

Newborn Critical Care Center (NCCC) Clinical Guidelines

Treatment with Inhaled Nitric Oxide for Patients Without Congenital Diaphragmatic Hernia

PURPOSE

Provide recommendations related to the clinical use of inhaled nitric oxide (iNO) for term and near-term neonates (infants \geq 34 weeks gestation) with hypoxemic respiratory failure associated with clinical or echocardiographic evidence of pulmonary arterial hypertension.

BACKGROUND

Persistent pulmonary hypertension of the newborn (PPHN) occurs as a primary developmental defect or as a condition secondary to other diseases such as meconium aspiration syndrome (MAS), pneumonia, sepsis, respiratory distress syndrome, congenital diaphragmatic hernia (CDH) and pulmonary hypoplasia. In these states, pulmonary vascular resistance (PVR) is high, which results in hypoxemia secondary to right-to-left shunting of blood through the patent ductus arteriosus and foramen ovale. iNO improves oxygenation by selectively dilating pulmonary blood vessels in **ventilated areas** of the lung. The redistribution of pulmonary blood flow to areas with normal ventilation/perfusion (V/Q) ratios increases the partial pressure of arterial oxygen (PaO₂).¹

INDICATIONS

A trial of inhaled nitric oxide (iNO) is recommended in newborns (\geq 34 wks gestation) with partial pressure of oxygen in arterial blood (PaO₂) $<$ 100 mm Hg on fraction of inspired oxygen (FiO₂) = 1.0 and/or an oxygenation index (OI) $>$ 20,^{2,3} **AFTER** optimal alveolar recruitment has been achieved and adequate systemic blood pressure. Consider surfactant administration for cases of respiratory distress syndrome, meconium aspiration syndrome and/or sepsis.⁴ Note that pre-ductal PaO₂ values are expected to be higher than post-ductal PaO₂ in these patients, though often post-ductal values are measured in these patients.

INITIATING THERAPY

1. The starting dose for iNO is 20 parts per million (ppm).
2. A response to a short trial (30–60 min) of iNO should be judged by an improvement in PaO₂ or oxygenation index (OI); if there is no response, the iNO should be discontinued.
3. For newborns with a response to iNO therapy, it is recommended that the dose should be weaned to the lowest dose that maintains the desired clinical response to avoid excessive exposure to nitric oxide (NO), nitrogen dioxide (NO₂) and methemoglobinemia. Literature suggests there is no difference in oxygenation response between 20 ppm and 5-6 ppm,⁵ though 20ppm is associated with an improved pulmonary-systemic blood flow ratio.⁶
4. The expected response is rapid, typically occurring in less than 30 minutes. Response defined as:
 - a. A PaO₂ increase \geq 20 mmHg or 20% improvement from baseline
 - b. An increase in oxygen saturation \geq 10%
 - c. 20-20-20 rule: consider starting at OI of 20 with iNO at 20ppm. Considered a

responder if there is an increase in PaO₂/FiO₂ ratio of 20 mmHg or more. ⁷

5. Methemoglobin
 - a. Obtain a methemoglobin level prior to starting iNO therapy
 - b. Obtain a methemoglobin level 1 hour after the initiation of therapy
 - c. Obtain a methemoglobin level daily while on iNO
 - d. The iNO should be weaned if the methemoglobin level concentration rises above 5% and an attending or fellow must be notified

WEANING THERAPY

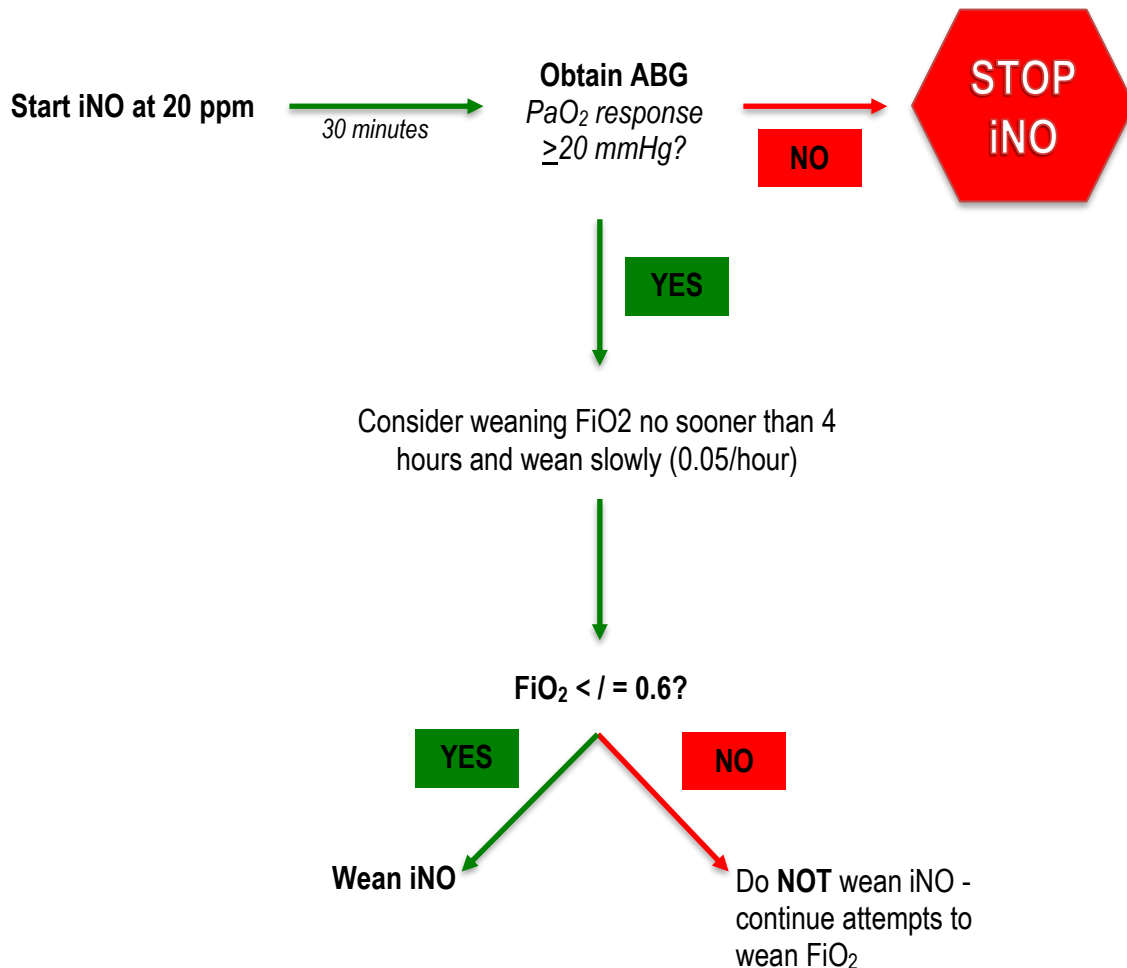
A **suggested** weaning schedule is as follows:

1. Consider weaning the iNO when the **FiO₂ is ≤ 0.60**
2. Wean iNO from 20 ppm to 10 ppm while assessing and maintaining the targeted oxygen saturations and PaO₂ values on stable FiO₂. The infant should remain on 10 ppm for a minimum of **60 minutes** before additional changes are considered. ⁸
3. Wean iNO from 10 ppm to 5 ppm while assessing and maintaining the targeted oxygen saturations and PaO₂ values. The infant should remain on 5 ppm for 60 minutes before additional changes are considered.
4. Once at 5 ppm, **wean the iNO more slowly** by 1 ppm no more rapidly than every 60 minutes while assessing and maintaining the targeted oxygen saturations and PaO₂ values.
5. Consider discontinuing iNO therapy from a dose of 1 ppm.

INITIATION OF iNO THERAPY (>= 34 WEEKS GESTATION)

Indications:

1. $\text{PaO}_2 < 100$ mmHg on $\text{FiO}_2 = 1.0$
2. Pre-ductal oxygen saturations $< 92\%$ on $\text{FiO}_2 = 1.0$
3. Evidence of PPHN while receiving oxygen as defined by:
 - a. Echocardiogram
 - b. Clinical judgement if echocardiogram is unavailable: fluctuating hypoxia ($\text{SpO}_2 > 10\%$) on stable oxygen requirement, pre-/post-ductal saturation gradient $> 10\%$.
 - c. Oxygenation Index (OI) ≥ 20



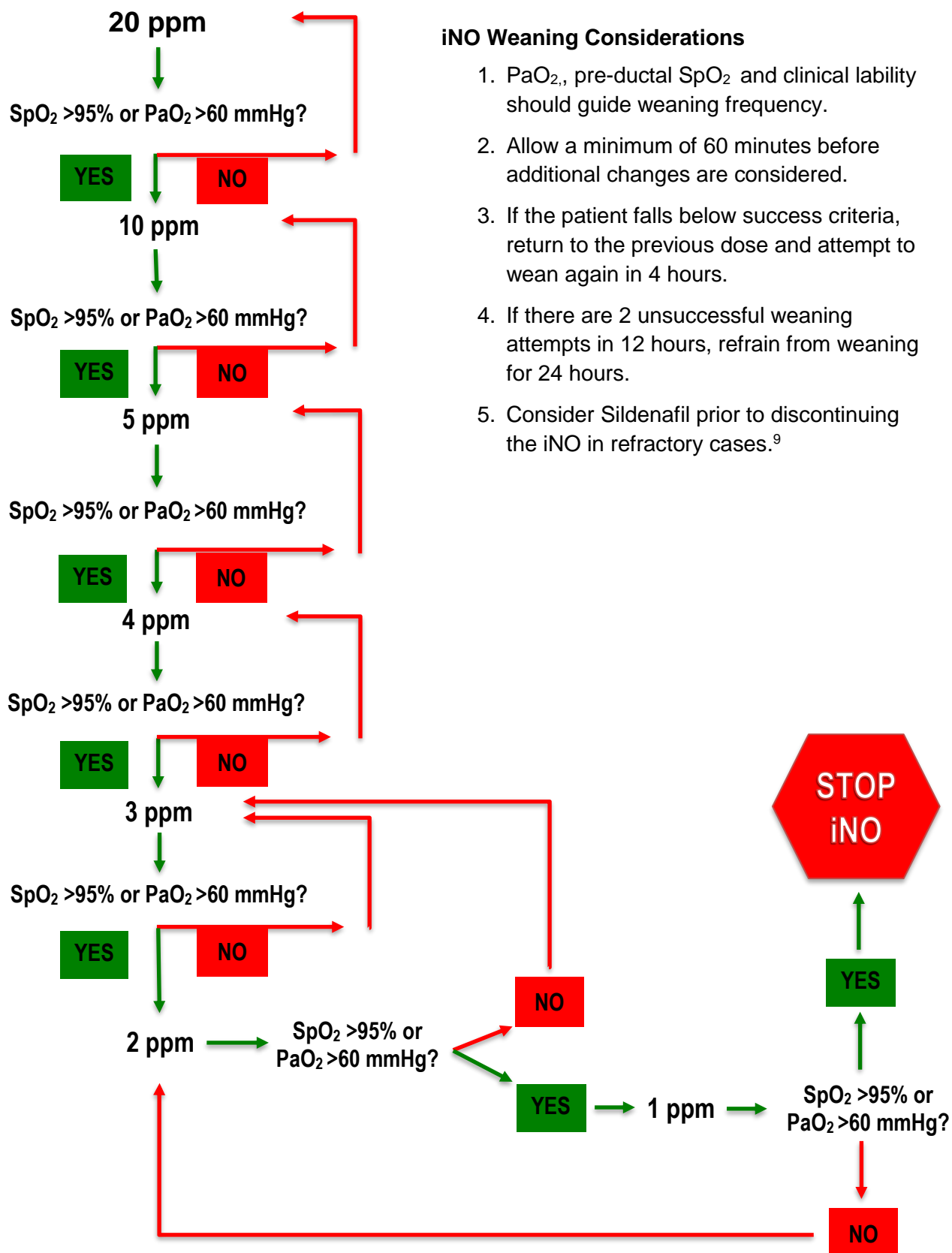
Positive response indicators

1. Increase in $\text{PaO}_2 > 20$ mmHg or 20% increase from baseline, PaO_2 goal > 60 mmHg
2. Increase in SpO_2 by 10% if PaO_2 is not available
3. Decrease in pulmonary artery pressure by 20% on echocardiography

Methemoglobin (normal $< 5\%$)

1. Obtain a level prior to initiating iNO therapy and 1 hour after initiating iNO
2. Obtain a level daily thereafter
3. If methemoglobin exceeds 5%, wean iNO or discontinue

SAMPLE iNO WEANING PROTOCOL



iNO Weaning Considerations

1. PaO₂, pre-ductal SpO₂ and clinical lability should guide weaning frequency.
2. Allow a minimum of 60 minutes before additional changes are considered.
3. If the patient falls below success criteria, return to the previous dose and attempt to wean again in 4 hours.
4. If there are 2 unsuccessful weaning attempts in 12 hours, refrain from weaning for 24 hours.
5. Consider Sildenafil prior to discontinuing the iNO in refractory cases.⁹

References:

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