**Purpose:** To provide an evidence-based guideline for the use of inhaled nitric oxide (iNO) in the infant population.

**Target Client Population:** This guideline applies to term and preterm infants in acute hypoxic respiratory failure who have not responded to conventional therapies.

**Background**

Acute respiratory failure can commonly occur in infants of all gestational ages. In the preterm infant, respiratory failure typically presents secondary to an insufficiency of surfactant, a soap-like material that lines the air-spaces of the lungs. Respiratory failure in the term and late preterm neonate can result from conditions such as sepsis, meconium aspiration at birth, pulmonary hypoplasia or congenital diaphragmatic hernia (CDH). These conditions can cause elevated pressure in the pulmonary vessels. The classic characteristics of persistent pulmonary hypertension of the newborn (PPHN) include increased pulmonary vascular resistance, right-to-left shunting and severe hypoxemia. (ACCR/AHA, 2009)

Treatment of the preterm infant with respiratory failure usually involves administration of exogenous surfactant. In the term and late preterm (≥ 34 weeks’ gestation) neonate, management of acute respiratory failure could include administration of oxygen, continuous positive airway pressure, conventional or high-frequency ventilation, pharmacological intervention or extracorporeal membrane oxygenation (ECMO) using a heart/lung machine.

Inhaled nitric oxide therapy involves the administration of gaseous nitric oxide which dilates pulmonary vessels and decreases pulmonary vascular resistance. Because nitric oxide affects vascular muscle tone regulation in the pulmonary system, it has become a treatment for hypoxemic respiratory failure which is associated with high pulmonary vascular pressure. This treatment provides a less invasive alternative to ECMO treatment although the American Academy of Pediatrics recommends centers that provide iNO therapy either have ECMO available or have a transfer plan in place to an ECMCO center in the event that iNO treatment is not successful. (AAP, 2010) Multicenter randomized clinical trials have demonstrated improved oxygenation and reduction in the need for ECMO in neonates with refractory hypoxemia when iNO has been utilized. (ACCR/AHA, 2009)

INOmax® is a commercially available gaseous nitric oxide product which received 510(K) approval from the FDA in 1999. There are INOmax delivery systems which can administer the iNO in conjunction with a ventilator or other mechanical gas administration system such as INOmax DSIR®, INOmax DS® and INOvent®. These delivery systems allow the administration of an operator-determined amount of nitric oxide and should be calibrated using a precise calibration mixture of nitric oxide and nitrogen dioxide such as INOcal®. They also provide monitoring of inspired O₂, NO₂ and NO with an alarm system.

The GeNOsyl™ MV-1000 nitric oxide delivery device received 510(K) clearance from the FDA in 2012. It is approved to provide a constant set concentration of nitric oxide to the patient via mechanical ventilation and also includes monitoring of inspired O₂.
NO₂ and NO with an alarm system.

| General Information | • INOmax® is contraindicated in infants known to be dependent on right-to-left shunting. (INOMAX [package insert]. Clinton, NJ: INO Therapeutics LLC, 2010)  
• There is a risk of methemoglobinemia and increased NO₂ levels when nitric oxide is administered at doses >20 ppm. (INOMAX [package insert]. Clinton, NJ: INO Therapeutics LLC, 2010)  
• The recommended starting dose of INOmax® is 20 ppm and treatment can be maintained up to 14 days or until the underlying hypoxic lung disease has resolved and the neonate is ready to be weaned from iNO. (INOMAX [package insert]. Clinton, NJ: INO Therapeutics LLC, 2010)  
• Although there is variation in iNO dosing between facilities, a retrospective study by Guthrie et al (2004) comparing low-dose (< 18ppm), mid-dose (18-22ppm) and high-dose (>22ppm) nitric oxide administration showed no evidence that a higher dose of iNO improved patient outcomes.  
• INO may be indicated when a neonate with hypoxic respiratory failure has an oxygenation index > 20 to 25 or when PaO₂ is < 100 mmHg while receiving 100% oxygen.  (Barrington, 2017; Finer, 2006) |
| Treatment Criteria | Clinical evidence supports the use of iNO in the following situations:  
Administration of iNO is indicated for term or late preterm newborns (at least 34 weeks gestation at birth) who:  
• Have hypoxic respiratory failure or echocardiographic evidence of persistent pulmonary hypertension of the newborn syndrome and have failed conventional treatments for hypoxic respiratory failure such as mechanical ventilation. (AAP, 2000)  
• Have pulmonary hypertension in the acute phase following recovery from complex cardiac surgery (e.g., excludes patent ductus arteriosus (PDA) repair). iNO treatment is a reasonable bridge therapy during the acute recovery phase. (Simsic, 2014)  
• Do not have congenital diaphragmatic hernia with the exception of extremely rare situations where the short term use of iNO (up to 24 hours) for infants at least 34 weeks gestation at birth may be beneficial as a bridge to ECMO.  (Puligandla, 2015)  
If there is lack of positive response, iNO should be discontinued within 12-48 hours.  
Taken as a whole, the available evidence does not support use of iNO in early routine early rescue, or later rescue regimens in the care of premature infants <34 weeks gestation who require respiratory support.  
There are rare clinical situations, including pulmonary hypertension or hypoplasia, that have been inadequately studied in which iNO may have benefit in infants <34 weeks gestation. In such situations, clinicians should communicate with families regarding the current evidence on its risks and benefits as well as remaining uncertainties. These clinical situations pertain to infants who have extreme lability of arterial oxygen saturation (SaO₂), occurring in the immediate newborn period, |
who are unresponsive to surfactant and maximal ventilatory support with oxygenation index (OI) >25 and demonstrate echocardiographic evidence of PPHN. (Aikio 2012) Infants that do not demonstrate immediate and significant response to iNO should have this therapy discontinued. Infants who show significant response to iNO should have the medication weaned in a systematic manner following a short period of initial stabilization. For those infants who cannot be weaned promptly from the therapy, long term use of iNO in these situations has not been shown to be of proven benefit. Alternative therapies (e.g. sildenafil, bosentan, iloprost) should be considered/instituted. (Lakshminrusimha, 2016) The majority of infants will not demonstrate a sustained positive response from iNO and therefore treatment should be discontinued when the benefit disappears.

- Implementation of a hospital protocol decreases provider practice variation and cost and foster compliance with evidence-based guidelines (Todd Tzanetos, 2015)
- Persistent fetal circulation is commonly observed in preterm infants and should not be confused with the specific diagnosis of pulmonary hypertension.

There is insufficient clinical evidence to support the use of iNO as a therapy to decrease the risk of bronchopulmonary dysplasia (BPD) nor as a treatment for BPD.

For infants with established chronic lung disease with a defined acute exacerbation (i.e., sepsis, RSV pneumonia), a trial of iNO may be considered as an adjunct therapy. Infants that do not demonstrate immediate and significant response to iNO should have this therapy discontinued. Infants who show significant response to iNO should have the medication weaned in a systematic manner following a short period of initial stabilization. For those infants who cannot be weaned promptly from the therapy, long term use of iNO in these situations has not been shown to be of proven benefit. Alternative therapies (e.g. sildenafil, bosentan, iloprost) should be instituted. (Lakshminrusimha, 2016)

Clinical Evidence

Preterm infants

- A study by Manja et al (2019) evaluated neonatologists’ clinical decision to utilize iNO in extremely premature infants with PH and HRF (hypoxic respiratory failure) associated with prolonged ROM. A survey was developed and distributed to AAP members inquiring as to whether their management strategy would be to: 1) initiate iNO, 2) engage parents in shared decision making, or 3) not consider administering iNO to the infant cohort above. Approximately 300 participants completed the survey with 42% offering iNO treatment after involving parents in shared decision making, 36.5% initiating iNO, and 21.5% not considering iNO treatment. The authors concluded the decision to initiate iNO for these infants was based on the neonatologists’ previous clinical experience and the need to provide all possible options of treatment.

- A retrospective cohort study by Carey et al (2018) utilized the Pediatric Group Medical Data Warehouse to retrieve information on singleton neonates with a gestational age of 22-29 weeks’ who were born from 2004 to 2014. Inclusion criteria involved the use of mechanical ventilation for RDS. Infants with anomalies were excluded from this sample. The primary outcome of this study was death before discharge. Infants who had received iNO during the first seven days of life were matched with infants who had not received iNO prior to the index age for the matched pair. The final two matched cohorts
each contained 971 infants. The authors did not identify a significant association between treatment with iNO and pre-discharge death. They concluded that this off-label use of iNO did not reduce in-hospital mortality for extremely premature infants experiencing RDS.

- A Cochrane systematic review by Barrington et al (2017) analyzed the effects of iNO treatment on death, BPD, intraventricular hemorrhage (IVH) and other adverse outcomes in preterm infants with hypoxic respiratory failure. Seventeen randomized controlled trials were included for the authors’ evaluation. Of these 17 studies, eight addressed iNO use for early rescue with no significant effect on mortality or BPD demonstrated. The routine use of iNO for infants with pulmonary disease was addressed in four studies and no significant decrease in death or BPD was reported. No clear effect was found on the frequency of the grades or severity of IVH and no effect was found on the incidence of neurodevelopmental impairment. Although the authors concluded later the use of iNO for the prevention of BPD might be effective, they noted the effect size is probably small and additional research is necessary.

- The Pediatric Pulmonary Hypertension Network (Kinsella 2016) proposed the following recommendations for the role of iNO in premature newborns:(1) iNO therapy should not be used in premature infants for the prevention of BPD, as multicenter studies 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 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.

- An AAP clinical report, specific to the use of iNO in preterm infants, was published in January 2014. This document evaluated the evidence and subsequently provided guidance on iNO use in this infant population. Following review of RCT results, meta-analyses and an individualized patient data meta-analysis study, a strong recommendation based on high quality evidence indicated neither rescue nor routine use of iNO improves survival in preterm neonates with respiratory failure. Another strong recommendation also indicates high quality evidence does not support the use of iNO for preventing or reducing the incidence of BPD, severe intraventricular hemorrhage or other neonatal morbidities.

- In 2011 the National Institutes of Health (NIH) published a Consensus Development Conference Statement which indicated the available evidence did not support the use of iNO in early-routine, early-rescue or later-rescue protocols for preterm infants < 34 weeks gestation who required respiratory support. This statement was supported by the information from a 2010 AHRQ Evidence Report/Technology Assessment (#195) which indicated there was currently no evidence to support NO administration to preterm infants with respiratory failure outside of a rigorously conducted randomized clinical trial.

- The American Academy of Pediatrics (AAP) published a policy statement in 2000 (reaffirmed in 2010) on the use of iNO in infants with respiratory distress. This statement indicates that there is limited data on the use of low-dose iNO
for hypoxic preterm neonates. The available data suggests iNO improves oxygenation but does not improve survival in this patient population. The AAP calls for additional large randomized trials of iNO for premature infants as they may experience more toxic effects than the term and near-term infants.

- INOmax® (nitric oxide gas) was FDA approved on 12/23/1999. The approved indication includes treatment of term and near-term (>34 weeks) neonates with hypoxic respiratory failure associated with clinical or echocardiographic evidence of pulmonary hypertension, where it improves oxygenation and reduces the need for extracorporeal membrane oxygenation. ([INOMAX [package insert]. Clinton, NJ: INO Therapeutics LLC, 2010])

- A meta-analysis by Askie et al (2011) included data from 12 randomized controlled trials and 3,298 infants assessing the effectiveness of iNO therapy in infants < 37 weeks gestation. The two primary end points included CLD or death and serious adverse neurological consequences. Death or CLD was found to occur in 59% of infants treated with iNO compared to 61% of control infants. Data on infants experiencing severe neurological events demonstrated occurrence in 25% of iNO-treated infants versus 23% of infants in the control group. The authors concluded that the routine early use of iNO treatment in preterm infants for respiratory failure did not demonstrate benefit and cannot be recommended. It was noted that there may be a suggestion of benefit in certain subgroups but that this result most likely was due to the selection of the specific trials in the meta-analysis.

- Ellsworth et al (2015) performed a retrospective cohort study to evaluate whether the use of iNO in preterm infants had been affected by the 2011 NIH Consensus Statement and 2014 AAP report which discouraged its routine administration in this patient population. The dataset included 5,676 infants who received iNO administration during their NICU hospitalization from 2009 to 2013. The authors identified a 23% relative increase in iNO utilization for preterm infants 23-29 weeks’ estimated gestational age during this study period. Inhaled nitric oxide utilization in neonates ≥ 30 weeks’ estimated gestational age did not appear to be altered but nearly 50% of iNO administration during 2013 was provided to infants < 34 weeks’ gestation. The results of this study demonstrated increased off-label use of iNO in preterm infants despite clinical evidence and expert opinion to the contrary. The authors concluded there was insufficient evidence to recommend the use of iNO in the premature infant population.

- A retrospective study by Cheng et al (2015) sought to identify subsets in the preterm population ≤ 34 weeks gestation that would benefit from the administration of iNO. Functional echocardiography (fEcho) was utilized to aid in identification of hemodynamically compromised infants. Eighty-five infants met the authors’ inclusion criteria and had received iNO at less than four weeks postnatal age as an ‘early rescue’ strategy. Sixty percent of these infants survived beyond seven days. Within this survival cohort, gestational age and birthweight were found to be significantly greater and there was earlier initiation of iNO at a lower oxygen index. Infants > 28 weeks gestation and birthweight > 1,500 grams were found to have the highest survival rate. Among the infants who survived to discharge, 59% were diagnosed with BPD. The authors indicated future trials should focus on the effectiveness of iNO for infants with echo-proven persistent pulmonary hypertension of the newborn.

**Congenital Diaphragmatic Hernia (CDH)**

- A retrospective chart review by Kumar et al (2018) evaluated the effects of iNO and milrinone in infants with CDH. Seventy-two CDH infants from two regional perinatal centers were identified and classified into three groups: no iNO received, iNO responder and iNO nonresponder. Fifty-four percent (39/72) of these infants were noted as having received iNO. Twelve of these infants (31%) were recognized as having a complete oxygenation response to iNO. This response did not correlate with a decrease in right ventricular pressure (RVP) or ECMO use. Milrinone was also noted to have been administered to four infants in the iNO-responder group and eight infants in the iNO-nonresponder group and was observed to lower RVP and improve ejection fraction (EF).

- A systematic review by Barrington et al (2017) confirmed the efficacy of iNO in term and near-term infants with hypoxic respiratory failure who did not have diaphragmatic hernia. Seventeen randomized controlled trials evaluating term and near-term infants with hypoxia were included in the authors’ analysis. Since infants with congenital diaphragmatic hernias may respond differently to the iNO treatment than the other included infants, the result for this particular population was evaluated separately. The outcomes of infants with diaphragmatic hernia were not found to be improved with the use of iNO and moderate-quality evidence supported that outcomes were even slightly, but not significantly, worse.

- Putnam et al (2016) reviewed patient data from the Congenital Diaphragmatic Hernia Study Group registry in order to evaluate the utilization of iNO among newborn infants with CDH. Seventy participating centers in 13 countries had entered data on 3,367 infants diagnosed with CDH. Out of these 3,367 infants, 2,047 received iNO treatment. More than one-third of the patients without pulmonary hypertension were identified as still having received iNO. The use of iNO was found to be highly variable among the 70 centers and a positive association was detected between the trend of iNO use and mortality per center. The authors acknowledge the paucity of data supporting the utilization of iNO in CDH patients and indicate the results of their study strengthen the conclusion that this treatment is likely ineffective and may even be harmful when used to treat CHD patients.

- Gien & Kinsella (2016) discussed the management pulmonary hypertension in infants with congenital diaphragmatic hernia. The authors indicated the use of pulmonary vasodilators such as iNO may have a limited role during the early transition period, may play an important role in subacute treatment, and in late or chronic PH the role of iNO is noted as unclear.

- Puligandla et al (2015) performed a systematic review on the management of congenital diaphragmatic hernia (CDH). The authors identified limited high-level evidence on this topic, thus hindering the development of CDH management guidelines. The available studies indicated iNO or other medical adjuncts administered for acute, severe pulmonary hypertension demonstrated no benefit in patients with CDH. It was recommended that multi-institutional studies to identify best practices need to be performed.

- The American Association for Respiratory Care (AARC) published an evidence-based clinical practice guideline on iNO for neonates with acute hypoxic respiratory failure in 2010. This guideline recommends that iNO...
should not be used routinely in newborns with congenital diaphragmatic hernia.

• Campbell et al (2014) analyzed data from the Pediatric Health Information System (PHIS) regarding neonates with congenital diaphragmatic hernia (CDH) who had been treated with iNO. Thirty-three pediatric hospitals included in the database demonstrated wide variability in the use of iNO with more than half of the 1,713 neonates with CDH treated with iNO during their inpatient stay. Hospital-specific mortality rates of the surgically repaired CDH infants did not correlate with the hospital-specific iNO utilization before or after the repair, case volume or rates of ECMO use. The authors indicated available evidence does not support a clearly defined role for iNO treatment in CDH patients and there is excessive iNO use for neonates with CDH. This study demonstrated there is increasing iNO utilization for neonates with CDH without any improvement in mortality.

• A retrospective study by Malowitz et al (2015) evaluated the efficacy of iNO in infants with congenital diaphragmatic hernia (CDH). The authors identified 760 infants with CDH ≥ 34 weeks’ gestation who had been treated with medical interventions including iNO, ECMO, sildenafil, milrinone. In the study period from 1999-2001 to 2008-2012, the use of iNO in these infants was observed to increase from 20% to 50%. However, the overall mortality was not altered despite the changing use of these medical interventions.

Bronchopulmonary Dysplasia (BPD)/Chronic Lung Disease (CLD)

• The NEWNO (Newborns Treated with Nitric Oxide) Trial Group (2018) sought to determine whether iNO could prevent BPD in preterm infants <30 weeks’ GA requiring positive pressure ventilation. A placebo cohort of 222 infants was compared to 229 infants who received iNO for 24 days. The authors indicated survival free BPD at 36 weeks’ PMA was similar in both cohorts. In addition, iNO did not appear to improve neurodevelopmental outcomes at 18-24 months.

• A randomized study by Hasan et al (2017) evaluated whether the use of iNO improves the survival of preterm infants without the development of BPD. A total of 451 infants <30 weeks gestation with a birth weight of <1250 grams, postnatal age of 5-14 days when entered into study and who required mechanical ventilation or positive pressure respiratory support were included. Randomization included placebo (n=222) or iNO (n=229) for a 24-day course of treatment. The infants were assessed at 36 weeks’ PMA, 1-year corrected age, and 18-24 months PMA. Respiratory and neurodevelopmental outcomes between the two cohorts did not differ at 18-24 months’ PMA. The share of infants who survived to or were diagnosed with BPD at 36 weeks’ PMA also did not differ between the groups. The authors concluded that the administration of iNO, initiated at 20ppm on post-natal day 5-14 for a 24-day course of treatment, did not affect the incidence of survival without BPD at 36 weeks’ PMA or alter respiratory and neurodevelopmental outcomes at 18-24 weeks’ PMA.

• Lakshminrusimha et al (2016) noted that iNO for the treatment of PPHN is less effective when the infant is extremely premature, has BPD or has CDH. The authors indicated that alternative therapies with other intravenous or oral pulmonary vasodilators should be considered during both the acute and chronic phases of PPHN.
In 2008, Hibbs et al reviewed the 12-month outcomes of preterm infants (<1,250 grams) from the Nitric Oxide Chronic Lung Disease Trial, a randomized clinical trial which sought to assess whether iNO treatment decreased long-term pulmonary morbidities in this patient population. The group of infants who had received iNO therapy contained fewer infants with BPD than the group of preterm infants who had not received iNO therapy. According to the authors, however, this difference did not reach statistical significance.

A systematic review of the literature on the use of iNO in preterm infants (≤ 34 weeks gestation) was performed by Donohue et al in 2011. Fourteen randomized controlled trials, 7 follow-up studies and one observational study was included in their review. Twelve of these RCTs provided information on BPD in infants 36 weeks PMA. Even though the definition of BPD varied among the studies, the authors indicated there were no statistically significant differences in the rates of BPD found among the infants who received iNO and the infants who did not. The authors concluded that the use of iNO in preterm infants with respiratory failure was not supported at that time.

Soll (2012) performed a systematic review including 14 randomized controlled trials evaluating the use of iNO in preterm infants with respiratory failure. Nine of these trials involved early rescue based on oxygenation criteria with results demonstrating no significant effect on mortality or BPD. The additional studies which focused on routine use for pulmonary disease and later treatment based on increased BPD risk also provided no evidence to support improved outcomes in these preterm infants.

In 2013, Berkelhamer et al provided a review on pulmonary hypertension in bronchopulmonary dysplasia (BPD). It was reported that 25-40% of infants with BPD have some degree of pulmonary hypertension. The authors indicated that although the prevalence of treatment with pulmonary vasodilator medication was increasing, there was a paucity of clinical studies that supported their long-term safety and efficacy in infants with BPD.

A review by Baker et al (2014) provided current clinical recommendations for managing pulmonary hypertension (PH) in preterm infants with bronchopulmonary dysplasia (BPD). The authors indicated there was an absence of randomized controlled trials evaluating the patient outcomes of various treatments for PH in BPD. Although iNO therapy was recommended in the situation of acute pulmonary hypertension, the authors acknowledged that additional trials are warranted to substantiate the long-term safety and efficacy of acute and chronic treatments in BPD.

Per December 2010 new pediatric labeling, the efficacy of INOMax® in preventing BPD in premature infants had not been demonstrated by additional studies. (INOMAX [package insert]. Clinton, NJ: INO Therapeutics LLC, 2010)

Recovery after surgical intervention for Congenital Heart Disease (CHD)

Ichinose and Zapol (2009) address the use of iNO following congenital heart disease surgery in the 7th ed. of Miller’s Anesthesia. Based on the results of studies by Roberts et al (1993), Russell et al (1998), and Goldman et al (1996) the use of iNO appears to improve postoperative pulmonary hypertension and decrease the need for postoperative extracorporeal membrane oxygenation.

Bernstein (2011) outlines the general principles of treatment of congenital
heart disease in the 19th ed. of Kliegman: Nelson Textbook of Pediatrics. This text indicates “postoperative pulmonary hypertension can be managed with hyperventilation and inhaled nitric oxide”.

- Simsic et al (2014) evaluated the effectiveness of an institutional quality initiative directed at decreasing the variation of iNO initiation and weaning in pediatric patients with surgically treated cardiac defects. 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.

**Costs and Hospital Resources**

- Konduri et al (2015) compared hospital resource use and costs associated with early versus standard use of iNO in HRF. Their analysis demonstrated that the early use of iNO at an oxygen index of ≥ 15 and < 20 may be associated with shorter hospitalizations and a decreased cost of care for term/late preterm infants with hypoxic respiratory failure associated with pulmonary hypertension.

- A retrospective cohort study by Todd Tzanetos et al (2015) evaluated the utilization of an iNO protocol in PICU on cost and patient outcomes. A statistically significant decrease in the subject cost of iNO treatment between the pre-protocol cohort (n=38) and post-protocol cohort (n=38) was demonstrated. No significant difference in mortality was identified between the two cohorts. The authors report that the use of evidence-based protocols can ensure prudent use of medical resources.

**Specialty Society Guidelines**

- American Academy of Pediatrics: Use of Inhaled Nitric Oxide in Preterm Infants (2014)
- Canadian Paediatric Society: Inhaled Nitric Oxide Use in Newborns (2012)

**Bibliography**


ECRI. Nitric oxide for treating pulmonary hypertension in pediatric cardiac patients. Health Technology Assessment Info Service (HTAIS), ECRI Institute, Plymouth: PA. [Hotline Response, 07/09/2013]


**Revision History**
The following are approved changes incorporated into the revision numbers indicated below.

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<tr>
<th>Revision</th>
<th>Date</th>
<th>Description of Change</th>
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<td>V1.0</td>
<td>05/01/2014</td>
<td>New medical necessity clinical guideline. (CE)</td>
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<tr>
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<td>05/01/2015</td>
<td>Annual review with update by RS. (CE)</td>
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<tr>
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<td>09/03/2015</td>
<td>Guideline revised with changes to treatment criteria. (CE)</td>
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<td>04/06/2016</td>
<td>Annual review with update by RS. Information on iNO weaning added. (CE)</td>
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<tr>
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<td>04/18/2016</td>
<td>Revision from medical necessity document to clinical guideline by RS. Renamed with removal of MD Escalation section. (CE)</td>
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<tr>
<td>V4.1</td>
<td>04/18/2017</td>
<td>Annual review with updated literature search. Recommendations by AJ and NRS medical directors. Revised clinical guideline will be published 11/30/2017 to sync up effective dates of all NRS guidelines. (CE)</td>
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<td>Revised guideline published. Additional information on discontinuation after lack of response and protocols for standardization included. (CE)</td>
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