Management of Persistent Pulmonary Hypertension of the Newborn (PPHN)

Guideline Responsibilities and Authorisation

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Guideline Review History

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Contents

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1 Overview

1.1 Purpose

To provide guidance on initial assessment and management of infants in NICU diagnosed with Persistent Pulmonary Hypertension of the Newborn (PPHN).

1.2 Staff group

Te Whatu Ora Waikato NICU medical staff (SMO, Medical Officer, NNP, CNS, Registrar, SHO) and nursing staff.

1.3 Patient / client group

- Term or late pre-term neonates > 34 weeks GA with PPHN in NICU.
- Used with caution in preterm infants < 34 weeks GA, as rescue treatment for severe hypoxic respiratory failure on a case by case basis.

1.4 Indications

- Symptomatic PPHN: proven clinically (i.e. at least 5-10% differential in pre/postductal saturations) or by echocardiography
- Severe hypoxaemic respiratory failure (i.e. OI >20, PaO2 <60 mmHg or <8kPa despite 100% FiO2). Refer Respiratory Indices Calculator https://starship.org.nz/health-professionals/calculators/respiratory-indices-calculator/
- Absence of lethal congenital malformation
- Careful consideration in presence of IVH (grade 2-4) or coagulopathy.

1.5 Definitions and acronyms

BP	Blood pressure
CHD	Congenital heart disease
CNS	Clinical nurse specialist
CVAD	Central venous Access Device
DA	Ductus Arteriosus
ECG	Electrocardiogram
ECHO	Echocardiogram
FiO2	Fraction of inspired oxygen
GA	Gestational age
Hb	Haemoglobin
iNO	Inhaled nitric oxide
IV	Intravenous line
IVH	Intraventricular haemorrhage
MABP	Mean arterial blood pressure
MAP	Mean airway pressure
MAS	Meconium aspiration syndrome
NNP	Neonatal nurse practitioner

OI	Oxygenation index
$PaCO_2$	Arterial partial pressure of carbon dioxide
PAL	Peripheral arterial line
PaO2	Arterial oxygen tension
PCV	Packed Cell Volume
PDA	Patent ductus arteriosus
PFO	Patent foramen ovale
PPHN	Persistent pulmonary hypertension
PVR	Pulmonary vascular resistance
RBC	Red blood cells
RDS	Respiratory distress syndrome
SHO	Senior house officer
TTN	Transient tachypnoea of the newborn
UAC	Umbilical arterial catheter
UVC	Umbilical venous catheter

2 Clinical management

2.1 Background

PPHN is associated with several diagnoses, and the pathophysiology is unique to each diagnosis. It is a challenging, dynamic, and labile process for which optimal care requires frequent reassessment.

Goals of care for PPHN are to optimize cardiopulmonary mechanics, prevent iatrogenic injury, and maintain adequate tissue oxygen delivery to support organ function.

Survivors of severe PPHN and/or ECMO treatment are at increased risk of developmental delay, motor disability, hearing deficits, and chronic health problems. iNO does not appear to increase the risk of adverse outcomes, including risk of neurodevelopmental impairment or pulmonary function.

2.2 Clinical diagnosis

Neonates with PPHN are hypoxemic with obligate right-to-left shunting across the PDA which produces the classic “differential saturations” that are virtually diagnostic of PPHN: pre-ductal (right arm) saturations measure **at least 5 - 10% greater** than post-ductal (lower extremity) saturations.

Physical examination may include:

- cyanosis,
- signs of respiratory distress,
- signs of intrauterine stress (i.e. meconium staining),
- Cardiac exam: prominent precordial impulse, narrowly split and accentuated second heart sound, sometimes a harsh systolic murmur consistent with tricuspid insufficiency.

2.3 Differential diagnosis /Aetiology

Appendix A outlines underlying aetiologies of PPHN, but the following conditions are often associated with an element of PPHN and should be considered as underlying causes:

- Cyanotic congenital heart disease
- Severe parenchymal lung disease (pneumonia, MAS, TTN, RDS)
- Sepsis
- Alveolar capillary dysplasia with misalignment of the pulmonary veins

2.4 Investigations

Necessary investigations include:

- Serial arterial blood gases (simultaneous pre- and post-ductal samples are helpful)
- Full blood count & differential
- Group & hold
- Blood cultures
- Blood glucose & electrolytes
- Chest radiograph
- Echocardiogram
- *Could consider baseline Electrocardiogram (ECG)*

2.5 Interventions

2.5.1 Vascular access

Early vascular access for intubated PPHN patients is recommended, with thoughtful de-escalation of lines and access once clinical stability is achieved

- **UVC or CVAD**: double lumen catheters may be more helpful to limit medication compatibility concerns and maximize access.
- **Peripheral IV**: consider at least one for administration of blood products, fluids, and medication boluses.
- **Arterial access (UAC/PAL)**: indicated for all ventilated PPHN patients to allow monitoring of serial blood gases and blood pressure. PAL should be considered in patients with severe PPHN, for whom concerns for escalation to ECMO exists.

2.5.2 Monitoring

- **Continuous pre and post ductal saturations**: provides real time assessments of PVR and provides a longitudinal marker of PH severity.
- **End-tidal or Transcutaneous carbon dioxide monitoring:** provides continuous monitoring of ventilatory status and acute changes.
- **Serial OI calculation** following each arterial blood gas measurement. This is used to assess the severity of hypoxemia in PPHN and to guide the timing of interventions, such as iNO administration or ECMO support.

  Typically, an OI threshold of 40 for at least 4 hours, or >20 for 24 hours despite medical optimization, is utilized for consideration of ECMO. (Fletcher 2018).

The OI is calculated as follows:

$$\textbf{OI} = 100 \times \textbf{FiO}_2 \times \frac{\textbf{MAP}}{\textbf{PaO}_2} \qquad \text{e.g. } 100 \times 0.8 \times \frac{18}{4.5} = 42.7$$

Note: FiO2 is in decimals, NOT percent e.g. 80% = 0.8

- **Continuous BP monitoring**: to monitor cardiovascular status.
- **Urinary catheter:** for measure of urine output, which is an important marker of end-organ perfusion.
- **Laboratory monitoring:** first 24h, then can be spaced as clinically indicated
  - **Arterial blood gas** (ABG) Q1-4h
  - **Serum lactate levels** Q1-4h
  - **Electrolytes and renal function, ionized calcium levels** Q6h

2.6 Management

General principles:

- Aim to lower PVR and reverse right-to-left shunting.
- Maintain adequate systemic BP and provide cardiac support for myocardial dysfunction. (recommend MABP>45-50 mmHg in term infant)
- Improve arteriolar oxygen saturation and oxygen delivery to the tissues, e.g. adequate Hb.
- Minimise barotrauma and impacts of procedures/handling.
- Quiet environment (reduce noise and light exposure as able)
- Aim target saturations ≥95% for first 24h (>36 weeks only)

2.6.1 Pulmonary optimization

Each patient's oxygen and ventilation requirements should be optimized prior to beginning iNO therapy. The specific approach to mechanical respiratory support should be guided by the infant's underlying lung disease, if any.

Oxygen

- Adequate oxygenation is core to PPHN management however both hypoxaemia and hyperoxia may worsen PVR and clinical status.

Ventilation

- Ensure adequate chest movement and optimal lung inflation (9 posterior ribs) with careful avoidance of both atelectasis and hyperinflation (both under- and over-inflation of the lung can increase PVR).
- Targeting a clinically "normal" pCO2 5-7 mmHg, because hypercarbia and acidosis increase PVR, attempt to establish and maintain normal ventilation .
- Utilize a *"gentle ventilation"* strategy focusing on optimized PEEP, low PIP, and high rate to minimize volutrauma. Ultimately, the strategy of ventilator support depends upon the presence or absence of pulmonary parenchymal disease, and the infant's response to treatment. HFOV may be the most appropriate modality to achieve this especially in following situations: RDS, congenital pneumonia or MAS. In these disease processes, HFOV ventilation decreases need for ECMO and augments iNO response more effectively than does conventional ventilation.
  - ***Suggested ventilator settings:***
  - Conventional ventilator settings:
    - PEEP 5 to 8mm Hg,
    - PIP 18 to 25mm Hg,
    - resp rate 30 to 40 breaths/min.
  - Maximum conventional ventilator settings:
    - PEEP 10 cm H2O,
    - PIP 25-28 cm H2O,
    - respiratory rate 45 to 50 breaths/min.
  - Initial HFOV settings:
    - MAP 13 to 18mm Hg,
    - Amplitude/delta P 30 to 40,
    - frequency 10Hz.
- Following transition to HFOV, increase MAP until appropriate oxygenation is achieved, or until hemodynamic impairment limits further MAP escalation.
- Reassess lung inflation status with a CXR at 1-2 hours and subsequently as required.

Surfactant

- Early surfactant therapy can be considered for PPHN associated with surfactant inactivation or deficiencies

Start Nitric oxide (iNO)

- iNO improves oxygenation and reduces the need for ECMO in term and late preterm infants greater than 34 weeks GA with severe PPHN (defined as an OI ≥25), and should be administered at a dose of 20 ppm. *(*refer* Nitric Oxide Usage in NICU Ref 1553).*

2.6.2 Cardiovascular optimisation

In patients with PPHN, right-to-left shunting increases as cardiac output and systemic BP decrease. Thus, maintaining optimal cardiac output and systemic BP is important to reduce the right-to-left shunting and to maintain adequate tissue oxygenation. Myocardial function is frequently poor, despite reasonable blood pressures.

Target an appropriate MABP for gestational age, usually 45 - 55mm Hg for most term newborns. However, clinically relevant measures of tissue perfusion, including urine output and serum lactate levels, may represent more important indices for adequacy of systemic perfusion pressure to achieve tissue oxygen delivery.

Hydrocortisone

Consider early hydrocortisone therapy for BP support (before vasoactive medication). It improves BP in cortisol-deficient neonates and improves responsiveness to inotropes.

Vasoactive medication

The goal of inotrope and vasopressor treatment of infants with PPHN is to optimize oxygenation by reducing right-to-left hemodynamic shunting. The infant's underlying pathophysiology is critically important in determining the appropriate inotrope(s) and/or vasopressor(s).

	Dose	Indications	Potential side effects
Primary Goal			
Increase cardiac output			
Dobutamine Dobutamine IV for neonates	5-20 microg/kg/min	cardiac dysfunction requiring rapid resolution	tachycardia (++) systemic vasodilation
Increase both Cardiac output and Systemic vascular resistance			
Dopamine* Dopamine for neonates	0.5-2 microg/kg/min	poor urine output	tachycardia (++), pulmonary vasoconstriction
	2-6 microg/kg/min	cardiac dysfunction	
	>6microg/kg/min	hypotension	
Adrenaline* Adrenaline for neonates	0.05-0.1 microg/kg/min	cardiac dysfunction	tachycardia (+++), lactic acidosis hyperglycaemia
	0.1-0.5 microg/kg/min	hypotension refractory to dopamine	
Increase systemic vascular resistance			
Noradrenaline Noradrenaline for neonates	0.05-0.5 microg/kg/min	hypotension	tachycardia (+) pulmonary vasoconstriction
Vasopressin	0.1-1.2 units/kg/min	hypotension	hyponatraemia
* dose ranges based on limited evidence and vary between patients			

Fluid resuscitation

Use caution in fluid resuscitation for hypoperfusion and/or hypotension as this can exacerbate right heart failure. Fluids should only be used as a bridge to establish inotropic and vasopressor support. Consider a slow 10mL/kg normal saline bolus. If BP response is observed, consider a second bolus while initiating vasopressor and/or inotropic support.

2.6.3 General medical optimisation

2.6.3.1 Infection

- Evaluate and consider empiric antibiotic therapy if infectious risk factors (i.e. sepsis, congenital pneumonia) are present. Refer Antibiotic Usage in Newborn Unit Ref 1659

2.6.3.2 Tissue oxygen delivery

- Aim for Hb 100-140g/dl, consider transfusion if <100g/dl
- Aim to keep the PCV/Hct between 0.40 and 0.45. Avoid iatrogenic polycythaemia, as it can increase blood viscosity and PVR, and impair tissue oxygen delivery

2.6.3.3 Acid-base status

Normalize pH to optimize pulmonary vasodilation and cardiac function. While alkalosis effectively decreases PVR, it decreases tissue oxygen delivery, impairs cerebral perfusion, and is associated with hearing loss and poorer neurodevelopmental outcomes. Acidosis causes paradoxical pulmonary vasoconstriction, impairs cardiomyocyte contractility, and may impair lung responsiveness to iNO.

- Maintain a minimum arterial pH of 7.25 – 7.3 (Goal arterial pH > 7.3 while critically ill.)
- Hyperventilation and/or IV administration of high doses of alkali therapy (i.e. sodium bicarbonate) to maintain "controlled" alkalosis is **not** recommended
    - However, sodium bicarbonate may be used to aggressively improve pH <7.2 (particularly with cardiac dysfunction)
- Use small boluses of bicarbonate (1-2 mmol/kg over 60 minutes) or a continuous infusion (0.5mmol/kg/hour initially). Ref Sodium Bicarbonate for neonates Ref 2963

2.6.3.4 Electrolytes & Nutrition

Electrolyte parameters should be measured and corrected. Ensure euglycemia to maintain adequate brain glucose delivery. Normalize cardiac-specific electrolytes to optimize cardiac function.

- Maintain **ionized calcium levels** >1.0 to 1.2mmol/L.
- Maintain **serum magnesium levels** >2.0 mg/dL, particularly if accompanying hypocalcemia.
- Maintain **potassium levels** >3.0mmol/L.

2.6.3.5 Comfort & Sedation

Pain and agitation cause catecholamine release, resulting in increased PVR and increased right-to-left shunting. In addition, agitation may result in ventilator asynchrony which can worsen hypoxemia.

a) Non-pharmacological pain management

Measures to enhance the infant's comfort and lower his/her stress include lowering light levels and background noise.

Comfortable positioning, addition of circumferential 'nest', and minimizing tactile stimulation and loud talking also are helpful.

Most babies with PPHN will be NBM, however, they can receive mouth care with breastmilk on a cotton swab to provide potential non pharmacological comfort.

b) Pharmacologic pain management:

Many infants require early use of narcotic infusions to achieve comfort and cardiopulmonary stability.

Morphine sulfate (loading dose of 100 – 150 mcg/kg over one hour followed by a continuous infusion of 10 – 20 micrograms/kg/hr) is an alternative analgesic for infants who are not hypotensive, as it is more effective in reducing PVR. Morphine for neonates Ref 2940

Fentanyl (1 – 5 micrograms/kg/hr) is a useful adjunct therapy in babies with hypotension. Fentanyl for neonates Ref 2916

Dexmedetomidine is increasingly being incorporated into sedation protocols but currently not used in Waikato NICU.

c) Management of agitation:

Agitation may complicate PPHN management, especially in achieving synchrony with mechanical ventilation. Ensure adequate analgesia and that mechanical issues (ie. misplaced endotracheal tube, airway obstruction, leak) are not contributing.

Use ear muffs to eliminate auditory stress factors, dim the light as much as possible, keep noise levels as low as possible

Benzodiazepines (Midazolam for neonates Ref 2939) use is potentially harmful to the developing brain and should be avoided but may be used temporarily if non-opioid sedation is required.

Short-term muscle relaxation may be considered when necessary to improve ventilator synchrony and oxygenation, while escalating or transitioning to alternate therapies, especially when it necessary to gain initial control in very vigorous labile babies who are not adequately sedated with narcotics and are fighting the ventilator to their detriment.

Single dose or intermittent **vecuronium** (Vecuronium for neonates Ref 2979) may be beneficial. But may have un-wanted side effect of tachycardia and hypotension. Prolonged continuous infusions causing muscle relaxation exacerbate oedema and associated with poorer outcomes.

2.6.4 Other specific PPHN therapies

Pulmonary vasodilator therapies represent a piece of optimal management of the neonate with PPHN. Data suggests the potential for synergistic therapeutic effects achieved with combination therapies utilizing agents that augment effectiveness both within a singular vasodilatory pathway and across alternate pulmonary vasodilator pathways.

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.
- Because data regarding efficacy and safety are insufficient, sildenafil is **not recommend as initial therapy** if iNO is available. But it may be beneficial for patient's refractory to iNO and other conventional therapies or in resource limited settings where iNO and HFOV are not available.

Prostaglandin

- Alprostadil (Alprostadil (Prostaglandin E1) for neonates Ref 2957) to maintain patency of the Ductus Arteriosus has been considered advantageous in the management of CHD and should be considered in other forms of PPHN where there is a right to left DA shunt. Allowing right to left shunting across the DA depressurises a potentially failing right ventricle. Alprostadil is also a vasodilator and may have direct beneficial effects on PVR. Higher doses than usual may be required to re-open a closed PDA (50-100 nanograms/kg/min).

3 When to refer to PICU for consideration of ECMO

It is appropriate to discuss infants who may potentially require ECMO with the PICU specialist early, rather than when ECMO or death are imminent. This will be done specialist-to-specialist. The neurological status of the infant may be an important factor in determining if ECMO is offered.

Consider discussion with PICU prior to retrieval from regional centres as transfer directly to PICU may be more appropriate.

Indications for ECMO: ANY of the following criteria AND underlying disease process which is likely to be reversible

1.	OI ≥30 - 60 for 0.5 - 6 hours	• OI = (MAP x FiO_2 x 100) / PaO_2 (mmHg) (click here to open the OI calculator https://starship.org.nz/health-professionals/calculators/respiratory-indices-calculator/)Standard criteria: OI ≥40 on conventional ventilation OI ≥50-60 for HFOV
2.	PaO_2 <5.3kPa (40mmHg) for >2 hours **or** PaO_2 <6.7-8.0kPa (50-60mmHg) for 2-12 hours	Despite maximal ventilatory support
3.	Acidosis and Shock	pH <7.25 due to metabolic acidosis Raised lactate Intractable hypotension

3.1 Contraindications to ECMO

Absolute

Grade 3 or 4 IVH

Severe and irreversible brain injury (as best as can be judged by consultant neonatologist)

Lethal malformations or congenital anomalies

Significant non-treatable congenital heart disease

Severe and irreversible lung, liver or kidney disease

Relative

Gestational age <34 weeks

Birth weight <2kg

> 14 days of mechanical ventilation	Congenital Diaphragmatic Hernia if pre-ductal PaO_2 never > 9.3kPa (70mmHg) or $PaCO_2$ never < 10.7-13.3kPa (80-100mmHg)
IVH Grade 1-2	
Disease states with a high probability of a poor prognosis	

Please refer to Starship PICU guidelines for primary required investigations
https://starship.org.nz/guidelines/ecmo-guidelines-for-consideration-in-newborn/

4 After care

All infants with severe PPHN who have been treated with iNO and/or ECMO should have neurodevelopmental follow-up. Assessment should be performed through infancy at 6- to 12-month intervals, and longer if abnormalities are present.

High risk audiology assessment is required, and should be tested prior to hospital discharge and at 18 – 24 months corrected age.

5 Patient information

- https://www.gosh.nhs.uk/conditions-and-treatments/conditions-we-treat/persistent-pulmonary-hypertension-newborn-pphn/

6 Evidence base

6.1 Bibliography / References

Guidelines

- Ball et al. Evidence-based guidelines for acute stabilization and management of neonates with persistent pulmonary hypertension of the newborn (2022). Thieme Medical Publishers, Inc.
- Bellhouse, S. Starship guidelines: Persistent pulmonary hypertension of the newborn (2013).
- Department of Paediatric Newborn Medicine, Brigham and Women's Hospital. Paediatric newborn medicine clinical practice guidelines: Diagnosis and management of the infant with suspected or known pulmonary hypertension of the newborn (2017).
- Staff specialist neonatologist. Sydney local health district guidelines: Persistent pulmonary hypertension of the newborn (2014).
- Stark A et al. Uptodate: Persistent pulmonary hypertension (2021).
- Western Australia Child and Adolescent Health Service Neonatology. Clinical guidelines: Persistent pulmonary hypertension of the newborn (2020).

6.2 Associated Te Whatu Ora Waikato Documents

- Adrenaline for neonates Ref 0559
- Alprostadil (Prostaglandin E1) for neonates Ref 2957
- Antibiotic Usage in Newborn Unit Ref 1659
- Dobutamine IV for neonates Ref 2909
- Dopamine for neonates Ref 0649
- Fentanyl for neonates Ref 2916
- Midazolam for neonates Ref 2939
- Morphine for neonates Ref 2940
- Nitric Oxide Usage in NICU Ref 1553
- Noradrenaline for neonates Ref 2946
- Poractant alfa (Curosurf) for neonates
- Sodium Bicarbonate for neonates Ref 2963
- Vecuronium for neonates Ref 2979

6.3 External Standards

Starship clinical guidelines https://starship.org.nz/guidelines/persistent-pulmonary-hypertension-of-the-newborn/

Appendix A – Aetiologies of PPHN

Table 1 Underlying etiologies of PPHN[8–11]

Etiologies of PPHN		Examples
Maladaptation of normal pulmonary vasculature (Normal fetal development, persistent pulmonary vasoconstriction)	Pulmonary	Meconium aspiration syndrome (MAS) Congenital/neonatal pneumonia, sepsis respiratory distress syndrome (RDS) Transient tachypnea of the neonate Delivery by cesarean section without labor Metabolic derangements (severe acidosis, hypocalcemia) Idiopathic
	Pulmonary venous congestion/ Cardiac dysfunction/ Systemic conditions	Perinatal asphyxia/HIE (and associated therapeutic hypothermia) Sepsis Polycythemia High-output heart failure Large arteriovenous malformation Total anomalous pulmonary venous malformation (TAPVR)
Maldevelopment of pulmonary vasculature *may result in "*fixed*" pulmonary vasoconstriction rather than "reactive" pulmonary vasculature, making vasodilator therapies ineffective.	Pulmonary hypoplasia	Congenital diaphragmatic hernia (CDH) Potter's sequence (lung hypoplasia due to renal anomalies) Omphalocele (typically large/giant) Thoracic dystrophies Conditions resulting in early oligohydramnios/anhydramnios
	Aberrant pulmonary vascular development	Fetal growth failure, small for gestational age Trisomy 21 Alveolar-capillary dysplasia (ACD) Surfactant protein deficiencies/ genetic abnormalities in surfactant function Other developmental lung disorders In utero ductal closure (as can occur with maternal NSAID use) Environmental "toxins," including maternal diabetes, obesity, smoking Arteriovenous malformation
Cyanotic critical congenital heart disease (CCHD)	Critically ill infants with undiagnosed CCHD may also demonstrate PPHN secondary to impaired perinatal transition, or refractory hypoxemia secondary to cyanotic heart disease. Always consider CCHD in the differential diagnosis of PPHN and consider empiric prostaglandin therapy until echocardiography can be performed.	

Abbreviations: HIE, hypoxic ischemic encephalopathy; NSAID, non-steroidal anti-inflammatory; PPHN, persistent pulmonary hypertension of the newborn

Table 1: Underlying aetiologies of PPHN (Ball et al. 2022)