PERSISTENT PULMONARY HYPERTENSION OF THE NEWBORN

East Bay Newborn Specialists Guideline

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Background: Persistent pulmonary hypertension of the newborn occurs in ~2 per 1,000 live births in the Unites States and can lead to significant morbidity and mortality. While only inhaled nitric oxide (iNO) and high frequency oscillation (HFOV) have shown benefit for term and near term infants, various other targeted therapies have been used for the treatment of infants who are non-responders to iNO.

Goals:

To reduce morbidity and mortality by:

- safely administering the lowest possible FiO2 in order to vasodilate the pulmonary vascular bed which oftentimes requires the use of inhaled nitric oxide (iNO). High FiO2 without PPV can lead to absorption atelectasis and worsening VQ mismatch. Prolonged hyperoxia may also induce vasoconstrictors and worsen pulmonary hypertension.
- optimizing ventilation with lowest effective mean airway pressure, while maintaining adequate lung volume
- reducing agitation if contributing to labile hypoxemia

Additional considerations:

- Hypoxemia disproportionate to severity of parenchymal disease on CXR suggests idiopathic PPHN or CCHD
- If R→L shunt only at atrial level, pre-ductal and post-ductal (lower extremity) SpO2 will both be low.
- PPHN generally has more labile hypoxemia than CCHD

Diagnosis: (any of 3 criteria)

1. Pre (right radial) and post-ductal (UA, lower extremity) pO2 /O2 sat may show a difference, indicating a right to left shunt at the PDA level. Saturation gradient >5-10% and/or PaO2 gradient 10-20mmHg. However, if the shunt is at the PFO level, pre and post-ductal blood gases may be the same.

2. Labile hypoxemia: Major swings in oxygenation caused by very small changes in BP, pH, FiO2, or agitation
3. Echocardiogram: signs of pulmonary artery hypertension include right-to-left shunting at PDA and/or PFO level, tricuspid regurgitation, elevated right sided pressures, flattened interventricular septum, right atrial enlargement with bulging of the intraatrial septum to the left, right ventricular enlargement

Management by Systems:

Access:

- Obtain at least 1-2 venous ports, 1 arterial line

Respiratory

- Place pre-ductal (right arm) and post-ductal (leg) pulse oximeters.
- Optimize lung recruitment
    - 8-9 rib expansion
    - Gentle ventilation (i.e. HFOV), passive hypercapnia as both under and overinflation can lead to PVR increase
        - If PIP >25-28 cmH2O or Vt >6 ml/kg to maintain PaCO2<60 on CV, switch to HFOV.
    - HFOV + iNO showed greatest improvement in oxygenation in PPHN associated with parenchymal lung disease (RDS, PNA, MAS) (Class IIa, Level B)
    - Surfactant promotes lung expansion and reverses inactivation (Class IIa, Level A)
- Maintain pre-ductal saturation $\geq$90-95% with suggested goal PaO2 50-80 mmHg. Tolerate post-ductal SpO2 70-80s if lactates (<3mM/L) and UOP ($\geq$1ml/kg/hr) are normal.
- Alkalosis not recommended because of lack of demonstrated long term benefit and potential for cerebral injury and increased risk of deafness (Class III, Level B)
    - Target pH 7.25-7.45, preferably 7.3-7.4
    - Goal pCO2 40-60
    - Goal PaO2 50-80
    - Goal pre-ductal SpO2 90-95%
- Consider iNO if patient not responsive to oxygen or OI $\geq$25.

- Pulmonary vasodilators
  - Start iNO at 20 ppm when OI ≥25. Doses >20ppm did not increase efficacy and were associated with more adverse effects.
    - Complete response = increase in PaO2/FiO2 ratio by 20mmHg ("20 20 20")
    - Methemoglobin monitoring per EBNS iNO guidelines
  - Weaning iNO – please refer to EBNS iNO guidelines
  - Evidence does not support the use of iNO in preterm infants, especially those <1 week of age and <1kg

Cardiovascular

- Obtain an echocardiogram prior to initiation of iNO or as soon as possible, consult cardiology. Need to assess pulmonary hypertension, rule out congenital heart disease, and assess cardiac function.
- If iNO not effective and hypoxemia persists, further management is based on systolic blood pressure and ventricular function.
  - If BP stable but hypoxemia persists, consider phosphodiesterase (PDE) 5 inhibitors, especially with R-L shunt at PFO/PDA
    - Sildenafil IV (preferred) or PO
      - Load 0.42 mg/kg x 3 hr, then 0.07mg/kg/hr infusion. Consider load if extremely ill and need more immediate response.
      - PO 1-2 mg/kg/dose q6hr
      - Have vasopressors readily available for possible hypotension with sildenafil load
  - If BP normal but ventricular dysfunction:
    - Consider milrinone (inodilator) which inhibits PDE3, increasing cAMP
      - Start at 0.25 mcg/kg/min, titrate to 0.3 mcg/kg/min per response. Do not give loading dose.
    - If RV dysfunction or ductal dependent pulmonary circulation (i.e. tricuspid atresia, pulmonary atresia/stenosis), start PGE1 0.05 mcg/kg/min to unload the right heart.
  - If systemic hypotension present with normal or depressed ventricular function, consider: (goal: adequate UOP and normal lactate)
    - 10-20 ml/kg fluid boluses
    - Dopamine 5-20 mcg/kg/min
    - Epinephrine 0.02-0.1 mcg/kg/min

        - 2nd line: Hydrocortisone 1 mg/kg/dose IV Q6 and/or epinephrine 0.1 mcg/kg/min or higher
        - 3rd line: norepinephrine, vasopressin (get cortisol level if using high doses)
    - Hypotension from worsening or poor cardiac function, rapid deterioration → ECMO
        - term and near-term with PPHN refractory to iNO after optimization of resp/CV function (Class I, Level A)
        - Criteria: persistent hypoxemia (OI >40 or alveolar-arterial gradient >600 despite aggressive medical management), hemodynamic instability

FEN/Metab
- Correct hypothermia if not being cooled, consider discontinuation of cooling in patients with HIE and severe PPHN with refractory hypoxemia
- Correct hypoglycemia, hypocalcemia, hypovolemia (all of which can contribute to pulm vasoconstriction)
- Consider feeds when FiO2 < 60%, ventilator support is being weaned and off pressors

Neuro
- Goal: to allow spontaneous movement as tolerated without compromising oxygenation or ventilation
- Minimize handling, light, and sound
- Analgesia with opiates: morphine drip
- Muscle relaxants should be avoided due to association with increased mortality

ID
- CBC w diff and antibiotics for pneumonia or suspected sepsis

Chronic pulmonary artery hypertension

Target population: neonates with CDH or BPD
- Consult pulmonology and cardiology before starting any of these meds (not strong enough evidence to support use)
    1. Sildenafil PO 1-2 mg/kg/dose q 6hr
    2. Bosentan PO 1 mg/kg BID

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