Persistent Pulmonary Hypertension of the Newborn (PPHN)

University Hospitals of Leicester NHS Trust

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Contents;

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 documents:

- Meconium Stained Liquor at Delivery UHL Neonatal Guideline.pdf
- Resuscitation at Birth UHL Neonatal Guideline.pdf
- https://www.emnodn.nhs.uk/network-guidelines PPHN 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

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 means pulmonary vascular resistance (PVR) remains abnormally elevated after birth, resulting in right-to-left shunting of blood through fetal circulatory pathways which are foramen ovale and ductus arteriosus leading to 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.
- Pulse oximetry assessment generally demonstrates a difference of >10 percent between the pre and post-ductal oxygen saturation. This differential is due to right-to-left shunting through the patent ductus arteriosus (PDA). However, it is important to recognize that the absence of a pre and post-ductal gradient in oxygenation does **not** exclude the diagnosis of PPHN, since right-to-left shunting can occur predominantly through the foramen ovale rather than the PDA.
- An early chest X ray should be performed to
    - exclude pneumothorax
    - but may show associated pulmonary condition like CDH, Pneumonia or Meconium aspiration
    - or suggest congenital heart disease which might mimic PPHN
- 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].In this situation, RV pressure can be

assessed qualitatively (e.g., flattened or displaced ventricular septum).
- Excludes structural congenital heart disease. If echocardiography is not immediately available, an ECG may be useful. The main differential diagnosis is of cyanotic congenital heart disease (e.g. Transposition of the Great Arteries)
- Assess function and guides fluid and vasoactive drug management

The severity of the PPHN is based on the comparison of estimated RvP to systemic Blood pressure.

Intensive Care Management (see flow chart):

Risk of PPHN is reduced by effective resuscitation and adequate oxygenation. 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, Heart Rate and temperature;
- Insert UAC and UVC
- Give antibiotics to cover sepsis
- Minimal handling if possible
- Aim for normothermia (Hypothermia can exacerbate PPHN. In life threatening PPHN with concurrent HIE, discuss target temperature)

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.

Ventilation:

Infants with hypoxaemia can enter a spiral of PPHN very quickly. There should be a **low threshold to intubate a term baby with a significant oxygen requirement** rather than manage on non-invasive modes of respiratory support such as nasal continuous positive airway pressure (CPAP) or high-flow.

- Ensure that the endotracheal tube is in the optimum position
- 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) if not responding to conventional ventilation
- To consider iNO e.g. OI> 20

Cardiovascular

- Supporting the systemic circulation will reduce right to left shunting
- Consider aliquots of 10ml/kg sodium chloride 0.9%, if clinically indicated or suggested by echo findings
- To maintain normal Ph is important and bicarbonate to correct significant acidosis can be considered as acidosis can increase PVR
- Use inotropes to keep the blood pressure optimal. (Generally higher mean arterial pressures are required to prevent right to left shunting)
- Optimise Haemoglobin , Platelets and aim normal coagulation

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

Metabolic

- Correct Hypoglycaemia and maintain normoglycaemia
- Keep ionized Ca >1 and Mg within the normal range.

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(See below)
- 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).
- Refer Weaning in the weaning section

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]

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 body's 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.

Monitoring

- **Pre and post ductal saturation – Titrate oxygenation based on pre ductal saturation.**
- **Serial clinical assessment including perfusion**
- **Invasive Blood pressure monitoring**

- **Serial ABG monitoring at least 4- 6 hours and less frequent when stablised. Right radial – is pre-ductal . If UAC is in place – it is post-ductal**
- **Serial level of lactate will give an idea of tissue perfusion**
- **Methaemoglobin levels (from Blood gas) to watch for toxicity**
- **Ventilator values: Most of the parameters are documented but close monitoring is required for Peak inspiratory pressure and tidal volumes.**
- **Chest X ray (After initiating HFOV) and any acute clinical change in clinical situation.**

ECMO

- ECMO is to be considered 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

Criteria for considering ECMO include (if in doubt, discuss with ECMO centre):

- Infants ≥ 34 weeks of gestation or birth weight ≥ 1.8kg with PPHN
- Respiratory failure or OI above 25(esp. in non-tertiary centres) despite optimal conventional ventilation including iNO, inotrope and/or HFOV
- Not maintaining adequate blood pressure with multiple inotropes
- No significant improvement or progression after 3 days
- No lethal congenital malformation (e.g. lethal chromosomal abnormality, major intracranial haemorrhage, major cardiac malformation or severe encephalopathy)

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]

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).

- Recent systematic review showed some milrinone combined with oral sildenafil had acceptable efficacy and reduced mortality[11]. Other 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 0.5mic/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)] and a prospective observational study[18] 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. Improvement in oxygenation and hemodynamics and thus mortality was noted

- 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].

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. There is some new literature on this benefit.[21]

Sildenafil (Oral /IV)

- Sildenafil is a selective phosphodiesterase-5 inhibitor that enhances NO mediated vasodilatation.

- 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 5 non-homogenous published RCTs Sildenafil used for treatment of pulmonary hypertension has potential for reducing mortality and improving oxygenation in neonates, especially in resource-limited settings where iNO is not available.

- 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].

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

3. Education and Training

None

4. Supporting References

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5. 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 AND REVIEW DETAILS			
Guideline Lead (Name and Title) Authors: Jonathan Cusack- Neonatal Consultant, Robin Miralles– Neonatal Consultant Reviewed by: Robin Miralles – Neonatal Consultant			**Executive Lead** Chief Medical Officer
Details of Changes made during review:			
Date	**Issue Number**	**Reviewed By**	**Description Of Changes (If Any)**
15/10/2008	**1**	Neonatal Guidelines Meeting	(original guideline ratified)
6/8/ - 17/09 2013	**2**	Neonatal Guidelines Meeting Neonatal Governance	**Ratified**
April – June 2018	**3**	**REM** Neonatal Guidelines Meeting Neonatal Governance	**Amendments**
July 2021	**4**	Neonatal Guidelines Meeting Neonatal Governance	**Ratified**

July 2024	**5**	Anzad Amanullah	Added to diagnosis of PPHN; pulse oximetry assessment RV pressure assessment The severity of the PPHN is based on the comparison of estimated RvP to systemic Blood pressure Management points; There should be a low threshold to intubate a term baby with a significant oxygen requirement To consider iNO e.g. OI> 20 Optimise Haemoglobin , Platelets and aim normal coagulation Added metabolic management Correct Hypoglycemia and maintain normglycemia Keep ionized Ca >1 and Mg within the normal range. Added new monitoring and ECMO sections Removed section on magnesium sulphate Updated research evidence information

Appendix: Management flowchart for a baby suspected of having PPHN