GUIDELINE

Persistent Pulmonary Hypertension of the Newborn (PPHN)

Scope (Staff):	Nursing and Medical Staff
Scope (Area):	NICU KEMH, NICU PCH, NETS WA

Child Safe Organisation Statement of Commitment

CAHS commits to being a child safe organisation by applying the National Principles for Child Safe Organisations. This is a commitment to a strong culture supported by robust policies and procedures to reduce the likelihood of harm to children and young people.

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Contents

Aim

To guide medical and nursing staff teams in timely diagnosis and management of PPHN.

Risk

Delayed diagnosis of infants with PPHN can lead to a delay in establishing adequate ventilation.

Key points

- PPHN should be considered in any infant with marked hypoxemia, especially if he/she is of late preterm or term gestation or is a growth-restricted preterm infant.
- When PPHN is suspected or iNO is required for PPHN management, the on-call neonatal consultant should be notified.
- PPHN can mimic congenital cyanotic heart diseases or sometimes can be an accompanying feature of cyanotic heart disease.
- Therapeutic interventions aim to optimise pulmonary gas exchange by reversing hypoxemia and respiratory acidosis, enhance cardiac output when there is myocardial dysfunction, decrease the abnormally elevated pulmonary vascular resistance by relaxing vascular smooth muscle within the pulmonary circuit, and increase systemic vascular resistance when it is inadequate.
- Infants <34 weeks GA, coagulopathy, active bleeding, stage 3 HIE, lethal congenital malformation, complicating structural and most forms of cyanotic heart diseases, and imminent death are contraindications for iNO use.

Pulmonary Causes

- Primary: Hypoplasia +/- congenital diaphragmatic hernia, congenital Pulmonary Airway Malformation (Severe forms of CCAM and Pulmonary sequestration), and alveolar capillary dysplasia
- Secondary: RDS, MAS, Pneumonia, and pleural effusion
- Iatrogenic: Ventilator-associated (high MAP) and air leak syndrome

Cardiac causes

- Congenital malformation: RV outflow obstruction, TGA, and anomalous pulmonary venous return
- Cardiac dysfunction: low cardiac output and poor contractility (Due to sepsis, HIE, acidosis, and cardiomyopathy)

Other causes

Systemic hypotension due to arteriovenous malformation (e.g., Vein of Galen aneurysmal dilatation and arteriovenous fistula), septic shock, and neurogenic shock

Diagnosis

Clinical presentation

Infants with primary PPHN mainly present with hypoxia and, therefore, can be misdiagnosed as cyanotic heart disease, whereas infants with secondary PPHN are expected to present with respiratory distress and sometimes respiratory failure, requiring increased oxygen and ventilator pressures. These infants may have prominent precordial impulses, loud second heart sounds, systolic parasternal murmurs due to tricuspid incompetence, and sometimes differential cyanosis between upper and lower limbs.

Cardiopulmonary monitoring

5-10% difference between pre- and post-ductal SpO2 can occur.

Blood gas interpretation

There can be a PO2 differentiation between upper and lower limbs. The degree of hypoxia is variable, and the pCO2 can be normal or low. Arterial blood gas is preferred to capillary or venous samples as it is more accurate in determining PO2; therefore, arterial access is highly recommended.

Chest x-ray

In primary PPHN, the lung fields are often clear or minimally opacified on x-ray. In secondary PPHN, the chest x-ray is mostly abnormal in keeping with the underlying respiratory condition (e.g., ground glass appearance in respiratory distress syndrome and patchy infiltration in Meconium Aspiration Syndrome). In both types of PPHN, a large cardiac shadow can be detected on a chest x-ray.

Oxygenation Index (OI)

The severity of PPHN is commonly assessed by oxygenation index (OI), reflecting the efficiency of oxygen uptake. OI calculation involves MAP (Mean airway pressure, in cmH2O), FiO2 (Fraction of inspired oxygen, in percentage) and PaO2 (Arterial partial pressure of oxygen, in mmHg).

Based on OI numbers, hypoxemic respiratory failure can be classified into mild (OI ≤ 15), moderate (OI > 15 to 25), severe (OI 25 to 40) and very severe (OI > 40) hypoxic respiratory failure.

$$OI = \frac{FiO2 \times MAP \times 100}{PaO2}$$

Echocardiography

Useful for:

- Excluding congenital cyanotic heart diseases,
- Evaluating pulmonary artery pressure by qualitative markers and comparing it to systemic blood pressure (E.g., Low ventricular output, myocardial dysfunction, bowing of the inter-atrial septum to the left atrium, prominent right-to-left shunting through ductus arteriosus, and flattening and bowing of interventricular septum toward left ventricle in moderate and severe PPHN, respectively)
- Measuring pulmonary artery pressure by quantitative markers (E.g., Peak velocity of Tricuspid Regurgitation (TR), as a direct indicator of right ventricular pressure and thus pulmonary arterial pressure [A velocity of > 2.8 m/s suggests PPHN], and right to left ductal shunt for more than 30% of the cardiac cycle).
- Assessing cardiac function, particularly for choosing inotropic agents, iNO, and other interventions affecting cardiac output and pulmonary perfusion and assessing the response to treatment (reduced velocity in left pulmonary artery as a sign of good response to iNO).

Management

Clinical examination/handling, pain, and agitation

Measures to enhance comfort and lower stress in infants include lowering the light level and background noise, avoiding excessive handling and tactile stimulation, positioning comfortably, and adding a circumferential ‘nest’. Most babies with PPHN will be kept NBM; however, they can receive mouthcare with sucrose 20% oral solution or breastmilk on a cotton swab to provide nonpharmacological comfort.

An opioid analgesic that minimises pain and might reduce adrenergic output, such as **Fentanyl** is a useful adjunct therapy in PPHN management. **Morphine sulphate** is an alternative analgesic for infants who are not hypotensive.

Agitation may complicate PPHN management, especially in achieving synchrony with mechanical ventilation. The first line in managing agitation is to ensure inadequate analgesia and mechanical issues (e.g., misplaced endotracheal tube) are not contributing. The addition of **Midazolam** adds synergy with analgesia. If ongoing non-

opioid sedation is required, Midazolam may also be useful in the absence of systemic hypotension.

Short-term muscle relaxation with a single dose or intermittent **Vecuronium** may be beneficial in labile infants. Although not routinely recommended, brief neuro-muscular relaxation occasionally is needed to achieve respiratory synchrony with mechanical ventilation. Muscle relaxants may have unwanted side effects such as hypoxemia, hypotension and bradycardia. Prolonged muscle relaxant infusions may also exacerbate oedema and are associated with prolonged muscle blockade and post-extubation muscle weakness.

Temperature and infection

Infants' temperature should be monitored and maintained in the normal range. Any associated infection should be treated with appropriate antibiotics. As secondary PPHN due to respiratory infection cannot be excluded, antibiotics are usually commenced in early critical phases. Along the progression course, they can be judiciously continued or ceased.

Ventilation/Oxygenation optimisation

Adequate ventilation should be provided by intubation and mechanical ventilation, ideally with premedication (sedation, muscle relaxant and judicious use of Atropine with potentially prolonged tachycardia), while aiming for pH near 7.4, PCO2 of 35-45 mmHg, SpO2 of 94-97%, and PaO2 of 60-90 mmHg. The aim is to keep the lungs well expanded, showing nine posterior ribs on the chest x-ray. Any PaO2 above 100 can cause lung injury and atelectasis without improving pulmonary vasodilation. This will worsen pulmonary vascular resistance (PVR) and will create oxygen free radicals. FiO2 should be weaned slowly as sudden changes in FiO2 will create hypoxemic episodes, which can worsen PVR.

Conventional mechanical ventilation (CMV) using a patient-triggered volume-targeted mode is the first option for most neonates. For conventional mechanical ventilated patients receiving peak pressures of more than 28 to 30 cmH2O and those who end up developing significant air leak on CMV, transitioning to high-frequency ventilation (HFV) should be considered. Specific ventilator strategies can be followed for different background lung conditions. High-Frequency Oscillation Ventilation (HFOV) is recommended for homogeneous low-volume lung diseases like surfactant deficiency, whereas High-Frequency Jet Ventilation (HFJV) is suggested for heterogenous high-volume lung diseases like meconium aspiration syndrome and air leak syndrome.

Haemodynamic support

Inserting both umbilical venous and arterial catheters is recommended. Optimal preload is crucial in maintaining cardiac output in the newborn. Haemodynamic status can best be assessed on cardiac ultrasound, looking at venous and atrial distension. If

indicated, volume expansion with saline boluses or blood should be considered to maintain mean arterial pressure (MAP) towards the higher side of the normal range for gestational age.

Inotropes

The use of inotropes in the management of PPHN is always a double-edged sword. In the past, a simplistic model of increasing pulmonary perfusion by increasing systemic blood pressure was adopted. We now know that this model is not always correct and that inotropes may lead to increased pulmonary vascular resistance, decreased cardiac output, and diminishing pulmonary blood flow (particularly in preterm infants). Tachycardia may worsen cardiac filling and diastolic function. The increased strain and afterload on an already compromised myocardium, particularly in preterm infants or the presence of left ventricular dysfunction, may hasten cardiac failure.

Optimal use and choice of inotropes should be guided by ultrasound assessment (Cardiac output, pulmonary flow, systemic output, and venous return). For detailed information about the choice of inotrope, please refer to the medication monographs and to the following table:

	Dose	Primary Receptor Effects	Indications	Potential Side Effects
Primary Goal:				
Increase Cardiac Output				
Dobutamine	5 – 20 mcg/kg/min	β_1, β_2	Cardiac dysfunction requiring rapid resolution	Tachycardia (++) Systemic vasodilation
Increase Cardiac Output and Decrease Pulmonary Vascular Resistance				
Milrinone	0.33 – 1 mcg/kg/min	PDE_3 inhibition	Cardiac dysfunction Pulmonary vasodilation	Systemic hypotension
Increase Both Cardiac Output and Systemic Vascular Resistance				
Dopamine*	0.5 – 2 mcg/kg/min	Dopaminergic	Poor urine output	Tachycardia (++) Pulmonary vasoconstriction
	2 – 6 mcg/kg/min	β_1, dopaminergic	Cardiac dysfunction	
	> 6 mcg/kg/min	α_1, β_1, dopaminergic	Hypotension	
Epinephrine*	0.05 – 0.1 mcg/kg/min	β_1, β_2	Cardiac dysfunction	Tachycardia (+++) Lactic acidosis Hyperglycemia
	0.1 – 0.5 mcg/kg/min	α_1, α_2, β_1, β_2	Hypotension refractory to dopamine	
Increase Systemic Vascular Resistance				
Norepinephrine	0.05 – 0.5 mcg/kg/min	α_1, α_2, β_1	Hypotension	Tachycardia (+) Pulmonary vasoconstriction
Vasopressin	0.1 – 1.2 mU/kg/min	V_1, V_2	Hypotension	Hyponatremia

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Blood parameters' correction

- Treat metabolic acidosis, electrolyte imbalance (Na, K, Ca, and Mg), abnormal blood sugar level. Magnesium may assist in pulmonary vasodilation; therefore, levels should be kept in the upper normal ranges (>1.00mmol/L).
- Treatment with bicarbonate is considered when serum pH is less than 7.
- Haemoglobin should be maintained at >100 g/L. On the other hand, polycythaemia and hyper-viscosity will increase PVR and will result in the release of vasoactive substances through platelet activation. Partial exchange transfusion aiming for a haematocrit level of 50% to 55% might be considered in an infant with PPHN whose central haematocrit exceeds 65%.

Nitric oxide (iNO)

iNO is a potent, selective vasodilator of the pulmonary vasculature and is considered the first line of treatment in PPHN to optimise ventilation-perfusion (VQ) match by preferential distribution to ventilated alveoli and increased perfusion. iNO has trivial effect on systemic vascular resistance because haemoglobin has a high affinity for NO and binds with NO when it reaches the circulation, thereby effectively inactivating any potentially adverse iNO-induced systemic vasodilation.

iNO is effective in term and near-term infants with hypoxic respiratory failure and reduces the incidence of death or use of ECMO (except for infants with congenital diaphragmatic hernia). The use of iNO in premature babies remains widespread in clinical practice: however, controversial, with limited evidence of clinical benefit. iNO should be used under the guidance and discretion of the Consultant Neonatologist.

Examples of clinical scenarios benefiting iNO are; Meconium Aspiration Syndrome, severe Hyaline Membrane Disease, congenital pneumonia, congenital respiratory malformations, and diaphragmatic hernia.

Infant >34 weeks gestation with hypoxic respiratory failure (SpO2 <85% despite FiO2 >80% and or high ventilation settings (e.g., PIP ≥ 30 cmH2O)) in the presence of clinical signs of PPHN and/or pre/post ductal saturation differentiation ≥ 10% are candidates for iNO. An Echo is not required for the initiation of iNO; however, it should be obtained as soon as possible to confirm the diagnosis of PPHN and to rule out congenital heart disease. Oxygen Index (OI) > 25 or OI > 15 in the presence of very rapid deterioration is also an indication to start iNO. iNO is used with a dose of 20 ppm for infants more than 37 weeks of gestational age, while its dose for infants less than this age is 10 ppm. Few neonatologists recommend doses above 20 ppm, although high doses of iNO have not been found to result in better therapeutic responses and are associated with an increased risk of toxicity. The desired response is a rapid improvement in oxygenation and a significant decrease in the gradient between

pre/post-ductal SpO2 levels, accompanying reduced pulmonary vascular resistance and right-to-left hemodynamic shunting.

Arterial blood gas should be checked after 15 minutes of initiation of iNO. If OI remains ≥40 for more than 30 mins or if OI stays >20 with a lack of improvement despite prolonged (>24 hrs) maximal medical therapy (iNO and mechanical ventilation), ECMO should be considered. iNO weaning from 20 to 15 ppm along with ventilator MAP decreasing can be commenced once the FIO2 is < 0.60 with a PaO2 > 60 mmHg and SpO2 > 92%. Subsequent weans in iNO dose should occur no sooner than 4 hours apart. iNO should be weaned by gradually dropping the dose if tolerated (20 ppm to 15 ppm, 15 ppm to 10 ppm, and 10 ppm to 5 ppm). From 5 ppm, the taper is in smaller steps: from 4, 3, 2, to 1 ppm. If, after performing an iNO wean, the SpO2 drops by > 5% and SpO2 is reading < 92% on > 0.60 FIO2, the wean is considered unsuccessful. In this case, the infant should be returned to the previous iNO dose (ppm) and/or FiO2 can be adjusted.

Close observation of haemodynamic changes and assessing lung volume by chest-x ray should be addressed optimise oxygenation and ventilation while avoiding excessive ventilation (PCO2 <40). Once the infant is at 1ppm and requiring FIO2 0.40 or less and has a SpO2 > 92%, a trial off iNO may be attempted. Few clinicians may increase the FIO2 as high as 0.60, if needed, to make this transition. After one hour, if FIO2 > 60%, SpO2 is labile, or if ventilator setting rises, restarting iNO at 1ppm should be considered. The next wean can again be attempted in 4-8 hours. Because iNO inhibits the endogenous production of NO by the endothelial cells in the blood vessels, when iNO is tapered, a sudden drop in SpO2 can occur associated with a spike in pulmonary vascular resistance with resultant pulmonary hypertension and resumption of right to left hemodynamic shunting. This is called the rebound phenomenon and is best avoided by gradual iNO tapering.

Prolonged bleeding times due to inhibition of platelet function by iNO have been reported; however, clinically significant bleeding has not been observed in term or late preterm infants.

Methemoglobin (MetHgb)

When iNO crosses from the alveoli to the pulmonary bed and binds with haemoglobin, it produces Methemoglobin (MetHgb), interfering with the oxygen-carrying capacity of haemoglobin. The higher the dose of NO, the greater the likelihood of an elevated MetHgb. This is less likely to occur at levels in the current recommended range of 20 ppm or less. Serum MetHgb levels should be checked in 24 hours after iNO is started and every 24 hours thereafter. If the infant demonstrates unexpected desaturation or other clinical deterioration, MetHgb levels should be rechecked. Concentrations above 5% are treated with Methylene blue as the first-line treatment, consider administration of Vitamin C and blood transfusion.

Staff Health and Safety with iNO

iNO is corrosive to the eyes, particularly for those wearing contact lenses. Wearing protective goggles is highly recommended in close proximity to the iNO cylinders. Removal of contact lens and immediate flush with large volumes of tepid water or saline for 15-20 minutes should be attempted when eyes are exposed to iNO. iNO is also an irritant for the nose and throat and can cause delayed cough, chest pain, nausea, dyspnoea, and haemoptysis.

Sildenafil

Sildenafil is a PDH5 inhibitor that raises cGMP in the smooth muscle cell, promoting vasodilation more selectively within the pulmonary vascular bed than systemic circulation. Evidence suggests it may benefit the patient's refractory to iNO and other conventional therapies or in resource-limited settings where iNO and high-frequency ventilation are unavailable. However, it is occasionally used as an adjunct to iNO (eg, if there is difficulty weaning from iNO). Sildenafil is available in both enteral and intravenous (IV) dosage forms.

Alprostadil (Prostaglandin E1)

Prostaglandin E1 is a vasodilator and may have direct beneficial effects on PVR and should be considered where there is a right-to-left Ductus Arteriosus (DA) shunt to maintain patency of the DA, allowing right to left shunting across the DA to depressurise a potentially failing right ventricle.

Other medications

- Surfactant
- Glucocorticoid
- Bosentan (Endothelin receptor antagonist)
- Magnesium Sulphate

There is insufficient evidence to support the use of the above-mentioned medications in the management of PPHN in neonates.

ECMO

Consideration of ECMO may be appropriate in neonatal patients with PPHN and severe hypoxic respiratory failure or right ventricular dysfunction despite maximal medical therapy and reaching OI>20. ECMO should be considered in infants whose oxygenation index stays ≥40 for more than 30 mins. See Extra Corporeal Membrane Oxygenation (ECMO) for the Neonate – Indications and Referral Process

Prognosis and follow-up

Survivors of PPHN require frequent follow-up post-discharge. Infants treated with iNO for more than 24 hours or ECMO should have neurodevelopmental assessments

performed at 6 to 12-month intervals through infancy and longer if abnormalities are present. Hearing should be assessed prior to hospital discharge and at 18 to 24 months of corrected age.

Related CAHS internal policies, procedures, and guidelines

Neonatal Medication Protocols

Neonatology Guidelines

- Extra Corporeal Membrane Oxygenation (ECMO) for the Neonate – Indications and Referral Process
- Nitric Oxide Therapy
- Meconium Aspiration Syndrome (MAS)

CAHS Guidelines

PCH Extracorporeal Membrane Oxygenation (ECMO) Guideline

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