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 >/= 34 weeks gestation) with hypoxemic respiratory failure associated with clinical or echocardiographic evidence of pulmonary arterial hypertension.

In preterm infants, the risks, and benefits of iNO use are controversial. Many scientific organizations do not recommend the use of iNO in preterm infants, except in unique clinical circumstances with echocardiographic findings of PPHN in the setting of presumed pulmonary hypoplasia.

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 (PaO_2).[1] iNO improves oxygenation and reduces the need for ECMO therapy in patients with diverse causes of PPHN.

INDICATIONS

A trial of inhaled nitric oxide (iNO) is recommended in newborns (≥34 wks gestation) with partial pressure of oxygen in arterial blood (PaO_2) <100 mm Hg on fraction of inspired oxygen (FiO_2) = 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). Higher doses are not recommended because they are associated with increased levels of nitrogen dioxide and methemoglobin.
2. A response to a short trial (30–60 min) of iNO should be judged by an improvement in PaO_2 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 (NO_2) 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 PaO_2 increase ≥20 mmHg or 20% improvement from baseline
    b. Post-ductal SpO2 increased ≥ 5% [12, 13]
    c. **20-20-20 rule**: consider starting at OI>/=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 (refractory patients may need slower wean)is as follows:

1. Consider weaning the iNO when the **FiO2 is ≤ 0.60**
2. Wean iNO **by 5ppm every 4 hours** while assessing and maintaining the targeted oxygen saturations and PaO2 values on stable FiO2.
3. The infant should remain at 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 frequently than every 60 minutes (can wean by 1ppm every 4 hours) while assessing and maintaining the targeted oxygen saturations and PaO2 values. (*If the infant does not tolerate wean, return to the previous iNO ppm and resume wean after 4 hours*)
5. Consider discontinuing iNO therapy from a dose of **1 ppm.**
6. Rapid weaning could result in rebound pulmonary hypertension due to iNO down regulation of endogenous NO production.

INITIATION OF iNO THERAPY (≥ 34 WEEKS GESTATION)

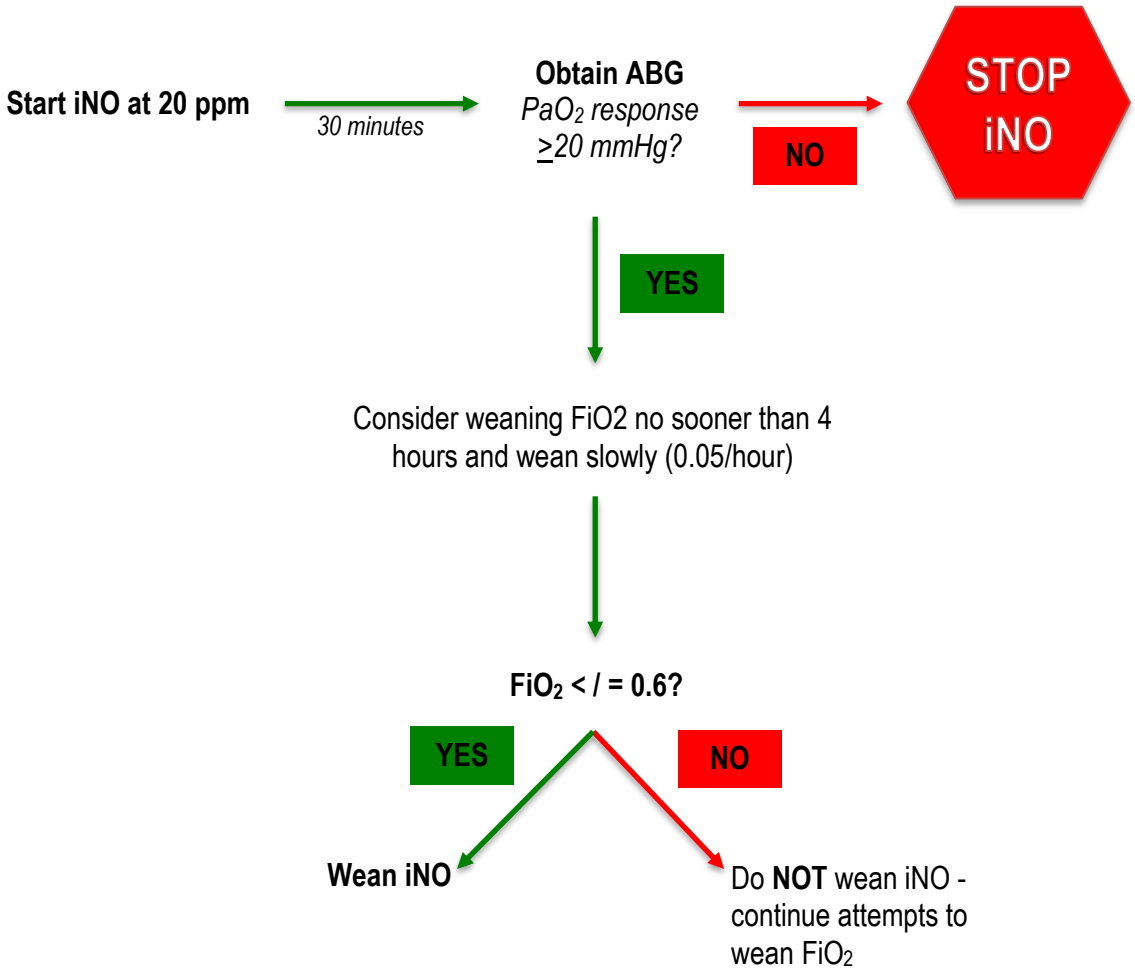
INDICATIONS

1. PaO_2 < 100 mmHg on FiO_2 = 1.0
2. Pre-ductal oxygen saturations < 92% on 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 (SpO2>10%) on stable oxygen requirement, pre-/post-ductal saturation gradient >10%.
    c. Oxygenation Index (OI) ≥ 20-25

POSITIVE RESPONSE INDICATORS

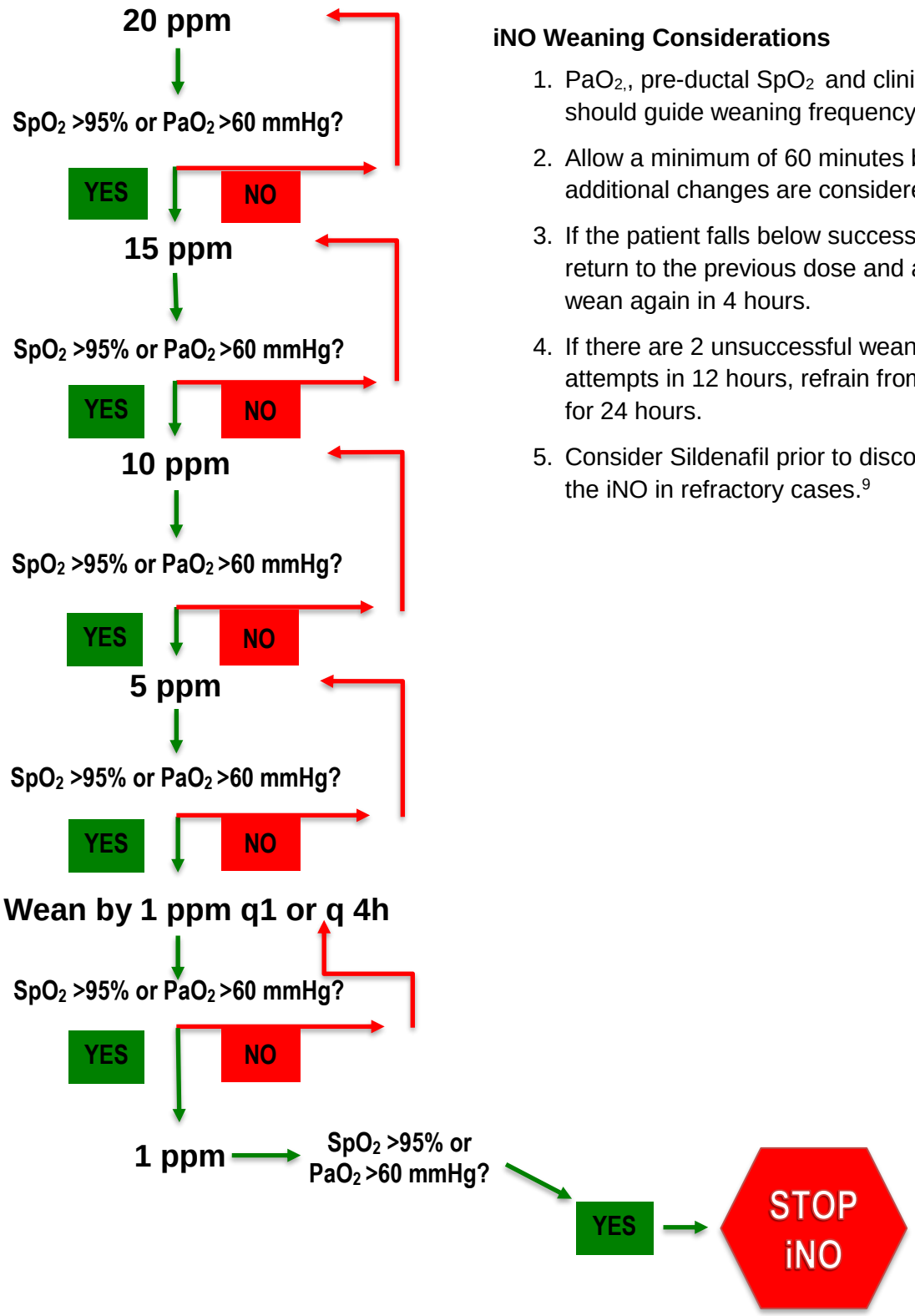
1. Increase in PaO_2 >20 mmHg or 20% increase from baseline, PaO_2 goal >60 mmHg.
2. Increase in SpO_2 by 10% if PaO_2 is not available.
3. Decrease in pulmonary artery pressure by 20% on echocardiography.

INITIATION ALGORITHM



Do not wean FiO2 faster than 10% per hour

SAMPLE iNO WEANING PROTOCOL



iNO Weaning Considerations

1. $PaO_{2,}$, pre-ductal SpO_2 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]

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