

Persistent Pulmonary Hypertension of the Newborn (PPHN)

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Background:

Fetal physiology is characterized by high pulmonary vascular resistance (PVR) due to hypoxia induced vasoconstriction, and lower systemic vascular resistance, due to the placenta, a low-resistance circuit. Pulmonary vascular growth and response to vasodilator and vasoconstrictor inducing factors, such as nitric oxide (NO), prostacyclin (PGI₂), and endothelin-1 (ET-1) develop with gestation.

When the newborn takes its first breath, lung aeration and increase in oxygen vasodilate the pulmonary vessels, increasing pulmonary blood flow eightfold, and drop in pulmonary pressures. Removal of the placenta increases systemic blood pressure, leading to closure of fetal shunts (ductus arteriosus (DA) and foramen ovale (FO)), improving oxygenation. PPHN occurs when there is failure to transition, resulting in persistence of fetal circulatory pattern with elevated pulmonary pressures and right – to -left shunting, causing the hallmark of PPHN, hypoxemic respiratory failure.

Etiology

Secondary to parenchymal lung disease (80-90%):

Meconium Aspiration Syndrome (MAS)

Respiratory distress syndrome (RDS)

Pneumonia

Transient tachypnea of newborn

Pneumothorax

Lung hypoplasia:

Congenital Diaphragmatic Hernia (CDH)

Prolonged oligohydramnios

Idiopathic PPHN (10-20%):

Associated with medications that interfere with intrauterine pulmonary vasoconstriction such as COX inhibitors and SSRIs.

Diagnosis:

PPHN should be suspected in hypoxemic respiratory failure and confirmed with echocardiogram.

Clinical signs:

Splitting (difference in pre- and post- ductal saturations greater than 5-10%), with pre-ductal saturations higher than post-ductal

Labile hypoxia, that is desaturation with agitation

Echocardiography (gold standard):

Right ventricular hypertrophy
Septal flattening and bowing presence
Right-to-left or bidirectional shunt through the DA or FO
Estimation of right ventricular systolic pressures (tricuspid regurgitation or ductal gradient)
Assessment of ventricular function
Rule out congenital heart disease

Clinical Management of Infants with Hypoxemic Respiratory Failure in the NICU:**(Pre-ductal OI $\geq$ 10-15 or OSI $\geq$ 9)**

$$OI = \text{MAP} \times \text{FiO}_2 \times 100 / \text{PaO}_2$$

$$OSI = \text{MAP} \times \text{FiO}_2 \times 100 / \text{SpO}_2$$

Supportive therapy (All infants with FiO₂ requirement $\geq$ 50%):

- Quiet dark room with minimal stimulation.
- Pre- and post- ductal saturations,
- Frequent blood pressure monitoring
- Chest X-ray and pre-ductal arterial blood gas are recommended
- Consider place pre-ductal arterial line (limit to two attempts). If unable, UAC for lab draws and invasive blood pressure monitoring.
- Frequent gases to monitor metabolic and respiratory acidosis
- Central venous access with umbilical venous catheter or PICC line
- Echocardiogram

Goals:

- Pre-ductal SpO₂ between 92-97% (wean FiO₂ if SpO₂ $\geq$ 94% to avoid hyperoxia)
- Pre-ductal PaO₂ between 50-80 mmHg. If no pre-ductal arterial line, consider using pre-ductal OSI to monitor oxygenation.
- OSI limitations: SpO₂ $\leq$ 65% and $>$ 95%, OI $>$ 25.
- Central venous access with umbilical venous catheter or PICC line is recommended
- PaCO₂ goal: 45-60 mmHg, pH $>$ 7.25

Surfactant:

- Early surfactant in infants with parenchymal lung disease and OI $\geq$ 15, has shown to decrease the need for ECMO and Death.
- Consider administration of surfactant in infants requiring FiO₂ $\geq$ 30-40% in the presence of lung disease.
 - o One exception is infants with CDH, in which surfactant has not demonstrated to bring clinical benefit.

Ventilation:

- Start with conventional ventilation.
- Consider HFV if:

- MAPs $\geq$ 17 or Peak Inspiratory Pressures > 25
- Severe respiratory acidosis
- Air leak
- Caution: higher MAPs > 17-18 can lead to decreased venous return, and worsened hypotension.

Oxygen targets:

- Both hypoxemia and hyperoxemia have been associated with mortality in infants with PPHN.
- Hypoxemia should be avoided as it can increase PVR in animal studies.
- Hyperoxia should also be avoided as it has been shown to decrease response to iNO, increase in oxidant stress in animal models. Hyperoxia has also been associated with death and worsening HIE in at-risk infants.
- Pre-ductal saturation between 92-97% and weaning of FiO₂ if SpO₂ > 94%.
- If FiO₂ persistently greater than 50-60%, consider other pulmonary vasodilator.

Pulmonary Vasodilators:

Inhaled Nitric Oxide (iNO):

- First-line treatment for PPHN. Decreases ECMO in randomized multicenter trials, although mortality remained unchanged. It is also the **only FDA approved medication to treat PPHN**.
- Start when OI $\geq$ 10-15, echocardiographic concern for PPHN, and should be started early in the disease cycle, as delay in treatment has been associated with increase in progression to severe disease and decreased response to iNO in a randomized controlled trial.
- Starting dose: 20 ppm. Methemoglobin should be monitored during treatment course.
- Weaning is recommended when FiO₂ requirements are below 60%, with pre-ductal saturation $\geq$ 94%. Our practice is to wean every 4-6 hours, initially by 5ppm, until a dose of 5 ppm, then by 1 ppm. When weaning off iNO, FiO₂ should be held at 40-60% until off. Exception is if infant's SpO₂ consistently $\geq$ 98%.
- Echocardiogram preferentially prior or shortly after starting iNO, considering some cyanotic heart diseases may worsen with this treatment.
- Contra-indication to iNO is severe left ventricular dysfunction or concern for left outlet obstruction.

Milrinone:

- PDE3 inhibitor that induces relaxation through increase in cAMP levels. It is a non-selective intravenous vasodilator.
- It is useful in situations of ventricular dysfunction, as it is an inotrope, lusitrope and pulmonary vasodilation.
- Caution in infants with hypotension, acute renal injury or hypoxic-ischemic encephalopathy (HIE) requiring cooling, as this drug has a prolonged half-life, and can worsen hypotension.

- Adjunctive treatment with a vasopressor such as vasopressin or norepinephrine may be necessary to support blood pressure.
- In infants with severe LV dysfunction or LVOT obstruction, iNO is contra-indicated, and milrinone or epinephrine are the first line of treatment.

Sildenafil:

- PDE5 inhibitor that induces relaxation through increase in cGMP.
- For poor or incomplete response to iNO and cardiac function is normal.
- Alternative to milrinone in infants with HIE.
- It can also be used in infants with prolonged iNO exposure, unable to wean from treatment, and in resource limited settings when iNO is unavailable.

Hypotension Management:

- Hypotension occurs in 2/3 of ventilated newborns with PPHN.
- It is important to maintain appropriate systemic blood perfusion, optimizing oxygen delivery. Avoid aiming for supraphysiologic BPs as that may lead to high vasopressor use and worsening of PVR.
- MAP goals ≥ 35 -40 mmHg are recommended, and gestational age should be considered. In the presence of appropriate perfusion such as urine output, perfusion, and absence of metabolic acidosis, with appropriate oxygenation, lower BPs may be tolerated.

Management of hypotension should consider the presence or absence of ventricular dysfunction.

- **All infants with hypotension:**
 - iCa goal ≥ 1.2 to optimize cardiac output.
 - Hydrocortisone should be considered in every infant with hypotension, as it was associated with improvement in BP and oxygenation in newborns with PPHN. Stress dose of 1 mg/kg every 6 hours is recommended.
 - Combination of pressors should be considered in this population whenever higher doses are required ie epinephrine + vasopressin, milrinone + vasopressin / norepinephrine.
 - Avoid Dopamine, as it has been shown to increase pulmonary/systemic arterial ratio in animal and humans with PPHN in higher dosages. Other pressors are more appropriate for this condition.
- **Absence of ventricular dysfunction:** vasopressin (0.1-2 mU/kg/min) should be considered. It is a pressor that increases SVR with minimal to negative effect on PVR.
- Most concerning side effects: hyponatremia and urinary retention.
- Vasopressin can also be considered in infants with ventricular dysfunction requiring milrinone.

- An alternative to vasopressin in infants with acute kidney injury or hyponatremia is norepinephrine (0.05-0.3 mcg/kg/min), a mainly alpha vasoconstrictor with neutral pulmonary effects, that can decrease cardiac output if used alone.
- **Presence of right ventricular dysfunction:** low-dose epinephrine (up to 0.03- 0.1 mcg/kg/min) is recommended, as it is mainly an inotrope.
- Higher doses of epinephrine have significant non-selective alpha effect, leading to an increased pulmonary/systemic arterial pressure ratio, therefore should be avoided. In this case, adjuvant treatment with **vasopressin** is appropriate.
- The most concerning side effects of epinephrine: lactic acidosis and hyperglycemia. Dobutamine is an alternative to epinephrine, when patients present with significant acidosis.
- Consider use of PGE1 to offload afterload and improve cardiac output, especially if DA is small.
- **Presence of moderate to severe left ventricular dysfunction:** low-dose epinephrine (up to 0.03-0.1 mcg/kg/min) is recommended, as it is mainly an inotrope.
- Higher doses of epinephrine have significant non-selective alpha effect, leading to an increased pulmonary/systemic arterial pressure ratio, therefore should be avoided. In this case, adjuvant treatment with **dobutamine** is appropriate.
- The most concerning side effects of epinephrine: lactic acidosis and hyperglycemia. Dobutamine is an alternative to epinephrine, when patients present with significant acidosis.
- Avoid vasopressin and norepinephrine as those substances increase afterload and worsen LV function. If increasing doses of epinephrine and severe LV dysfunction to maintain BP, consider transfer to ECMO center
- Consider use of PGE1 to offload afterload and improve cardiac output, especially if DA is small.

Sedation Management:

Sedation is an important step to manage infants with PPHN, as lability is characteristic of those patients. However, paralysis should be reserved for infants with severe illness when all other management has been attempted, as it has been shown to increase mortality in those infants. Oversedation can also lead to hypotension and decreased cardiac output in those neonates.

- Dexmedetomidine (0.2 – 1.2 mcg/kg/hour): an analgesic and sedative agent being increasingly used in the neonatal population. It appears to be a safe drug with few adverse events, and provides adequate treatment for neonates. Additional benefits such as less time under mechanical ventilation, and decreased need for adjuvant treatment have been reported. It should be considered first-line in infants with PPHN as it has fewer hemodynamics effects. It can induce bradycardia, without significant effect on hypotension. It can be used individually, or as an adjunct to Fentanyl or Morphine.

- Fentanyl is a strong opiate commonly used in neonates that can be given intravenously in bolus or continuous infusion. It is short-acting, and fast-acting. Doses between 1-2 mcg/kg/hour are recommended. Fentanyl can lead to hypotension and respiratory depression, especially in higher doses. There are also concerns for prolonged mechanical ventilation, feeding intolerance, and worsened long-term neurodevelopmental outcomes.

ECMO Referral:

- Infants that do not respond to treatment or requiring higher doses of vasopressors or mean airway pressures should be considered for referral to an ECMO center: if:
 - Persistent OSI ≥ 16 or pre-ductal OI ≥ 25
 - Worsening hypotension despite two vasopressors
 - Need for Paralytics drip to maintain SpO₂
 - Mean Airway Pressure > 18-20 cm H₂O to achieve goal SpO₂
 - Severe LV dysfunction on Echocardiogram