CLINICAL GUIDELINE	
Persistent Pulmonary Hypertension of the Newborn (PPHN)	
Scope (Staff):	Nursing and Medical Staff
Scope (Area):	NICU KEMH, NICU PCH, NETS WA

This document should be read in conjunction with this DISCLAIMER

Persistent Pulmonary Hypertension of the Newborn (PPHN) is a complex condition with inappropriate resistance to blood flow through the pulmonary vascular bed resulting in Hypoxic Respiratory Failure (HRF).

It may present with failure of circulatory adaptation following birth, with lack of a reduction in pulmonary vascular resistance normally associated with lung aeration and postnatal transitioning. A persistent right to left shunt occurs across fetal channels (ductus arteriosus and foramen ovale) and at an intrapulmonary level contribute to labile hypoxaemia. PPHN may also occur secondary to parenchymal lung disease and dysfunction which should be promptly identified and treated where possible:

- Under ventilation and atelectasis.
- Collapse / consolidation.
- Pneumothorax, pneumomediastinum.
- Pulmonary effusion.
- Mechanical problems (airway leak, disconnects etc.).

PPHN may occur in the context of the following anatomical and physiological conditions:

Anatomical

- Congenital heart disease:
  - RV outflow obstruction
  - TGA
  - Anomalies of pulmonary veins
- Pulmonary anomalies:
  - Pulmonary hypoplasia (PPROM, diaphragmatic hernia)
  - Alveolar Capillary Dysplasia
  - Severe cystic CCAM / Sequestration

Low Cardiac Output

- Low preload:
  - Hypovolaemia
  - Systemic venous obstruction
- Poor contractility:
  - Prematurity
  - HIE

- Sepsis
- 1^{o} cardiomyopathy

Pulmonary Vascular Reactive Constriction

- 1^{o} Respiratory Distress Syndrome (RDS)
- Meconium Aspiration Syndrome (MAS)
- Pneumonia (particularly GBS)
- 2^{o} to metabolic triggers (acidosis, hypoxia etc.)
- Mechanical - obstruction by high MAP

Hypoxemic respiratory failure can be classified in terms of an oxygenation index into mild (OI ≤ 15), moderate (OI > 15 to 25), severe (OI 25 to 40) and very severe (OI > 40). Alternatively, a pragmatic assessment of FiO_2 requirement > 60% to maintain pulse oximetry saturations above 90% indicative of significant hypoxic respiratory failure may be used. (Appendix 1)

Management

Once amenable causes of HRF have been excluded ongoing management should aim for optimisation all other physiological parameters whist minimising risk of long term harm. Clinical care strategies targeting relaxation of vascular smooth muscle within the pulmonary circuit underpin management. (Appendix 2)

Infants with PPHN are often unstable, care should be taken to minimise the impacts of handling and procedures. Premedication may optimise intubating conditions and reduce adverse physiological responses, but routine use of atropine warrants consideration of the potential for prolonged effect of tachycardia.

Optimise Ventilation

Ensure adequate chest movement and expansion.

Primary aim should be to improve efficiency of ventilation while minimising long term harm to the lungs. High Frequency Jet Ventilation (HFJV) may be the most appropriate modality to achieve this.

- **CO_2:**
  - Aim to reduce respiratory acidosis by keeping CO_2 35 to 45 mmHg.
- **pH:**
  - Aim to keep pH as near to 7.4 as possible.
  - Adequate ventilation (see above).
  - Optimal perfusion (see below). Remember bicarb is not an efficient buffer above pH >7.0 and should be used sparingly. Beware of pH above 7.40 this is associated with reduced cerebral blood flow and sensineural hearing loss.
- **FiO_2:**
  - Adequate oxygenation is core to PPHN management however both hypoxaemia and hyperoxia may worsen pulmonary vascular resistance and clinical status. There is currently no evidence based guidance on targeting optimal pulse oximetry saturations and arterial oxygen tension in term and preterm infants with PPHN, however pragmatic consensus supports maintaining Spo2 in the upper/normal range 94-97% and PaO_2 between 60-90 mmHg for term and preterm infants.[1]

  - Hyperoxia (PaO_2 > 100 mmHg) may cause lung injury and atelectasis without improving pulmonary vasodilation [2] and actually worsen PVR with the formation of oxygen free radicals and inhibition of natural mediators.
  - Since sudden hypoxemic episodes worsen PVR and cause rapid deterioration, slow wean of FiO_2 in small increments to avoid hyperoxia–hypoxemia fluctuations, is one of key components of PPHN management.
- **Lung Volume:**
  - Aim for well expanded lungs but beware of over-distention, 9 posterior ribs on an X-ray is current standard.

iNO

Nitric Oxide is a potent selective vasodilator of the pulmonary vasculature and can help optimize VQ match by preferential distribution to ventilated lung and increased perfusion of these segments. Inhaled nitric oxide is effective at an initial concentration of 20 ppm for term and near-term infants with hypoxic respiratory failure reducing the incidence of death or use of ECMO, with the exception of infants with congenital diaphragmatic hernia (high-quality evidence)[3]. The use of iNO in premature babies remains widespread in clinical practice however controversial with limited evidence of clinical benefit [2] and therefore should be used under the guidance and discretion of the Consultant Neonatologist.

Volume Expansion

Optimal preload is crucial in maintaining cardiac output in the newborn (particularly in the preterm). This can only really be assessed on cardiac ultrasound looking at venous and atrial distension. Where there is any doubt volume expansion with saline (or blood if indicated) should be given. Ideally preload should be re-assessed after administration of a fluid bolus.

Optimise Metabolic Status

Electrolyte parameters should be measured and corrected. Na, K, Ca and Mg. Mg may assist pulmonary vasodilation and levels should be in the upper normal ranges (>1.00mmol/L). Glucose should be maintained in the normal range. Haemoglobin should be maintained >100 g/L.

Sedation

Infants may be unsettled warranting consideration to general sedation and in relation to procedures/cares and may help minimise tachycardia. Fentanyl or morphine may be useful in settling and preventing clinical instability. Be mindful of the potential vasodilatory effects of morphine in reducing afterload but risk of furthering systemic hypotension. Sedation with Benzodiazepines (Midazolam) is potentially harmful to the developing brain and should be avoided.

Muscle Relaxation

Short term muscle relaxation with single dose or intermittent vecuronium may be beneficial in labile infants. Both panuronium and vecuronium may have an un-wanted side effect of tachycardia. Prolonged continuous infusions causing muscle relaxation exacerbate oedema and associated with poorer outcomes.

Inotropes

The use of inotropes in the management of PPHN is always a double edged sword. In the past a very 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 in fact lead to increased pulmonary vascular resistance decreased cardiac output and diminishing pulmonary blood flow (particularly in the preterm). Tachycardia may

worsen cardiac filling and diastolic function. The increased strain and afterload on an already compromised myocardium, particularly in the preterm infant or presence of left ventricular dysfunction may hasten cardiac failure. Optimal use and choice of inotropes should be guided by ultrasound assessment and response of cardiac output including pulmonary flow, systemic output and venous return.

Dobutamine or Noradrenaline are often first-line agents and in situations of high cardiac output failure (usually low systemic resistance and increased CO from septic shock) vasopressors may be particularly helpful in maintaining the circulation.

Inodilators, such as PDH3 inhibitors (milrinone), may have potential benefit in improving oxygenation status in infants unresponsive to iNO. [5] Vasopressin may be a potential adjunctive therapy for improving the efficacy of oxygenation and systemic hypotension in refractory PPHN, [6] although prospective randomised trials are lacking.

Prostin

Prostin to maintain patency of the Ductus Arteriosus (DA) has been considered advantageous in the management of CDH 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. Prostin is also a vasodilator and may have direct beneficial effects on PVR.

Sildenafil

Sildenafil is a PDH5 inhibitor that raises $_{C}$GMP in the smooth muscle cell promoting vasodilation more selectively within the pulmonary vascular bed than systemic circulation. Evidence suggests it may be beneficial for patient's refractory to inhaled nitric oxide (iNO) and other conventional therapies or in resource limited settings where inhaled nitric oxide and high frequency jet ventilation are not available. However, large-scale randomised trials comparing effectiveness and long-term safety of sildenafil versus other pulmonary vasodilators are needed. [7]

Prostacyclins

Iloprost *Prostacyclin (PGI_2)* mediates vasodilation by activating adenylate cyclase and increasing cAMP in the pulmonary arterial smooth muscle cell and may be beneficial in neonates where PPHN is refractory to inhaled nitric oxide and other conventional therapies. Iloprost is administered as an IV continuous infusion and caution must be taken as has the potential to cause severe hypotension or cardiac arrhythmias.

Surfactant

Early surfactant administration may be beneficial where PPHN is secondary to parenchymal lung disease e.g. MAS; however the value of repeated doses associated with potential clinical instability warrants consideration.

Steroids

There is no clear trail data supporting or refuting the use of steroids in managing PPHN and documentation of adequate cortisol response is reasonable or use of Hydrocortisone in augmentation of systemic circulation. Postnatal systemic steroids have been shown to decrease the duration of hospital length of stay and oxygen dependence in MAS [5]. In the fetal lamb model of PPHN, hydrocortisone treatment postnatally has been shown to improve oxygenation, increase cGMP levels and reduce ROS levels. [6]

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. The process requires for referral multidisciplinary consultation via NETS involving the

KEMH, PCH and NETS Neonatologists, Cardiology Consultant, PCC Consultant and Cardiothoracic Surgeon and informed parental consent.

Role of Echocardiography

Value-adding information of cardiac function and the relative systemic and pulmonary pressures may be gained observing adequacy of preload, ventricular contractility and calculated outputs, prominence of the right ventricle and flattening or paroxysmal movement of interventricular septum, tricuspid regurgitation and presence and direction of shunt across the foramen ovale and DA. Concern of right-to-left shunt across the atrial septum or DA warrants immediate cardiology consultation and it is an expectation that confirmation of normal cardiac anatomy will be documented at the earliest opportunity in all PPHN patients receiving therapy.

Mild degrees of PPHN where pulmonary pressures remain sub-systemic may be more challenging to define and given a likelihood of patient instability it is advisable only those experienced in clinician performed ultrasounds assess infants with suspected PPHN.

Related CAHS internal policies, procedures and guidelines

Neonatology Guidelines

- Extra Corporeal Membrane Oxygenation (ECMO) for the Neonate
- Meconium Aspiration Syndrome (MAS)
- Nitric Oxide Therapy (iNO)
- Pneumonia
- Respiratory Distress Syndrome (RDS)
- Ventilation: High Frequency Jet Ventilation (HFJV)

Neonatal Medication Protocols

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Appendix 1

Oxygenation Index (OI)

Severity of PPHN is commonly assessed by oxygenation index (OI) reflecting the efficiency of oxygen uptake and takes into consideration MAP (mean airway pressure in cmH_2O), FiO_2 (fraction of inspired oxygen) and PaO_2 (partial pressure of oxygen in arterial blood (in mmHg).

$$\mathbf{OI = \frac{FiO_2 \times MAP \times 100}{PaO_2}}$$

Support	FiO_2	MAP cmH_2O	PaO_2 mmHg	OI
CPAP	0.21	5	85	1
SIPPV	0.30	7	85	2
HFOV	0.60	14	85	10
HFJV	1.00	14	85	16
HFJV	1.00	16	55	30

Oxygen Index may be useful in determining eligibility criteria for ECMO therapy.

Appendix 2
Pathophysiology of PPHN

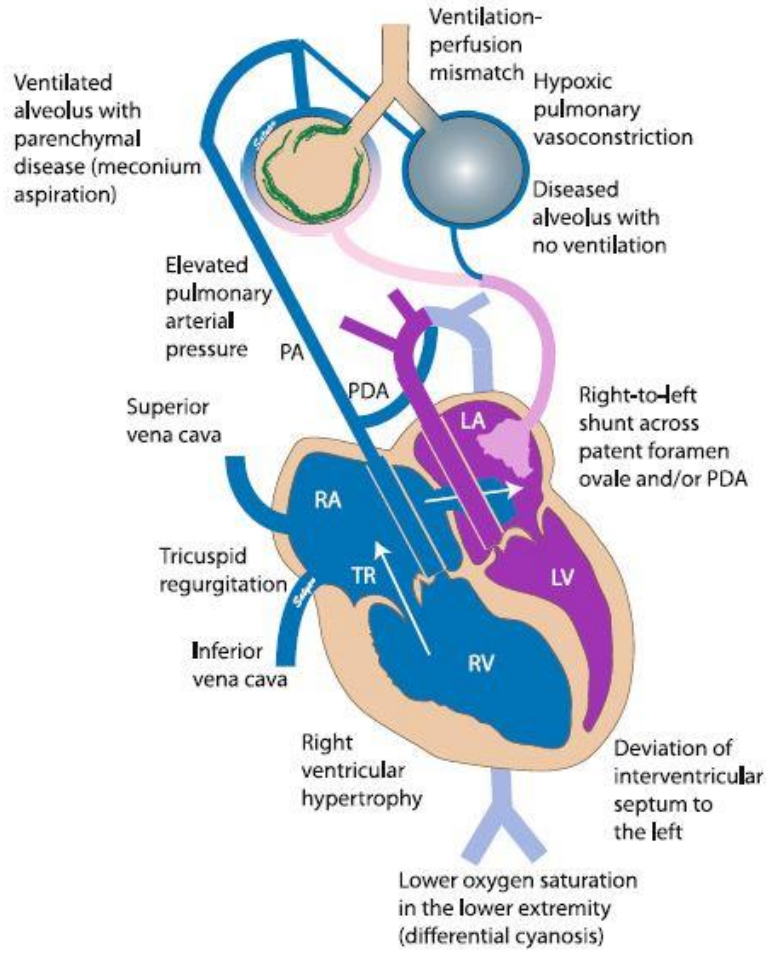

Figure 3 Pathophysiology of PPHN. Parenchymal lung disease and ventilation-perfusion (V/Q) mismatch result in hypoxemia. Increased pulmonary vascular resistance results in reduced pulmona ry blood flow and right to left shunt through PDA and/or PFO. Pulmonary hypertension is often associated with systemic hypotension with deviation of the interventricular septum to the left. The right subclavian artery (and blood flowing to the right upper extremity) is always preductal. The left subclavian artery may be preductal, juxtaductal or postductal. Hence, preductal oxygen saturations should be obtained from the right upper extremity and compared with lower extremity to assess differential cyanosis. PA – pulmonary artery; RV – right ventricle; LV – left ventricle; TR – tricuspid regurgitation; RA – right atrium; LA – left atrium; PDA – patent ductus arteriosus; PFO – patent foramen ovale. *(copyright Satyan Lakshminrusimha).*

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Appendix 3

Drugs and PPHN

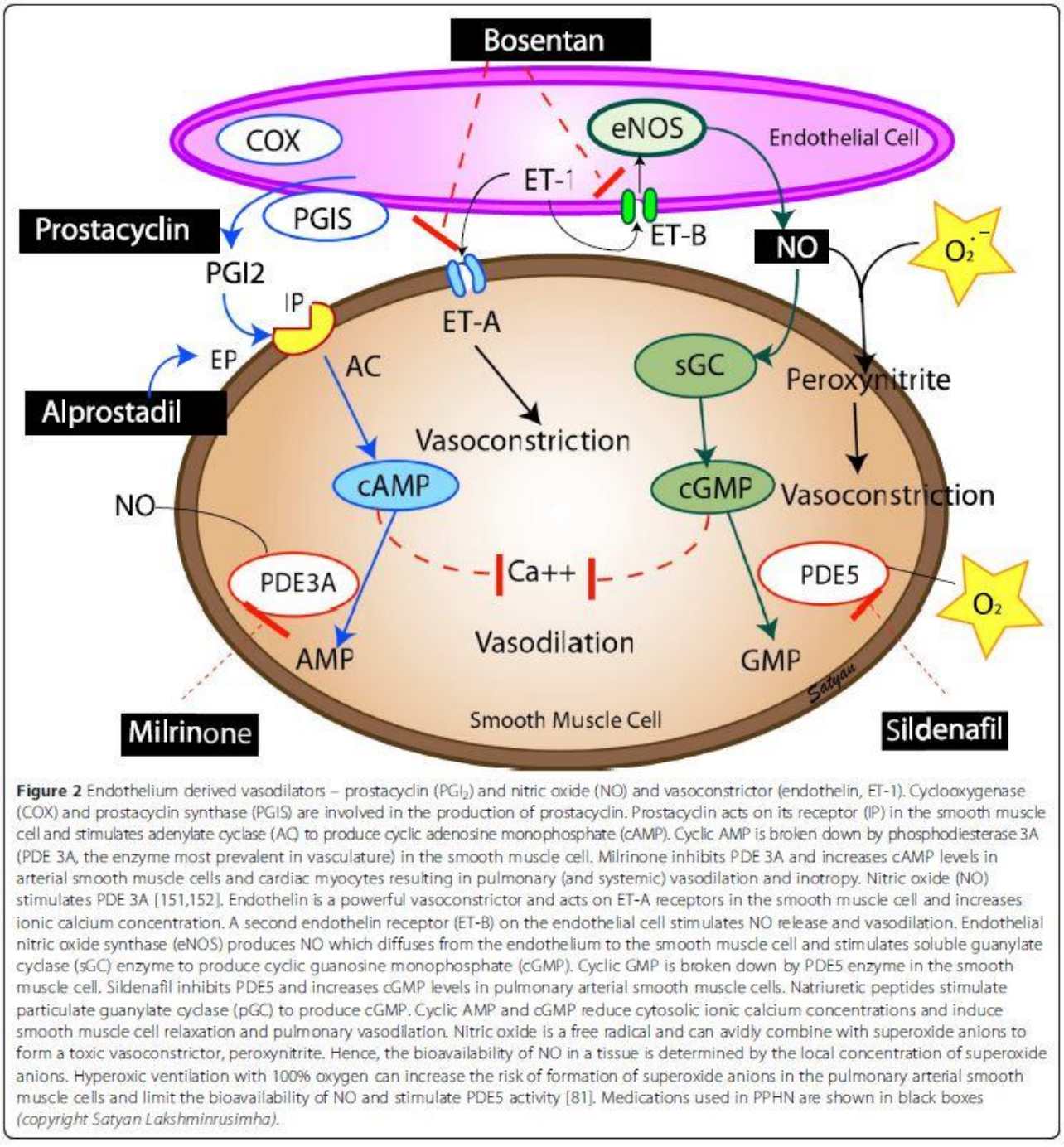

Figure 2 Endothelium derived vasodilators – prostacyclin (PGI_2) and nitric oxide (NO) and vasoconstrictor (endothelin, ET-1). Cyclooxygenase (COX) and prostacyclin synthase (PGIS) are involved in the production of prostacyclin. Prostacyclin acts on its receptor (IP) in the smooth muscle cell and stimulates adenylate cyclase (AC) to produce cyclic adenosine monophosphate (cAMP). Cyclic AMP is broken down by phosphodiesterase 3A (PDE 3A, the enzyme most prevalent in vasculature) in the smooth muscle cell. Milrinone inhibits PDE 3A and increases cAMP levels in arterial smooth muscle cells and cardiac myocytes resulting in pulmonary (and systemic) vasodilation and inotropy. Nitric oxide (NO) stimulates PDE 3A [151,152]. Endothelin is a powerful vasoconstrictor and acts on ET-A receptors in the smooth muscle cell and increases ionic calcium concentration. A second endothelin receptor (ET-B) on the endothelial cell stimulates NO release and vasodilation. Endothelial nitric oxide synthase (eNOS) produces NO which diffuses from the endothelium to the smooth muscle cell and stimulates soluble guanylate cyclase (sGC) enzyme to produce cyclic guanosine monophosphate (cGMP). Cyclic GMP is broken down by PDE5 enzyme in the smooth muscle cell. Sildenafil inhibits PDE5 and increases cGMP levels in pulmonary arterial smooth muscle cells. Natriuretic peptides stimulate particulate guanylate cyclase (pGC) to produce cGMP. Cyclic AMP and cGMP reduce cytosolic ionic calcium concentrations and induce smooth muscle cell relaxation and pulmonary vasodilation. Nitric oxide is a free radical and can avidly combine with superoxide anions to form a toxic vasoconstrictor, peroxynitrite. Hence, the bioavailability of NO in a tissue is determined by the local concentration of superoxide anions. Hyperoxic ventilation with 100% oxygen can increase the risk of formation of superoxide anions in the pulmonary arterial smooth muscle cells and limit the bioavailability of NO and stimulate PDE5 activity [81]. Medications used in PPHN are shown in black boxes *(copyright Satyan Lakshminrusimha).*

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