Name of Policy: Inhaled Nitric Oxide

Policy #: 440
Category: Therapy

Latest Review Date: October 2014
Policy Grade: B

Background/Definitions:
As a general rule, benefits are payable under Blue Cross and Blue Shield of Alabama health plans only in cases of medical necessity and only if services or supplies are not investigational, provided the customer group contracts have such coverage.

The following Association Technology Evaluation Criteria must be met for a service/supply to be considered for coverage:

1. The technology must have final approval from the appropriate government regulatory bodies;
2. The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes;
3. The technology must improve the net health outcome;
4. The technology must be as beneficial as any established alternatives;
5. The improvement must be attainable outside the investigational setting.

Medical Necessity means that health care services (e.g., procedures, treatments, supplies, devices, equipment, facilities or drugs) that a physician, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury or disease or its symptoms, and that are:

1. In accordance with generally accepted standards of medical practice; and
2. Clinically appropriate in terms of type, frequency, extent, site and duration and considered effective for the patient’s illness, injury or disease; and
3. Not primarily for the convenience of the patient, physician or other health care provider; and
4. Not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient’s illness, injury or disease.
**Description of Procedure or Service:**
Inhaled nitric oxide is proposed as a treatment of hypoxic respiratory failure in neonates and adults to improve oxygenation and reduce mortality rates. In neonates, the treatment may also 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 when other therapies fail. Inhaled nitric oxide is both a vasodilator and a mediator in many physiologic and pathologic processes.

INOmax, an FDA-approved form of inhaled nitric oxide, is indicated for term and near-term (>34 weeks) neonates. Inhaled nitric oxide has also been proposed for use in preterm infants. Another potential application of inhaled NO is to improve oxygenation in patients with acute hypoxemic 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 postoperative pulmonary hypertension, which can prevent weaning from ventilation and is associated with substantial morbidity and mortality.

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 two 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 by the Blue Cross and Blue Shield Association in 2012 indicated that:
- Prolonged use of INO [inhaled NO] beyond one to two weeks has not been shown to improve outcomes. Use of INO beyond two 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.

**Policy:**

**Inhaled nitric oxide meets** Blue Cross and Blue Shield of Alabama’s medical criteria for coverage as a component of treatment of hypoxic respiratory failure in neonates born at more than 34 weeks of gestation.

**Other indications for inhaled nitric oxide do not meet** Blue Cross and Blue Shield of Alabama’s medical criteria for coverage and are considered investigational, including, but not limited to, its use in adults with respiratory distress (ARDS) or premature neonates born at less than or equal to 34 weeks of gestation, adults and children with acute hypoxemic respiratory failure and postoperative management of pulmonary hypertension in children with congenital heart disease.

*Blue Cross and Blue Shield of Alabama does not approve or deny procedures, services, testing, or equipment for our members. Our decisions concern coverage only. The decision of whether or not to have a certain test, treatment or procedure is one made between the physician and his/her patient. Blue Cross and Blue Shield of Alabama administers benefits based on the member's contract and corporate medical policies. Physicians should always exercise their best medical judgment in providing the care they feel is most appropriate for their patients. Needed care should not be delayed or refused because of a coverage determination.*

**Key Points:**

This policy includes literature found via MEDLINE search through September 15, 2014.

**Term or Near-Term Neonates**

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 2006, identified 14 trials. Eleven trials compared INO to control (placebo or standard neonatal intensive care) in infants with moderate severity of illness scores; four of these trials allowed back-up treatment with nitric oxide (NO) if infants continued to satisfy the same criteria after a pre-specified period of time. Another two 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, 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 as follows:
Table 1: Combined Outcome: Death or ECMO

<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>Backup use of nitric oxide not allowed</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n=6</td>
<td>149/418 (36%)</td>
<td>194/335 (58%)</td>
<td>0.65 (0.55-0.76)</td>
</tr>
<tr>
<td>Backup use of nitric oxide allowed</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n=3</td>
<td>20/87 (23%)</td>
<td>14/75 (19%)</td>
<td>1.15 (0.67-1.97)</td>
</tr>
<tr>
<td>All studies</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N=9</td>
<td>169/505 (33%)</td>
<td>208/410 (51%)</td>
<td>0.68 (0.59-0.79)</td>
</tr>
</tbody>
</table>

Table 2: 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>
</tr>
</thead>
<tbody>
<tr>
<td>Backup use of nitric oxide not allowed</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n=6</td>
<td>35/417 (8%)</td>
<td>33/337 (10%)</td>
<td>0.92 (0.58-1.48)</td>
</tr>
<tr>
<td>Backup use of nitric oxide allowed</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n=3</td>
<td>9/79 (11%)</td>
<td>12/83 (13%)</td>
<td>0.86 (0.37-1.98)</td>
</tr>
<tr>
<td>All studies</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>n=9</td>
<td>44/496 (9%)</td>
<td>45/420 (11%)</td>
<td>0.91 (0.60-1.37)</td>
</tr>
</tbody>
</table>

Table 3: ECMO

<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>Backup use of nitric oxide not allowed</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n=6</td>
<td>128/418 (31%)</td>
<td>181/337 (54%)</td>
<td>0.61 (0.51-0.72)</td>
</tr>
<tr>
<td>Backup use of nitric oxide allowed</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n=2</td>
<td>11/24 (20%)</td>
<td>11/31 (35%)</td>
<td>1.14 (0.63-2.02)</td>
</tr>
<tr>
<td>All studies</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n=8</td>
<td>139/442 (31%)</td>
<td>192/368 (52%)</td>
<td>0.63 (0.54-0.75)</td>
</tr>
</tbody>
</table>

The investigators found that inhaled nitric oxide in hypoxic infants reduced the incidence of the combined endpoint of death or need for extracorporeal membrane oxygenation compared to controls. In a pooled analysis of eight 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 six studies in which back-up oxygen was not allowed (RR=0.65, 95% CI=0.55-0.76), but this was not the case in an analysis of the two studies in which nitric oxide was allowed (RR=1.15, 95% CI=0.67-1.97). Inhaled nitric oxide did not have a significant effect on mortality as the sole outcome measure. In a pooled analysis of nine studies, the risk ratio was 0.91 (95% CI=0.60-1.37). There was, however, a significant effect of inhaled nitric oxide on need for ECMO only. When findings of eight studies were pooled, the risk ratio was 0.63 (95% CI=0.54-0.75).

Another meta-analysis was published in 2010 by Golombek and Young. This study, however, was not based on a systematic review of the literature, and it included three industry-sponsored trials. The three trials (sample sizes of 235, 155, and 248, respectively) all compared INO at a...
starting dose of 20 ppm with a control treatment (100% oxygen, INO at 0ppm, 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 INO group (54.9 mmHg) than the control group (14.1 mmHg) (p<0.001). Duration of mechanical ventilation in patients who survived without ECMO, a secondary outcome of the analysis, was significantly lower in the INO group (11 days) than the control group (14 days) (p=0.003). The article did not report survival or need for ECMO.

Evidence from RCTs and meta-analyses of RCTs support the use of INO in term or near-term infants to improve the net health outcome. These data have established that the use of INO 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 two 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 INO for premature infants (<35 weeks’ gestation) was published. Thirty-one articles were initially selected; these included 14 unique RCTs. Studies had sample sizes ranging from 29 to 800, and data from 3461 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 seven 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 eight trials reporting BPD at 36 weeks’ postmenstrual age among survivors resulted in a RR of 0.93 (95% CI, 0.86 to 1.00).

A 2010 Cochrane review by Barrington and Finer also identified 14 RCTs that evaluated the efficacy of INO as a treatment of respiratory failure in preterm infants. The authors categorized studies into three categories depending on entry criteria. There were nine trials that selected patients for treatment based on oxygenation criteria, three studies that routinely used inhaled NO in infants with pulmonary disease, and two studies of late treatment based on risk of bronchopulmonary dysplasia. Study findings were not pooled. The authors of the Cochrane
review concluded that inhaled NO was not effective at reducing mortality or BPD in any of the three categories.

The largest trial to date was published in 2010 by Mercier and colleagues. This was a multicenter industry-sponsored study known as the European Union Nitric Oxide trial and it 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 5ppm (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.

Primary outcomes were survival without BPD at 36 weeks’ postmenstrual age, overall survival (OS) 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 INO 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). OS at 36 weeks’ postmenstrual age was attained by 343 (86%) in the INO group and 359 (90%) in the control group (RR=0.74; 95% CI, 0.48 to 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 to 1.17; p=0.29). The secondary end point of 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=0.23). This end point was attained by 181 (69%) patients in the INO group and 188 (76%) patients in the placebo group.

Rates of serious adverse events (AEs) (i.e., intraventricular hemorrhage, periventricular leukomalacia, patient ductus arteriosus, pneumothorax, pulmonary hemorrhage, necrotizing enterocolitis, sepsis) were 158 (40%) of 395 patients in the INO group and 164 (41%) of 397 patients in the control group, p=0.72. The most common AE was intracranial hemorrhage, which affected 114 (29%) in the INO group and 91 (23%) in the control group (exact p value not reported).

In 2013, Durrmeyer et al published two-year outcomes of the European Union Nitric Oxide trial. Of the original 800 patients, 737 (92%) were evaluable at this time point. The evaluable children excluded those who did not receive treatment or who were lost to follow-up. A total of 244 (67%) of 363 evaluable children at two years in the INO group survived without severe or moderate disability compared with 270 (72%) of 374 evaluable children in the placebo group. The difference in disability rates was not statistically significant (p=0.09). There were also no statistically significant differences between groups in other outcomes such as hospitalization rates, use of respiratory medications, or growth.

Newer studies, such as an RCT with 124 premature newborns published by Kinsella et al in 2014, continue to find a lack of benefit of INO for reducing the rate of mortality or BPD, or reducing the need for mechanical ventilation.
A large number of RCTs evaluate INO for premature neonates, with most trials reporting no difference on primary end points. Meta-analyses of these RCTs have not found better outcomes with INO in premature neonates. This evidence does not support the routine use of INO in preterm infants.

**Adults and Children With Acute Hypoxemic Respiratory Failure**

A number of RCTs and several meta-analyses of RCTs have been published on the efficacy of INO for treating acute respiratory distress syndrome (ARDS) and acute lung injury (together known as acute hypoxemic respiratory failure [AHRF]). Most recently, a 2014 meta-analysis by Adhikari et al identified nine RCTs conducted with adults or children (other than neonates) in which at least 80% of patients, or a separately reported subgroup, had ARDS. 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. A pooled analysis of data from the nine trials (total n=1142) 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 PaO2/ fraction of expired oxygen [FiO2] ≤100 mmHg) or in patients with mild to moderate ARDS (baseline PaO2/FiO2 >100mmHg).

Other systematic reviews and meta-analyses had similar findings. 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 hypoxemic respiratory failure). Studies of neonates were excluded. The authors identified a total of 24 papers that underwent full review. They excluded eight trials, leaving 16 reports of 14 trials. Most trials included adults with a mixture of ARDS and acute lung injury; three trials included pediatric populations, and one 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: 0.93-1.22). Findings were similar for analyses of mortality after one 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 four 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: 1.17-2.16). Exact numbers of events were not reported for most secondary or sub-group analyses. The results of this analysis does not support of a benefit for inhaled NO in children and adults with hypoxemic respiratory failure.

A 2003 Cochrane systematic review identified five RCTs comparing inhaled NO and placebo for acute hypoxemic respiratory failure. All of these trials were included in the 2011 Afshari et al meta-analysis. The Cochrane authors conducted only one pooled analysis, and it combined findings from two 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: 0.66-1.44).

The largest individual trial was published by Taylor and colleagues in 2004 and did not report improvements for patients treated with inhaled NO. 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 nonpulmonary 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. A total of 92 of 385 (24%) randomized patients participated in the six-month follow-up, 55 in the inhaled NO group and 41 in the placebo group. Of 14 pulmonary function measures reported, five 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 five 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.

Evidence from numerous RCTs and multiple systematic reviews of these RCTs did not find significant effects of INO on mortality or duration of mechanical ventilation in adults and children with AHRF. This evidence suggests that INO is not an effective treatment for this patient population.

Postoperative Use in Adults and Children With Congenital Heart Disease

Children

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. All of the trials included participants who were identified as having pulmonary hypertension in the preoperative or postoperative period. Sample sizes in the four 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 two studies did not find a significant difference in mortality between the group receiving INO compared to the control group (OR: 1.67; 95% CI: 0.38-7.30). Among the secondary outcomes, a pooled analysis of two studies did not find a significant between-group difference in mean pulmonary arterial hypertension (pooled treatment effect: -2.94 mmHg; 95% CI: -9.28 to 3.40), and a pooled analysis of three studies did not find a significant difference between groups in mean arterial pressure (pooled treatment effect: -3.55 mmHg; 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. The study included 124 infants (median age three 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 INO gas 10ppm (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 INO after surgery had significantly fewer PHTC (median=4) than those receiving placebo (median=7); unadjusted relative risk: 0.66; 95% CI: 0.59-0.74, p<0.001. Among secondary outcomes, the median time until eligibility for extubation was significantly shorter in the INO than placebo group, 80 versus 112 hours, respectively, p=0.019. There were five deaths in the INO group and three 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 INO in adult patients undergoing left ventricular-assist device (LVAD) implantation for congestive heart failure. This double-blind trial was conducted at eight centers in the United States and Germany. Patients were randomized to receive INO (40ppm) (n=74) or placebo (n=77) beginning at least five minutes before the first weaning attempt from mechanical ventilation. The primary study outcome was right ventricular dysfunction (RVD). Patients continued use of INO 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 INO 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 INO occurred in 15 of 73 patients (21%) in the INO 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 INO 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 INO group and 11.1 in the placebo group (p=0.77), and the mean number of days in the hospital, 41 in each group.

Evidence from a number of small RCTs, and one 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 INO for adults.
with congenital heart disease. One RCT did not find a significant effect of treatment with INO on reduction of postoperative outcomes in adults with congestive heart failure who had LVAD surgery.

Summary

There is evidence from a Cochrane systematic review of fourteen randomized controlled trials that inhaled nitric oxide (INO) improves the net health outcome in hypoxic term or near-term infants. Other systematic reviews of randomized controlled trials did not find evidence of a net benefit from inhaled nitric oxide among preterm infants when used in the first three days of life for severe respiratory failure or after the first three days of life to prevent bronchopulmonary dysplasia. In children and adults with acute hypoxemic respiratory failure, systematic review of randomized controlled trials did not find that INO treatment had a significant effect on mortality or duration of mechanical ventilation. Thus, INO 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. The statement was based on the AHRQ-sponsored systematic review of the literature, described above. 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. 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 INO 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 AAP policy statement does not address the use of INO in premature infants.
U.S. Preventive Services Task Force Recommendations
Use of inhaled nitric oxide is not a preventive service.

Key Words:
Inhaled Nitric Oxide, Treatment of Respiratory Failure, Nitric Oxide, Inhaled, Respiratory Failure, INOmax™, iNO

Approved by Governing Bodies:
In 1999, INOmax™ (Ikaria®, Clinton, NJ) was approved by the 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 (>34 weeks) neonates with hypoxic respiratory failure associated with clinical or echocardiographic evidence of pulmonary hypertension.”

Benefit Application:
Coverage is subject to member’s specific benefits. Group specific policy will supersede this policy when applicable.

ITS: Home Policy provisions apply
FEP: Special benefit consideration may apply. Refer to member’s benefit plan. FEP does not consider investigational if FDA approved and will be reviewed for medical necessity.

Coding:
CPT Codes:

There is not a specific CPT code.

This service is usually billed on the hospital bill with revenue code 412 for inhalation services. The physician component is included in critical care services.

References:

Policy History:
Medical Policy Group, July 2010 (3)
Medical Policy Administration Committee, July 2010
Available for comment July 23-September 6, 2010
Medical Policy Panel, July 2011
Medical Policy Group, August 2011 (2): Description, Policy, Key Points, References updated
Medical Policy Administration Committee, September 2011
Available for comment September 22 through November 7, 2011
Medical Policy Group, August 2013 (2): 2013 Updates to Description, Key Points and References
Medical Policy Panel, October 2013
Medical Policy Group, December 2013 (2): No change in policy statement. Key Points and References updated with literature review through August 2013. Old references to Clinical Trials removed.
Medical Policy Panel, October 2014
Medical Policy Group, October 2014 (3): 2014 Updates to Description, Key Points & References; no change in policy statement

This medical policy is not an authorization, certification, explanation of benefits, or a contract. Eligibility and benefits are determined on a case-by-case basis according to the terms of the member’s plan in effect as of the date services are rendered. All medical policies are based on (i)
research of current medical literature and (ii) review of common medical practices in the treatment and diagnosis of disease as of the date hereof. Physicians and other providers are solely responsible for all aspects of medical care and treatment, including the type, quality, and levels of care and treatment.

This policy is intended to be used for adjudication of claims (including pre-admission certification, pre-determinations, and pre-procedure review) in Blue Cross and Blue Shield’s administration of plan contracts.