Newborn Critical Care Center (NCCC) Clinical Guidelines

Persistent Pulmonary Hypertension of the Newborn (PPHN) Guidelines

Executive Summary PPHN

Persistent Pulmonary Hypertension of the Newborn (PPHN) is a clinical syndrome characterized by hypoxemic respiratory failure due to persistently elevated pulmonary vascular resistance (PVR) at birth. Persistent elevations in PVR lead to increased right-to-left shunting across the PFO and PDA, reducing pulmonary blood flow and manifesting as refractory hypoxemia. PPHN should be considered in any infant with marked hypoxemia, especially infants of term or late-preterm gestation or growth restricted preterm infants. For each patient with suspected PPHN, thorough evaluation of all potential pathophysiological etiologies is critical to optimize the therapeutic approach. Therapeutic interventions aim to optimize respiratory support, cardiac output, and systemic hemodynamics by accomplishing the following goals:

1. Reverse hypoxemia and respiratory acidosis
2. Provide cardiac support for myocardial dysfunction
3. Reduce pulmonary vascular resistance
4. Enhance systemic vascular resistance when inadequate
5. Treat underlying infections or inflammatory conditions which may exacerbate PPHN

Background PPHN

At birth, pulmonary circulation must undergo a rapid and dramatic decrease in PVR to facilitate the 8-fold increase in pulmonary blood flow for successful transition to postnatal life. This decrease in PVR at birth is initiated by the onset of ventilation, increased oxygen tension, and vascular shear stress, which produces vasodilation through enhanced release of vasodilators such as NO and PGI2. PPHN represents the failure to achieve and sustain the normal drop in PVR and the increase in pulmonary blood flow and oxygenation required for neonatal adaptation. Mechanisms that disrupt this process before birth resulting in PPHN remain incompletely understood. PPHN complicates many neonatal cardiopulmonary diseases and should be considered a possible cause of neonatal cyanosis.

PPHN is secondary to impaired or delayed relaxation of the pulmonary vasculature associated with a diverse group of cardiopulmonary pathologies such as meconium aspiration syndrome (MAS), congenital diaphragmatic hernia (CDH), congenital pneumonia, hypoxic ischemic encephalopathy (HIE/perinatal asphyxia), premature prolonged rupture of membranes (pPROM), pulmonary hypoplasia, respiratory distress syndrome (RDS) and underlying or associated congenital heart disease (CHD) (1,2). It is critical to understand the etiology, pathogenesis, altered physiology and impact of the interventions on the pathophysiology in order to manage these patients effectively. A physiology-based approach towards PPHN is essential to decrease morbidity and mortality. (3) Timely recognition and therapy are important because PPHN is associated with high rates of neonatal mortality and morbidity, including significant neurodevelopmental sequelae. (4)

Diagnosis of PPHN

1. Initial evaluation
    a. History and Physical Examination: Obtain a thorough history of risk factors for PPHN. Perform a comprehensive physical examination.
    b. Oxygen Saturation: Measure pre- and post-ductal oxygen saturation. A >3% difference in the absence of structural heart disease suggests PPHN, but its absence does not rule out PPHN if the ductus is closed or small. A >10% difference suggests significant shunting.
        i. The oxygenation index (OI= [MAP x FIO2 / PaO2] x 100) is used to assess the severity of hypoxemia, serial measurements should be performed
    c. Chest radiography: Differentiate etiology of PPHN (ie MAS, pneumonia, RDS, CDH). Evaluate for pneumothorax. Monitor lung expansion, targeting nine posterior ribs.
    d. Echocardiography: STAT echo is necessary to confirm PPHN and exclude cyanotic congenital heart disease (CHD). Assess the severity of PPHN (estimated RVP, evidence of RV dysfunction, septal flattening or bowing, blood flow direction across the PDA and PFO) and LV function.
        i. Structural heart disease (ie TAPVR, severe aortic coarctation, and hypoplastic left heart syndrome) may present as PPHN; empiric use of iNO in these patients may result in pulmonary edema, worsening hypoxemia, and systemic hypoperfusion.
        ii. The use of pulmonary vasodilators, like iNO or sildenafil, in cases of LV dysfunction, may worsen respiratory status.
2. Lab Evaluations
    a. Admission labs:
        i. CBC/diff, blood type and screen, chemistries, and blood culture.
    b. Arterial blood gas (ABG):
        i. Every 30-60min following ventilator adjustments until pH >7.2, then every 2 to 4 hours in ventilated patients for the initial 24 hours of life, pending clinical status and ongoing interventions.
    c. Serum lactate:
        i. Every 1 to 4 hours for the initial 24 hours, then trend if elevated or as indicated with level of metabolic acidosis, impaired organ perfusion, or with clinical change.
        ii. Reassess potential causes for lactic acidosis (ie hypovolemia, hypoperfusion, cardiac dysfunction, seizures, fevers, increased metabolic demands and/or high-dose vasopressors causing excessive vasoconstriction and impaired tissue perfusion)
    d. Chemistries
        i. Initially every 12 hours, then daily based on clinical scenario.

ii. Normalize “cardiac electrolytes” (calcium, potassium and magnesium) every 6 hours for the initial 24 hours, with de-escalation as indicated, based on replacement needs and clinical stability with normalized cardiac function.

Management

1. General Management Principles
    a. The severity of PPHN can range from mild hypoxemia with minimal respiratory distress to severe hypoxemic respiratory failure and cardiopulmonary instability. Interventions aim to reduce PVR, minimize shunting at the atrial and PDA level, optimize ventilatory support to achieve adequate oxygenation & ventilation, and optimize hemodynamic support to achieve adequate cardiac output.
        i. Prompt escalation of treatment including intubation, timely optimization of ventilation and oxygenation, early initiation of pulmonary vasodilators and inotropic support may prevent some infants from clinically deteriorating.
    b. Access: Place umbilical arterial (UAC) and venous catheters (UVC) for continuous blood pressure and blood gas monitoring, and need for multiple infusions
        i. Place a double lumen UVC
        ii. If a UVC is unsuccessful, consider placement of a peripherally inserted central catheter (PICC)
        iii. If UAC is unsuccessful, place a peripheral arterial line (PAL)
    c. Antibiotics: Collect blood culture, CBC/diff, and start broad-spectrum empiric antibiotic therapy to rule out pneumonia and/or sepsis, common causes of PPHN.
    d. Surfactant: Indicated for primary (RDS) or secondary surfactant deficiency (MAS, pneumonia, sepsis). Early administration of surfactant and lung recruitment is associated with better outcomes and reduced risk of ECMO or death.
    e. Correct metabolic abnormalities:
        i. Metabolic acidosis increases PVR and should be avoided. Acetate may be added to IVF. Rapid infusion of sodium bicarb should be avoided in infants with impaired ventilation as it may worsen intracellular acidosis.
        ii. Monitor and avoid hypoglycemia and hypocalcemia
        iii. Avoid polycythemia (maintain <60-65%) as hyperviscosity increases PVR
    f. Nutrition: Make NPO and provide adequate parenteral nutritional support. Maintain euglycemia and stable electrolytes.
    g. Temperature: Maintain normothermia to minimize O2 consumption.
    h. Pain and agitation: Decrease stimulation, minimize handling, light and sound. Employ sedation and analgesia as needed. Consider paralysis in severe cases with escalating respiratory support.
    i. For infants diagnosed with HIE and PPHN, therapeutic hypothermia is not contraindicated. Cooling, however, imposes some unique challenges in management.
        i. Therapeutic hypothermia and rewarming modify loading conditions and blood flow and careful adjustment of inotropic agents is recommended with

avoidance of those that contribute to increased pulmonary artery pressures if possible.

ii. A combination of pulmonary vasodilators to reduce RV afterload and inotropes supporting ventricular function and vasoactive agents supporting SVR is needed to optimize hemodynamics in PH during TH.

iii. Exercise caution in using pulmonary vasodilators in the presence of LV dysfunction. (5)

2. Respiratory Management

a. General Principles:

i. Respiratory support should be dictated by the clinical status and nature of the pulmonary parenchymal disease.

ii. Oxygenation and ventilation should be optimized prior to initiating iNO therapy

iii. Initial management may include nasal cannula, oxyhood or CPAP based on whether initial concerns are primarily related to oxygenation vs evidence of impaired ventilation.

iv. Infants with moderate to severe PPHN require intubation and mechanical ventilation or high frequency ventilation.

b. Supplemental Oxygen

i. Oxygen remains the first-line therapy for PPHN.

ii. O2 results in pulmonary vasodilation through endogenous NO production

iii. Use preductal oxygen levels to guide management as they represent oxygenation to coronary and carotid arteries.

iv. High FiO2 1.0 may be required initially but hyperoxia is to be avoided. It may contribute to oxidative stress, production of reactive oxygen species which impair NO production, inflammation, and pulmonary vascular injury.

c. Optimal Oxygen Levels and Target Blood Gas Measures:

i. Pre-ductal SpO2 93-97%

ii. pH 7.30 – 7.40

iii. PaO2 >80-100

iv. PaCO2 40-55 mmHg

d. Conventional Ventilator Management

i. Typically conventional ventilation will be initiated after intubation.

ii. Gentle ventilation strategies with optimal PEEP, relatively low peak inflation pressure or tidal volume, and a degree of permissive hypercapnia are recommended to ensure adequate lung expansion while limiting barotrauma and volutrauma.

iii. PPHN requires optimal lung recruitment (nine posterior rib expansion) to establish adequate gas exchange, optimize functional residual capacity (FRC), minimize ventilation-perfusion mismatch, and decrease PVR. Avoid

both under and overinflation which increase PVR. The presence of heterogenous areas of atelectasis should be factored into determining adequacy of inflation.

iv. Providing adequate sedation is key as agitation and ventilator dysynchrony can increase PVR and worsen hypoxemia.

e. High Frequency Ventilation

i. HFOV should be considered if conventional support is escalating (MAPs 12-14) and there is low-volume lung disease (MAS, pneumonia, atypical RDS).

- Consider a MAP setting that is 2-4 above the conventional MAP.
- In setting frequency (Hz), 10 is a typical starting point but if evidence of significant parenchymal disease without air trapping, lower Hz, 8-9, may optimize oxygenation and ventilation.

ii. Consider HFJV for parenchymal disease that is complicated by air leak or air trapping.

iii. Obtain an ABG 30 minutes following and a CXR 1 hour following transition to HFV.

3. Pulmonary Vasodilator Therapy

a. Inhaled Nitric Oxide (iNO)

i. iNO is a selective pulmonary vasodilator that transits ventilated alveoli to increase endothelial cGMP production, causing V/Q matching with minimal systemic effect.

ii. iNO is the preferred initial therapy following confirmation of PPHN without significant LV dysfunction.

iii. The oxygenation index is a critical measure in deciding when to initiate iNO.

iv. A trial of iNO is recommended in infants ≥34 wks gestation, with an OI >20, and confirmation of PPHN by echo and absence of structural heart disease

- In the presence of clinical signs of PPHN, an echo is not required for initiation of iNO but should be obtained as soon as possible to confirm the diagnosis and rule out CHD

v. Refer to iNO guidelines for details of initiating, monitoring and weaning iNO therapy

vi. Adequate lung recruitment strategies can improve the efficacy of iNO therapy and should be performed in patients with PPHN associated with parenchymal lung disease

b. Milrinone

i. Milrinone is a PDE3A inhibitor and increases cAMP levels, resulting in pulmonary vascular vasodilatation and decreased ventricular afterload

ii. Milrinone may be combined with iNO to augment pulmonary vasodilation

iii. It may be used in infants where iNO is contraindicated, such as in the presence of LV dysfunction and evidence pulmonary venous hypertension from raised left atrial pressure or in iNO non-responders.

iv. Systemic vasodilation is the most common, dose-limiting adverse effect. Use intravenous infusion without loading dose in neonates because of the risk of systemic hypotension.

v. Exercise caution with use in patients undergoing TH or with compromised renal function due to risk of drug accumulation.

c. Sildenafil

i. Sildenafil is a PDE5 inhibitor and causes pulmonary vascular dilatation by increasing cGMP levels.

ii. It may be considered in consultation with cardiology for infants with poor or no response to iNO and without systemic hypotension.

iii. May also be considered in infants who develop rebound PH or are at risk for chronic PH to facilitate weaning from iNO.

iv. Intravenous route is preferred over oral route in critically unwell infants. However, intravenous infusion may lead to systemic hypotension, so inotropic support should be anticipated.

d. Prostacyclin

i. Alternate agents for iNO-resistant PPHN include aerosolized prostaglandin E1 and inhaled prostaglandin I2 (PGI2). These are rarely used in the NCCC.

ii. The intravenous formulation epoprostenol carries a significant risk of systemic hypotension and is often avoided in critically unwell infants with PPHN.

iii. Iloprost is a synthetic prostacyclin (PGI2) that can also be delivered by aerosolization. Discuss with RT and PICU staff before initiating as PICU has more experience at UNC with this treatment.

e. Prostagalndin E1 (Prostin)

i. Infants with failing right ventricle may benefit from a patent ductus arteriosus (PDA), which can work as a “pop off” valve in cases with severely elated PVR.

ii. In infants with a constricting PDA, prostaglandin E1 will open the ductus arteriosus and keep it patent.

iii. This will decrease the RV afterload by allowing right to left shunt (5).

iv. Prostaglandin E1 use should be guided by echocardiography, consider consultation with cardiology and the PICU, and it would be specifically useful in infants with failing RV and a constricting ductus arteriosus.

4. Hemodynamic Support

a. General Principles:

i. Maintaining normal and mildly elevated mean arterial blood pressure (MAP) is vital in reducing right-to-left shunting of blood to a lower resistance systemic vascular circuit.

- Blood pressure may need to be supported at or beyond normal levels (MAP 50-60 mmHg).
- Consideration needs to be given, however, to the impact elevated SVR may have on patients with impaired cardiac function

ii. Hypotension in critically ill infants with PPHN should be treated promptly.

iii. The goals in the care of PPHN include not only respiratory support but concentrated attention to maintaining adequate SVR, optimal intravascular volume, good cardiac function, and augmenting systemic blood pressure with the proper vasoactive medications.

iv. Strategies used to achieve these goals vary for each patient and requires consideration of underlying pathology of the PPHN- sepsis, intrinsic lung disease, HIE and cardiac injury. Based on etiology, therapies employed to achieve the goals of hemodynamic support will vary.

b. Intravascular Volume Support

i. Adequate preload is critical to support an infant with severe PPHN

ii. Clinical exam including extremity temperature, perfusion, cap refill, and heart rate are useful indicators of adequate volume status.

iii. Hypotension may be a later finding for inadequate volume status

iv. Acidosis and elevated lactate levels may indicate inadequate volume

v. Arterial pressure tracings may show decreases in pressure during mechanical inspiration when intravascular volume is diminished.

vi. Treatments to Support Intravascular Volume

- 10 ml/kg fluid boluses with NS guided by observations of heart rate and perfusion response when intravascular volume is felt to be inadequate. If multiple boluses are indicated in the setting of metabolic acidosis, consider the use of LR.
- Maintain hematocrit at 40% and use PRBC transfusions as indicated

c. Improved Cardiac Contractility

i. Epinephrine (6)

- Should be considered as a first line inotropic support in PPHN (starting dose 0.05mcg/kg/min).
- Acts as a dose-dependent inotrope (at low doses via β1 and β2 adrenergic receptors up to 0.3 mcg/kg/min)
- At higher doses it can cause vasoconstriction via α1 and α2 adrenergic receptors.

- The potential advantage of epinephrine in PPHN relates to beta effects of epinephrine lead to reductions in PVR in the beta dense pulmonary circulation while increasing SVR.
- While imperfect as an IV medication, epinephrine may dilate the pulmonary vasculature while increasing systemic vascular resistance.
- There is the potential for hyperglycemia related to epinephrine infusion

ii. Milrinone

- A selective phosphodiesterase-3 inhibitor, has both inotropic and vasodilatory properties and modest chronotropic effects. It is associated with less tachycardia than some other agents.
- As a phosphodiesterase-3 inhibitor, it reduces the breakdown of cyclic AMP and can act synergistically with cyclic GMP promoters, such as iNO.
- Milrinone may be used to support right ventricular systolic function.
- It enhances lusitropy (cardiac relaxation), which in turn increases diastolic filling, stroke volume and cardiac output.
- Milrinone should be considered in neonates with PPHN refractory to 100% oxygen and iNO (assuming optimization of ventilatory support, sedation, etc.) with evidence of poor cardiac function on echocardiogram.

iii. Dobutamine

- Has been traditionally utilized for cardiac dysfunction in the setting of PPHN.
- It has predominantly β1 adrenergic effects followed by β2 adrenergic effects.
- Is effective in increasing cardiac contractility and thus may be useful in the setting of PPHN accompanied by decreased cardiac contractility

d. Vasopressors

i. Vasopressin

- A V1 receptor agonist, selectively vasodilates coronary, cerebral, pulmonary, and renal vascular beds while causing vasoconstriction in other systemic vascular beds.
- The mechanism of vasodilation in the pulmonary vasculature is thought to be from stimulation of oxytocin endothelial receptors and subsequent NO pathway activation.
- There are few published studies of the use of AVP in neonates. Limited observational data suggest that low-dose AVP (6 milliunits/kg/hr to 72 milliunits/kg/hr) might improve blood pressure, urine output, and oxygenation index in some infants with PPHN.

- A known complication of AVP is fluid retention and associated hyponatremia. Electrolytes should be carefully monitored.

ii. Norepinephrine

- Norepinephrine is more selective than dopamine with regards to receptor stimulation, acting primarily on α1 receptors resulting in vasoconstriction and minimal inotropic effect on β1 receptors.
- The vasoconstriction mechanism could affect both systemic and pulmonary arterial pressure. Interestingly, fetal lamb models have shown norepinephrine may decrease the basal pulmonary vascular tone through stimulation of α2 receptors and nitric oxide release.
- In newborns with PPHN, norepinephrine has been shown to increase pulmonary arterial pressure; however, unlike dopamine, the ratio of pulmonary/systemic arterial pressure decreased following norepinephrine infusion (0.98 to 0.87, $p < 0.001$).(9)
- This study also noted decreased oxygen requirement and increased post-ductal oxygen saturation supporting the notion of increased pulmonary blood flow following norepinephrine infusion.

iii. Hydrocortisone

- The mechanisms of cardiovascular effects of hydrocortisone administration are not completely understood, but both genomic and nongenomic steroidal effects seem to play a role.
- Hydrocortisone administration to preterm and term infants with vasopressor-resistant hypotension is associated with an improvement in BP, stoke volume (and a trend to increase in cardiac output) with a decrease in heart rate and need for vasoactive medications.
- Genomic upregulation of cardiovascular adrenergic and angiotensin receptors and inhibition of inducible nitric oxide synthase and prostaglandins are potential mechanisms.
- In addition, non-genomic effects such as better capillary integrity, inhibition of catecholamine metabolism and increase in intracellular calcium may be mainly responsible for the rapid onset of the hydrocortisone-induced BP improvement.
- Corticosteroids (hydrocortisone) are administered as an adjuvant or rescue therapy to neonates with hypotension not responding to the first or second-line vasoactive medications
- Hydrocortisone dosing is initiated per guidelines at 20 mg/m2/day divided Q 8 hours.

iv. Dopamine

- Has at lower doses renal and mesenteric vasodilator properties via dopaminergic receptors), is an inotrope at moderate doses via beta1 adrenergic receptors), and a vasoconstrictor at high doses via alpha1 adrenergic receptors)
- With the advent of agents with more specific impacts in PPHN, dopamine is potentially less effective
- Dopamine may cause *increased* pulmonary vascular resistance at higher doses and may impair oxygenation. (6-9)

Table 1. Summary of vasoactive medications

DRUG	DOSE RANGE	PRIMARY RECEPTOR EFFECT	PRIMARY GOAL	INDICATION	PVR	SIDE EFFECTS
Milrinone	0.25 - 0.5 mcg/kg/min	PD3 Inhibition	Increase CO, Decrease PVR	Cardiac dysfunction, Pulmonary Vasodilation	Decrease	Hypotension
Dobutamine	5 - 20 mcg/kg/min	β1, β2	Increase CO	Cardiac dysfunction	Decrease	Tachycardia, Vasodilation
Epinephrine	0.05 - 0.1 mcg/kg/min	β1, β2	Increase CO	Cardiac dysfunction, Hypotension	Decrease	Tachycardia Hyperglycemia
	0.1 - 0.3 mcg/kg/min	α1, α2, β1, β2	Increase CO and SVR		Decrease	
Dopamine	1 - 3 mcg/kg/min	Dopaminergic	Increase renal perfusion	Poor renal perfusion	No effect expected	None anticipated
	3 - 10 mcg/kg/min	β1, dopaminergic	Increase CO and SVR	Cardiac dysfunction, Hypotension	May increase	Tachycardia
	10 - 20 mcg/kg/min	α1, β1	Increase CO and SVR		Increase	
Norepinephrine	0.05 - 0.5 mcg/kg/min	α1, α2, β1	Increase SVR	Hypotension	Increase (higher doses)	Tachycardia
Vasopressin	6 - 72 mU/kg/hour	V1, V2	Increase SVR	Refractory hypotension	Decrease	Hyponatremia
Hydrocortisone	20 mg/m^2/day divided q8h	Uncertain	Enhances catecholamine responsiveness, improved vascular tone	Refractory hypotension	May decrease	Hyperglycemia

5. **Management of Pain, Discomfort, and Agitation**
    a. Because catecholamine release activates pulmonary α-adrenergic receptors, thereby potentially raising PVR, every effort should be made to minimize pain, discomfort, and overstimulation of infants with PPHN.
    b. Nonpharmacologic Pain Management
        i. Measures to enhance the infant's comfort and lower stress include lowering light levels and background noise.
        ii. In addition, comfortable positioning of the infant, addition of circumferential 'nest', minimizing tactile stimulation and loud talking, and ensure mechanical issues (misplaced ETT) are not contributing.
        iii. Most babies with PPHN will be NPO, however, they can receive mouthcare with sucrose 20% oral solution or breastmilk on a cotton swab to provide potential nonpharmacological comfort.
    c. Pharmacologic Pain and Agitation Management
        i. Opioid Analgesia
            - Fentanyl (1 to 4 mcg/kg/hour infusion) is an opioid analgesic that minimizes pain, may reduce adrenergic output, and improve synchrony with the ventilator
            - Morphine sulfate (0.05 to 0.1 mg/kg/hour infusion) is an alternative analgesic for infants who are not hypotensive.
        ii. Benzodiazepine
            - Midazolam (0.2 mg/kg IV) adds synergy with opioid analgesia. If ongoing non-opioid sedation is indicated, consider a Midazolam infusion at 0.05 mg/kg/hr
        iii. Neuromuscular blockade
            - Although not routinely recommended, brief neuromuscular relaxation is occasionally needed to achieve respiratory synchrony with mechanical ventilation. Treatment with Vecuronium (0.1 mg/kg/dose) initially as single or PRN doses may be considered though a continuous infusion may be beneficial if repeated PRN doses are needed.

6. **ECMO Consultation**
    a. Critically ill infants with PPHN should have a head US and renal US performed early in their course given the possibility of progressing to need for ECMO
    b. For infants with PPHN special attention regarding ECMO consultation should be paid to RV function on echocardiograms as evolving RV failure could lead to acute decompensation.
    c. Consider ECMO consultation for infants with PPHN and signs of significant barotrauma such as:
        i. Pneumothorax
        ii. Pneumomediastinum
        iii. Pneumopericardium
        iv. Pneumoperitoneum
        v. Subcutaneous emphysema

vi. PIE

d. Also consider ECMO consultation per ECMO guidelines for
   i. Oxygenation Index (OI) >30 on consecutive blood gases over 3 hours despite escalating intervention for support
   ii. Acidosis and shock unresponsive to medical management (requiring two pressors at escalating doses)

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