UC DAVIS HEALTH | CHILDREN'S HOSPITAL

Inhaled Nitric Oxide Use in Preterm Infants <34 Weeks of Gestation at Birth, aged <14 days with Persistent Pulmonary Hypertension (PPHN) in the NICU

Exclusion Criteria:
- Structural CHD
- Congenital abnormalities of the respiratory system (ie. CDH, TEF)
- Bleeding disorders (plt <50k)
- Known or suspected major hemorrhage (grade III or IV IVH)

Preterm Infant <34 Weeks of Gestation at birth, aged <14days with PPHN

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Obtain ECHO
(prior to starting iNO if possible OR shortly after starting)

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Initiating iNO 5-ppm
1. Obtain Baseline ABG*
2. Initiate iNO 5-ppm
3. After 30-60 mins, repeat ABG*

*CBG when arterial access not available

Optimize ventilator settings with adequate lung expansion (8-9 ribs)

Responsive to iNO 5-ppm
Post-ductal PaO_2 increase ≥20 mmHg if available
OR
FiO_2 decrease ≥20%
OR
Post-ductal SpO_2 increase ≥10%

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Maintain iNO 5-ppm
Wean FiO_2 (titrate for post-ductal SpO_2 92-98%)

Non-Responsive to iNO 5-ppm
Post-ductal PaO_2 increase <20 mmHg if available
AND
FiO_2 decrease <20%
AND
Post-ductal SpO_2 increase <10%

↓

Escalate iNO to 20-ppm
After 30-60 mins, repeat ABG*
(*CBG when arterial access not available)

Responsive to iNO 20-ppm
Post-ductal PaO_2 increase ≥20 mmHg if available
OR
FiO_2 decrease ≥20%
OR
Post-ductal SpO_2 increase ≥10%

↓

Maintain iNO 20-ppm
Wean FiO_2 (titrate for post-ductal SpO_2 92-98%)

Non-Responsive to iNO 20-ppm
Post-ductal PaO_2 increase <20 mmHg if available
AND
FiO_2 decrease <20%
AND
Post-ductal SpO_2 increase <10%

↓

Wean and discontinue iNO due to persistent non-response
Consider discontinuing iNO

Obtain repeat ECHO within 12-30h of iNO initiation

iNO Weaning – once the FiO_2 is at or below 0.60 note the baseline SpO_2 and begin weaning iNO every 2hrs per steps below.

Step 1: Decrease iNO to 10-ppm (if starting dose is 20-ppm)
Step 2: Decrease iNO to 5-ppm
Step 3: Decrease iNO to 4-ppm (if starting dose is 5-ppm)
Step 4: Decrease iNO to 3-ppm
Step 5: Decrease iNO to 2-ppm
Step 6: Decrease iNO to 1-ppm
Step 7: If preductal SpO_2 stays within 4% of baseline increase FiO_2 by 0.1 and stop iNO
Step 8: After 60 minutes assess patient and restart iNO at 1-ppm if FiO_2 > 0.6 to maintain SpO_2 ≥92%.

Failed weaning criteria: If preductal SpO_2 decreases by 5% or more from baseline go back to previous iNO dose and re-attempt in 12-24 hours.

Updated: (LM, 10/2026

Medical Disclaimer

Background

During the transition from fetal to neonatal circulation, nitric oxide (NO) plays an important role in regulating pulmonary vascular tone. In normal physiology, the rise in oxygen tension at birth is thought to contribute to an increased production of NO by the vascular endothelial cells, which promotes vasodilation of the pulmonary vasculature, improves ventilation-perfusion mismatch and decreases inflammation (Kinsella et al, 1997). When this transition doesn't develop properly and the pulmonary vasculature fails to adapt after birth, the circulation shunts blood away from the lungs across the ductus arteriosus and the foramen ovale, and ultimately leads to hypoxia (Rajiv et al, 2019). Numerous randomized controlled trials (RCTs) have demonstrated that inhaled nitric oxide (iNO), a selective pulmonary vasodilator, improves oxygenation and decreases the need for extracorporeal membrane oxygenation (ECMO) in term and near-term infants with hypoxic respiratory failure (Barrington et al, 2017).

iNO is an FDA-approved drug for use in term and near-term infants ≥34 weeks of gestation, but is commonly used off-label as rescue therapy for acute pulmonary hypertension and acute hypoxic respiratory failure in infants born at <34 weeks of gestation. In the PiNO trial (Inhaled Nitric Oxide for Premature Infants with Severe Respiratory Failure), 5-ppm iNO significantly increased PaO_2 and reduced oxygenation index when compared with placebo in preterm infants with severe respiratory failure ($p<0.001$). Escalation from 5-ppm to 10-ppm in non-responders did not provide additional significant benefit (Van Meurs et al 2005). Similarly, in another dose-response study of inhaled nitric oxide in hypoxic respiratory failure in preterm infants, no difference in response to iNO was reported between 5-ppm, 10-ppm, 20-ppm, and 40-ppm in preterm infants (Ahluwalia et al, 2006). Low dose iNO may adequately improve oxygenation while higher doses may increase methemoglobinemia, nitrogen dioxide exposure, and formation of oxidative and nitrosative metabolites. In addition, rapid decrease in pulmonary vascular resistance (PVR) in extremely preterm infants can potentially increase fluctuation on cerebral blood flow increasing the risk for intraventricular hemorrhage (IVH). Hence, at UC Davis, we propose to start iNO at 5-ppm in preterm infants <34 weeks of gestation and who are <14 days old after birth, and escalate to 20-ppm if the patient fails to respond in 30-60 minutes.

Inclusion Criteria – suspicion or confirmation of:

- Persistent pulmonary hypertension of the newborn
- Acute hypoxemic respiratory failure

Exclusion Criteria

- Obstructed Total Anomalous Venous Pulmonary Venous Connections (TAPVC); for other congenital heart disease (CHD) etiologies discuss with pediatric cardiology prior to use
- Known or suspected major hemorrhage (Grade III or IV IVH) due to risk of platelet dysfunction

- Left ventricular dysfunction (primary, not secondary to RV dysfunction)

iNO Initiation, Responsiveness, and Patient Monitoring

- In addition to routine cardio-respiratory intensive care monitoring, the following monitoring and workup are also recommended:
    - Initiation:
        - Obtain baseline vitals
        - Obtain ABG (CBG when arterial access is not available)
        - Baseline Methemoglobin
        - Obtain ECHO (prior to starting iNO if possible)
            - Does not need to precede the clinical decision to initiate iNO; however, it should be obtained as soon as possible
        - **Start iNO at 5-ppm**
    - Monitoring:
        - Evaluate clinical response 30-60 minutes after initiation and obtain ABG (CBG is no arterial access):
            - Post-ductal PaO_2 increase ≥20 mmHg if available
              OR
            - FiO_2 decrease ≥20%
              OR
            - Post-ductal SpO_2 increase ≥10%
        - If no improvement seen, increase iNO dose to 20-ppm. Evaluate clinical response after 30-60 minutes and obtain ABG (CBG if no arterial access):
            - Post-ductal PaO_2 increase <20 mmHg if available
              OR
            - FiO_2 decrease <20%
              OR
            - Post-ductal SpO_2 increase <10%
        - Check a blood gas at least every 24 hours while on iNO.
        - Check methemoglobin at 1-hour, 4-hours and 24-hours after initiating iNO. Continue monitoring MetHgb at least every 24 hours while the patient remains on iNO. Monitoring of methemoglobin can be stopped once weaning is initiated.

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- Weaning:
    - Gradually wean as tolerated and per unit protocol, while monitoring closely for rebound pulmonary hypertension. Once the FiO2 is at or below 0.60 note the baseline SpO2 and begin weaning iNO every 2hrs per steps below:
    - Weaning Steps:
        - Step 1: Decrease iNO to 10-ppm (if starting dose is 20-ppm)
        - Step 2: Decrease iNO to 5-ppm
        - Step 3: Decrease iNO to 4-ppm (if starting dose is 5-ppm)
        - Step 4: Decrease iNO to 3-ppm
        - Step 5: Decrease iNO to 2-ppm
        - Step 6: Decrease iNO to 1-ppm
        - Step 7: If preductal SpO2 stays within 4% of baseline increase FiO2 by 0.1 and stop iNO
        - Step 8: After 60 minutes assess patient and restart iNO at 1-ppm if FiO2 > 0.6 to maintain SpO2 ≥92%.
    - Failed weaning criteria: If preductal SpO2 decreases by 5% or more from baseline go back to previous iNO dose and re-attempt in 12-24 hours.
    - For patients receiving an initial iNO dose of 5-ppm, begin the weaning protocol at Step 3.

Possible Adverse Events:

- Methemoglobinemia—generated by the oxidation of hemoglobin by nitric oxide
- Peroxynitrite/Nitrotyrosine formation—cytotoxic oxidant that can interfere with surfactant functioning and can cause vascular constriction
- Impaired platelet adhesion and aggregation

References:

Ahluwalia J, Tooley J, Cheema I, Sweet DG, Curley AE, Halliday HL, et al. A dose response study of inhaled nitric oxide in hypoxic respiratory failure in pre-term infants. Early Hum Dev. (2006) 82:477–83. doi: 10.1016/j.earlhumdev.2005.12.003

Barrington KJ, Finer N, Pennaforte T. Inhaled nitric oxide for respiratory failure in preterm infants. Cochrane Database Syst Rev. 2017 Jan 3;1(1):CD000509. doi:10.1002/14651858.CD000509.pub5. PMID: 28045472; PMCID: PMC6464861.

Bhatt DR, Braun D, Dizon RA, Shi JM, Weerasinghe S, Sabio A, et al. Retrospective study of preterm infants exposed to inhaled nitric oxide in Kaiser Permanente Southern California: morbidity, mortality and follow-up. Journal of perinatology: official journal of the California Perinatal Association. 2024.

Dixon F, Ziegler DS, Bajuk B, Wright I, Hilder L, Abdel Latif ME, et al. Treatment with nitric oxide in the neonatal intensive care unit is associated with increased risk of childhood cancer. Acta paediatrica (Oslo, Norway : 1992). 2018;107:2092-8.

Kinsella JP, Neish SR, Shaffer E, Abman SH. Low-dose inhalation nitric oxide in persistent pulmonary hypertension of the newborn. Lancet. (1992) 340:819–20. doi: 10.1016/0140-6736(92)92687-B

Kinsella JP, Neish SR, Ivy DD, Shaffer E, Abman SH. Clinical responses to prolonged treatment of persistent pulmonary hypertension of the newborn with low doses of inhaled nitric oxide. J Pediatr. 1993 Jul;123(1):103-8. doi: 10.1016/s0022-3476(05)81551-3. PMID:8320602.

Kinsella JP, Parker TA, Galan H, Sheridan BC, Halbower AC, Abman SH. Effects of inhaled nitric oxide on pulmonary edema and lung neutrophil accumulation in severe experimental hyaline membrane disease. Pediatr Res. 1997 Apr;41(4 Pt 1):457-63. doi: 10.1203/00006450-199704000-00002. PMID: 9098845.

Timberline S, Bhatt A, Sunderji S, Tancredi DJ, Lakshminrusimha S, Siefkes H. Novel scoring tool of hypoxemic respiratory failure and pulmonary hypertension for defining severity of persistent pulmonary hypertension of newborn. J Perinatol. 2023 Oct;43(10):1281-1287. doi: 10.1038/s41372-023-01762-w. Epub 2023 Aug 25. PMID: 37626160; PMCID: PMC10541330.

Vali P, Vento M, Underwood M, Lakshminrusimha S. Free radical damage can cause serious long-lasting effects. Acta paediatrica (Oslo, Norway : 1992). 2018;107:2099.

Van Meurs KP, Wright LL, Ehrenkranz RA, Lemons JA, Ball MB, Poole WK, Perritt R, Higgins RD, Oh W, Hudak ML, Laptook AR, Shankaran S, Finer NN, Carlo WA, Kennedy KA, Fridriksson JH, Steinhorn RH, Sokol GM, Konduri GG, Aschner JL, Stoll BJ, D'Angio CT, Stevenson DK; Preemie Inhaled Nitric Oxide Study. Inhaled nitric oxide for premature infants with severe respiratory failure. N Engl J Med. 2005 Jul 7;353(1):13-22. doi:10.1056/NEJMoa043927. PMID: 16000352

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