level. For example, the mean forced expiratory volume (FEV) (percent predicted) was 80.2% in the inhaled NO group and 69.6% in the placebo group (p=0.042). One of the 5 measures, total lung capacity (percent predicted) differed significantly between groups at the p<0.01 level (93.3% in the inhaled NO group and 76.1% in the placebo group). The analysis was limited by the small number of randomized patients having participated.

Conclusions: Evidence from numerous RCTs and 2 systematic reviews of these RCTs did not find significant effects of inhaled NO on mortality or duration of mechanical ventilation in adults and children with acute hypoxic respiratory failure. This evidence suggests that inhaled NO is not an effective treatment for this patient population.

Postoperative use in adults and children with congenital heart disease

Children

A 2007 Cochrane review identified 4 RCTs comparing postoperative inhaled NO versus placebo or usual care in the management of children with congenital heart disease. (11) All of the trials included participants who were identified as having pulmonary hypertension in the preoperative or postoperative period. Sample sizes in the 4 studies were 12, 35, 44, and 124. Three trials were parallel group trials and one was a crossover trial. Mortality was the primary outcome of the Cochrane meta-analysis. Two trials with a total of 162 patients reported mortality prior to discharge. A pooled analysis of findings from these 2 studies did not find a significant difference in mortality between the group receiving inhaled NO compared to the control group (OR: 1.67; 95% CI: 0.38 to 7.30). Among the 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, but the wide confidence intervals around the pooled treatment effects reflects the relatively small amount of data available on each outcome.

The trial with the largest sample size was published by Miller and colleagues in Australia in 2000. (12) 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, \(p<0.001\). 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, \(p=0.019\). There were 5 deaths in the inhaled NO group and 3 deaths in the placebo group; this difference was not statistically significant, \(p=0.49\). 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, \(p>0.05\). 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.

**Adults**

A 2011 trial by Potapov and colleagues evaluated the prophylactic use of inhaled NO in adult patients undergoing left ventricular assist device (LVAD) implantation for congestive heart failure. (13) This double-blind trial was conducted at 8 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.

Conclusions: Evidence from a number of small RCTs, and one systematic review of these trials did not find a significant benefit for inhaled NO on mortality and other health outcomes in the postoperative management of children with congenital heart disease. There is less evidence on inhaled NO for adults with congenital heart disease. One RCT did not find a significant effect of treatment with inhaled NO on reduction on postoperative outcomes in adults with congestive heart failure who had LVAD surgery.

Ongoing Clinical Trials

Inhaled nitric oxide for the treatment of bronchopulmonary dysplasia in preterm infants (NCT00931632). (14): This multicenter double-blind randomized trial, sponsored by INO Therapeutics, is comparing inhaled nitric oxide to placebo in preterm infants who require intubation during days 5 to 14 after birth. The primary outcome will be survival without bronchopulmonary dysplasia at 36 weeks’ postmenstrual age.

Examining the use of non-invasive inhaled nitric oxide to reduce chronic lung disease in premature infants (NCT00955487). (15): This multicenter double-blind randomized trial, sponsored by the National Heart, Lung and Blood Institute (NHLBI), is examining whether early treatment with low-dose inhaled nitric oxide reduces the incidence of bronchopulmonary dysplasia, pulmonary hypertension, and death in premature infants. It includes infants with a gestational age of less than 34 weeks who have a birth weight of 500 to 1,250 grams.

Clinical Input Received Through Physician Specialty Societies and Academic Medical Centers

In response to requests, clinical input was received while the policy was under review in 2010 and 2012. 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.

2012

Input was received through 2 Physician Specialty Societies and 9 Academic Medical Centers. There was consensus agreement with the medically necessary statement that inhaled NO 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 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 inhaled NO should be considered investigational. Several reviewers stated that they thought inhaled NO is clinically useful for the post-operative treatment of selected patients with congenital heart disease.

In addition, clinician reviewers generally agreed that inhaled NO should be discontinued when ECMO is initiated. There was near-consensus agreement that prolonged use of inhaled NO (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 inhaled NO 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 was received through 4 Physician Specialty Societies and 5 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 inhaled NO therapy.

Summary

There is evidence from a systematic review of randomized controlled trials that inhaled nitric oxide improves the net health outcome in hypoxic term or near-term infants. Other systematic reviews of RCTs did not find evidence of a net benefit from inhaled nitric oxide among preterm infants when used in the first 3 days of life for severe respiratory failure or after the first 3 days of life to prevent bronchopulmonary dysplasia. For preterm infants, the largest trial published to date had 800 participants and did not find that use of inhaled nitric oxide in preterm infants improved survival without bronchopulmonary dysplasia or survival without brain injury. In children and adults with acute hypoxemic respiratory failure, a systematic review of randomized controlled trials did not find that inhaled nitric oxide treatment improved the net health outcome; there was no significant effect on all-cause mortality or duration of mechanical ventilation. There was no significant difference in adverse events overall, but there was a significantly higher rate of renal impairment with inhaled nitric oxide treatment. Thus, inhaled nitric oxide may be considered medically necessary to treat term and near-term infants and investigational for other indications.
Practice Guidelines and Position Statements

In 2011, a National Institutes of Health (NIH) Consensus Development Conference Statement on inhaled nitric oxide for premature infants was published. (16) The statement was based on the AHRQ-sponsored systematic review of the literature, described above. (3) Conclusions include:

“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.”

In 2000, the American Academy of Pediatrics (AAP) issued recommendations regarding the use of inhaled nitric oxide in pediatric patients. (17) The recommendations were reaffirmed on April 1, 2010. They stated that “Inhaled nitric oxide therapy should be given using the indications, dosing, administration and monitoring guidelines outlined on the product label.” This recommendation is consistent with the policy statement. In addition, the AAP recommended the following:

- Inhaled nitric oxide should be initiated in centers with extracorporeal membrane oxygenation capability.
- Centers that provide inhaled nitric oxide therapy should provide comprehensive long-term medical and neurodevelopmental follow-up.
- Centers that provide inhaled nitric oxide therapy should establish prospective data collection for treatment time course, toxic effects, treatment failure, and use of alternative therapies and outcomes.
- Administration of inhaled nitric oxide for indications other than those approved by the U.S. Food and Drug Administration (FDA) or in other neonatal populations, including compassionate use, remains experimental.

The policy statement of the AAP does not address the use of inhaled nitric oxide in premature infants.

V. DEFINITIONS

ALKALOSIS is a condition of excess base in the body fluids; this is the opposite of excess acid.

ASPIRATION refers to a material or substance accidentally getting into the respiratory tract during the act of inhaling.
EXTRACORPOREAL MEMBRANE OXYGENATION (ECMO) refers to artificial blood gas exchange while mechanically oxygenating the blood while the lungs heal.

HYPOXIA refers to lack of oxygen.

MECONIUM is the first stool of the newborn.

NEUROMUSCULAR BLOCKADE refers to the administration of medication to induce muscular paralysis.

PULMONARY HYPERTENSION refers to abnormally high blood pressure in the arteries of the lungs.

RESPIRATORY DISTRESS SYNDROME (RDS) is a life-threatening condition in which inflammation of the lungs and the accumulation of fluid in the air sacs lead to low oxygen levels.

SEPSIS is a serious illness caused by infection of the blood.

VASODILATOR is a medication that increases the diameter of blood vessels, which increases blood flow and lowers blood pressure.

VI. BENEFIT VARIATIONS

The existence of this medical policy does not mean that this service is a covered benefit under the member’s contract. Benefit determinations should be based in all cases on the applicable contract language. Medical policies do not constitute a description of benefits. A member’s individual or group customer benefits govern which services are covered, which are excluded, and which are subject to benefit limits and which require preauthorization. Members and providers should consult the member’s benefit information or contact Capital for benefit information.

VII. DISCLAIMER

Capital’s medical policies are developed to assist in administering a member’s benefits, do not constitute medical advice and are subject to change. Treating providers are solely responsible for medical advice and treatment of members. Members should discuss any medical policy related to their coverage or condition with their provider and consult their benefit information to determine if the service is covered. If there is a discrepancy between this medical policy and a member’s benefit information, the benefit information will
VIII. REFERENCES


[Note: Final page is signature page and is kept on file, but not issued with Policy.]


IX. CODING INFORMATION

Note: This list of codes may not be all-inclusive, and codes are subject to change at any time. The identification of a code in this section does not denote coverage as coverage is determined by the terms of member benefit information. In addition, not all covered services are eligible for separate reimbursement.

Covered when medically necessary:

<table>
<thead>
<tr>
<th>CPT Codes®</th>
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<tbody>
<tr>
<td>94799</td>
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<table>
<thead>
<tr>
<th>ICD-9-CM Diagnosis Code*</th>
<th>Description</th>
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<tbody>
<tr>
<td>765.27</td>
<td>33-34 COMPLETED WEEKS OF GESTATION</td>
</tr>
<tr>
<td>765.28</td>
<td>35-36 COMPLETED WEEKS OF GESTATION</td>
</tr>
<tr>
<td>765.29</td>
<td>37 OR MORE COMPLETED WEEKS OF GESTATION</td>
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The following ICD-10 diagnosis codes will be effective October 1, 2014:

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<tr>
<td>P07.32</td>
<td>Other preterm newborn, 32-36 completed weeks</td>
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<tr>
<td>P07.32</td>
<td>Other preterm newborn, 32-36 completed weeks</td>
</tr>
<tr>
<td>P07.30</td>
<td>Other preterm newborn, unspecified weeks</td>
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<tr>
<td>P22.0</td>
<td>Respiratory distress syndrome of newborn</td>
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<tr>
<td>P28.5</td>
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*If applicable, please see Medicare LCD or NCD for additional covered diagnoses.

**X. POLICY HISTORY**

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<td>Consensus – Policy statement unchanged. References updated.</td>
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<tr>
<td></td>
<td>Policy statement revised, language regarding required prior echocardiogram removed.</td>
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<tr>
<td></td>
<td>CAC 11/29/11</td>
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<tr>
<td></td>
<td>Minor revision. Title changed to “Inhaled Nitric Oxide.” Medically necessary statement changed to “more than 34 weeks of gestation” to be consistent with age range of FDA-approved indication. Investigational policy statement changed to “less than or equal to 34 weeks of gestation” and several additional indications were specifically mentioned.</td>
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|          | Minor. “Postoperative management of pulmonary hypertension in children with congenital heart disease” removed from investigational policy statement. Information added to Policy Guidelines on recommended duration of use of inhaled nitric oxide (NO). In addition, statement added to Policy Guidelines that...
MEDICAL POLICY

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If ECMO is initiated in near-term neonates inhaled NO should be discontinued as there is no benefit to combined treatment. Added FEP variation to reference FEP Medical Policy Manual MP-8.01.37 Inhaled Nitric Oxide. Codes reviewed, no specific CPT-skb

CAC 1/28/14 Consensus review. References updated but no changes to the policy statements. Rationale added. Codes reviewed.

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