Persistent Pulmonary Hypertension of the Newborn (PPHN)

University Hospitals of Leicester NHS Trust

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1. Introduction and Who Guideline applies to

Persistent Pulmonary hypertension of the newborn (previously known as 'persistent fetal circulation') occurs when there is a failure of the neonatal circulation to adapt to extrauterine life. It is primarily a condition of term infants and is characterised by:

- Profound Hypoxia
- 'Worse' clinical features than would be expected from the chest x-ray
- Evidence of Right to Left Shunting

This guideline is aimed at all Health Care Professionals involved in the care of infants within the Neonatal Service.

Related UHL documents:

- Meconium Stained Liquor at Delivery UHL Neonatal Guideline
- Resuscitation at Birth UHL Neonatal Guideline

Key Points:

- The risk of PPHN is reduced by effective resuscitation and adequate oxygenation
- Inhaled Nitric Oxide reduces the need for ECMO [1] (Grade A)
- Consideration of ECMO is indicated if the OI is approaching 40[2] (Grade A)
- A management flow chart included as an appendix

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Aim / indications:

- To identify PPHN and distinguish it from cyanotic congenital heart disease
- To optimise intensive care management, including the administration of inhaled nitric oxide

Evidence Criteria.

Evidence according to RCPCH

Grade A	At least 1 randomised controlled trial addressing specific recommendation
Grade B	Well conducted clinical trials but no randomised trial on specific topic
Grade C	Expert committee report or opinions

2. Guidelines/Recommendations:

Pathogenesis:

At birth the pressure in the pulmonary circulation should drop. Pulmonary hypertension occurs when there is a vasoconstriction of the pulmonary blood vessels. This leads to right to left shunting across the foramen ovale and ductus arteriosus and subsequent hypoxia.

Pulmonary hypertension can be primary (rare) or secondary. Secondary pulmonary hypertension can occur with a number of conditions including:

- Hypoxia
- Meconium aspiration
- Congenital lung problem- e.g. congenital diaphragmatic hernia
- Pulmonary Hypoplasia
- Sepsis (especially Group B Streptococcus)
- Polycythaemia

Diagnosis of PPHN:

- PPHN should be suspected in babies with significant hypoxia despite adequate chest movement.
- The main differential diagnosis is of cyanotic congenital heart disease (e.g. Transposition of the Great Arteries)
- An early chest X ray should be performed to exclude pneumothorax

Echocardiography will usually demonstrate features of raised pulmonary pressure, including tricuspid regurgitation and dilatation of the right heart with right to left shunting at the level of the foramen ovale and the ductus arteriosus.

Remember that absence of tricuspid regurgitation does not exclude PPHN [3]. An early echocardiogram should be performed to exclude congenital heart disease. If echocardiography is not immediately available, an ECG may be useful.

Intensive Care Management (see flow chart):

Pulmonary vasoconstriction is worsened by hypoxia, stress and acidosis and the initial intensive care management is aimed at reducing these.

General Management:

- Monitor pre and post ductal saturations, invasive blood pressure, HR and temperature;
- Insert UAC and UVC
- Give antibiotics to cover sepsis
- Correct anaemia and coagulation problems

- Minimal handling if possible
- Aim for normothermia (Hypothermia can exacerbate PPHN. In life threatening PPHN with concurrent HIE, discuss target temperature)

Ventilation:

- Ensure that the endotracheal tube is in the correct place
- Exclude other causes of hypoxia, including pneumothorax
- Monitor Pre and post ductal oxygen saturations
- Aim for pre-ductal saturations 95 -98%, (note lower saturations can potentiate hypoxia and further exacerbate PPHN)
- Optimise the mean airway pressure: options include increasing the PIP, using a longer inspiratory time and slower rate
- Consider the use of surfactant if clinically indicated (e.g. RDS or MAS)
- Aim to keep the carbon dioxide in the 'low normal' range (4-5KPa) (lower carbon dioxide levels are associated with cerebral vasoconstriction) and normal pH (7.35-7.45)
- Consider High Frequency Oscillation [4] [5] (discuss with consultant)

Cardiovascular

- Supporting the systemic circulation will reduce right to left shunting
- Consider aliquots of 10ml/kg normal saline, if clinically indicated
- Consider bicarbonate to correct any acidosis
- Use inotropes to keep the blood pressure optimal. (Generally higher mean arterial pressures are required)

Neurology

- Sedate using morphine infusion.
- There may be a need to start muscle relaxation
- Be aware that there may be hypoxic injury to the brain- CFM can be useful if there are concerns about neurological function
- Perform cranial ultrasound scan particularly if ECMO is being considered

Pulmonary Vasodilators

- Inhaled nitric oxide is effective as a pulmonary vasodilator in term babies (discuss with consultant) [6] (Grade A Evidence). Nitric Oxide is usually started if the oxygen index is greater than 20
- There is no evidence that nitric oxide is effective in preterm babies [7] **although there is an increasing evidence about the successful use of nitric oxide in selected infants- for instance babies with oligohydramnios and pulmonary hypoplasia sequence [8]**

- Start iNO with 20ppm and consider stopping it early if there is no response. (It is unusual to need more than 20 ppm and most babies that respond to iNO, do so at up to 20ppm iNO).

Others

- Keep ionized Ca >1 and Mg within the normal range.

Oxygen Index (OI):

The oxygen index (oxygenation index) is a useful guide: monitor regularly in babies with PPHN

Oxygen Index (OI):

$$\frac{\text{Mean Airway Pressure X FiO2 x 100}}{\text{PaO}_2 \text{ (in kPa) x 7.5}}$$

Note: FiO2 is the inspired fraction (e.g. 21% = 0.21, 100% = 1.0),

kPa x 7.5 converts to the equivalent PaO2 in mmHg.

- ECMO is indicated if the OI is greater than 40 [2] and early liaison with the ECMO team is advised if there is a rising OI. (referral should only take place after discussion with the Consultant Neonatologist)
- If a baby is being transferred for ECMO, discuss with a consultant about consent
- The baby should be transferred with a maternal blood sample. **2 adult units of blood MUST be available (either sent with the baby or in blood bank at the ECMO centre)**
- A cranial ultrasound should be performed, and blood clotting should be measured and corrected as appropriate prior to transfer for ECMO

Weaning

- Once a clinical response has been obtained, it is appropriate to wean the nitric oxide and ventilation.
- Commonly used value of FiO2 is <40%-50% to consider nitric oxide weaning.
- Remember that using inhaled nitric oxide 'switches off' the bodies natural nitric oxide production and it is important to wean the inhaled nitric oxide **slowly** to avoid rebound pulmonary hypertension
- Once decided to wean, wean every 6-8 hours (if tolerated). Wean the iNO by 50% every 6-8 hours until a dose of 5 ppm is reached. Once at 5 ppm, wean in 1 ppm decrements every 2-4 hours, as

needed.

- It is usually a good idea to keep the oxygen saturations high (>95) as oxygen is a good pulmonary vasodilator.
- Similarly, ventilation should be weaned carefully, avoiding sudden changes that may precipitate pulmonary hypertension.

Prognosis

- 75% of babies treated in the NINOS trial had a normal developmental outcome [1]
- The prognosis for those babies that receive ECMO is good [9]

Methaemoglobin

Methaemoglobin (MetHb) levels should be recorded 1 and 6 hours after starting inhaled nitric oxide (iNO) and then twice a day. Methaemoglobin is measured on the blood gas machine. The half-life of iNO is 5 hours.

Normal range of MetHb: <1-3 % optimal
5-10% Reduce iNO dose by 50%.
>10 % Stop iNO
>20% Methylene blue 1-2 mg/kg IV. [10]

Other medications that may be considered in the Management of PPHN

Milrinone

- Milrinone is a selective PDE-3 inhibitor in cardiac myocytes as well as in the vascular smooth muscle. Milrinone's pharmacological effects include relaxation of vascular smooth muscle via cAMP pathway, enhanced myocardial contractility (inotropy) and improved myocardial relaxation (lusitropy).

- Current evidence for milrinone use in neonatal PPHN is limited to case series publications [13,14] and pharmacokinetic study to establish dosage profile and safety [15].

- Case series publications have shown that administration of intravenous milrinone infusion in severe PPHN (iNO non-responders) leads to an early improvement in oxygenation index, reduction in tachycardia, improved response from iNO, better systemic BP, improved LV and RV outputs and reduction in R-L shunt across PDA, improved urine output and better blood pH values, reduction in blood lactate levels and an overall reduction in inotropic score [13,14].

- Dosage regimen varies from 0.25mic/kg/min to maximum 0.75micrograms/kg/min by continuous infusion. Loading dose preceding infusion should NOT be used in sick neonates to avoid hypotension.

Vasopressin

Usually only used after discussion with the ECMO team

- There is experimental evidence to show that low-dose arginine vasopressin leads to selective vasodilatation in pulmonary, cerebral, renal and coronary vasculature bed under hypoxic conditions by its action on V1 receptors whose stimulation induces the release of endothelial-derived NO.

- Published case series [16,17] has shown that very low dose vasopressin is an effective adjunctive therapy in neonates with a diagnosis of PPHN where there is refractory systemic hypotension and hypoxemia despite conventional treatments.

- In these case series, vasopressin use was associated with improvement in systemic BP, reduction in OI, steady reduction in iNO use and enabled weaning of other inotropes.

- Recommended dose used was 0.02 - 0.1 unit/kg/min in UK case series [16]. If an infant responds to vasopressin, one should reduce dose of adrenaline and dopamine infusions to avoid excessive tachycardia and intense peripheral vasoconstriction.

- Concomitant use of milrinone and vasopressin has been shown to stabilise sick neonates who have not responded to nitric oxide and awaiting ECMO transfer [16].

Magnesium sulfate

- Magnesium decreases influx of extracellular calcium ions in vascular smooth muscle cells (therefore lower Ca++) and hence causes relaxation of blood vessels. However, being a non-selective vasodilator, it can cause systemic hypotension.

- A Cochrane review [11] did not show any RCT evidence for its use. One RCT [12] involving magnesium sulfate and nitric oxide followed by cross over if no response in either arm was terminated early due to excessive mortality in overall study group, especially in the nitric oxide arm.

- The current recommendation would be to maintain normal magnesium levels. **Consider keeping the level within the normal range for the babies with PPHN.**

Prostaglandin E1/E2 (prostin) infusion

Various centres have reported benefit of use of IV infusion of Prostin to relieve RV dysfunction, associated with Congenital Diaphragmatic Hernia and PPHN (but there is a lack of published literature).

Sildenafil (Oral /IV)

- Sildenafil is a selective phosphodiesterase-5 inhibitor that enhances NO mediated vasodilatation. Our use of IV sildenafil for PPHN is restricted to participation in a multicentre trial at the current time (trial recruitment may be considered).

- In developed countries like the UK, there has been not much experience in use of oral sildenafil for acute PPHN, as inhaled nitric oxide is easily available. In a Cochrane review [18] involving 3 small non-homogenous published RCTs, sildenafil use has been shown to improve oxygenation index and reduce all-cause mortality

- There is paucity of publications on IV sildenafil use and only one multi- national study involving 36 patients showed that its use is associated with improved oxygenation [19]. There is another large multinational study in progress, involving concurrent use of nitric oxide.

- In UK, IV sildenafil experience is mostly limited to ECMO centres.

3. Education and Training

None

4. Monitoring Compliance

None identified at present

What will be measured to monitor compliance	How will compliance be monitored	Monitoring Lead	Frequency	Reporting arrangements

5. Supporting References

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6. Key Words

Hypoxia, Inhaled nitric oxide, Persistent fetal circulation, Pulmonary, Vasodilator, Ventilation

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The Trust recognises the diversity of the local community it serves. Our aim therefore is to provide a safe environment free from discrimination and treat all individuals fairly with dignity and appropriately according to their needs. As part of its development, this policy and its impact on equality have been reviewed and no detriment was identified.

Contact, Review and Record Details

Guideline Lead (Name and Title)	Executive Lead
Authors: Jonathan Cusack- Neonatal Consultant, Robin Miralles– Neonatal Consultant Reviewed by: Robin Miralles – Neonatal Consultant	Chief Medical Officer

15/10/2008	Neonatal Guidelines Meeting (original guideline ratified)
6/8/2013	Neonatal Guidelines Meeting
17/9/2013	Neonatal Governance (ratified)
April 2018	Amendments (REM)
April & June 2018	Neonatal Guidelines and Governance Meetings (ratified)
July 2021	Neonatal Guidelines and Governance Meetings (ratified)

Details of Changes made during review July 2021:

- **General management**; added aim for normothermia, with concurrent HIE- discuss target temperature
- **Ventilation**; added Monitor Pre and post ductal oxygen saturations
  Aim for pre-ductal saturations 95 -98% & aim for normal Ph
- **Cardiovascular**; removed advice to keep BP mean at least 40mmHg in term babies
- **Neurology**; Amended statement to muscle relax with atracurium to 'there may be a need to start muscle relaxation'.
- **Pulmonary vasodilators**; Added - increasing evidence about the successful use of nitric oxide in babies with oligohydramnios and pulmonary hypoplasia sequence
  Starting dose of iNO increased from 10ppm to 20ppm and to keep ionized Ca >1 and Mg within the normal range.
- **Weaning** off nitric oxide & ventilation guidance updated
- Added maintain Mg levels within normal range rather than closer to 1mmol/L as stated in previous guidance.

Appendix: Management flowchart for a baby suspected of having PPHN