Persistent Pulmonary Hypertension of the Newborn (PPHN)
Neonatal Clinical Guideline
V2.0

August 2019
Summary

Clinical Suspicion of PPHN
- FiO2 >50% or PaO2 <8kpa in >35 week infant
- Pre post ductal saturation difference >4% with respiratory distress

1. Inform consultant on call
2. Give antibiotics (if not given)
3. Intubate and ventilate
4. Give Surfactant (200mg/kg)
5. Urgent CXR (pre line insertion if any delay)
6. Insert UVC and UAC (consider peripheral ART if unsuccessful)
7. Optimise blood pressure (10ml/kg saline) and treat shock
8. Sedate and Muscle Relax (Bolus then infusion)

If oxygen requirement remains > 40% or PaO2 remains <8Kpa

1. Optimise ventilation (start at minimum SIMV 24/7 Ti 0.6 Rate 25 100% O2)
2. Optimise blood pressure (10ml/kg 0.9% sodium chloride if shocked) then inotropes to keep MAP >60 (as per hypotension guideline)
3. Consider ECHO if available
4. Consider setting up Nitric if FiO2 remains high

Discuss with Derriford Neonatal Transport Team or Derriford Neonatal on-call Consultant

Further management as directed by Derriford Consultant (may include)
- Inhaled Nitric Oxide (commencing at 20ppm)
- Optimise Magnesium (give correction if <0.8)
- Increase ventilatory pressures / optimise ventilation strategy
- Further doses of sedation
- HFOV if persistent ventilatory/ oxygenation failure
1. **Aim/Purpose of this Guideline**

1.1. To provide guidance of the acute clinical management of neonatal Persistent Pulmonary Hypertension of the Newborn, (PPHN), to all neonatal staff.

1.2. This version supersedes any previous versions of this document.

1.3. **Data Protection Act 2018 (General Data Protection Regulation – GDPR) Legislation**

The Trust has a duty under the DPA18 to ensure that there is a valid legal basis to process personal and sensitive data. The legal basis for processing must be identified and documented before the processing begins. In many cases we may need consent; this must be explicit, informed and documented. We can’t rely on Opt out, it must be Opt in.

DPA18 is applicable to all staff; this includes those working as contractors and providers of services.

For more information about your obligations under the DPA18 please see the ‘information use framework policy’, or contact the Information Governance Team rch-tr.infogov@nhs.net

2. **The Guidance**

2.1. **Background:**

PPHN is being increasingly recognised in neonatal practice with an estimated incidence of 2-6/1000 births. It can occur in both term and preterm neonates and is perhaps the most common cause of death in infants of birth weight > 1000g. The need to ventilate a baby in 40-50% oxygen needs serious consideration, depending upon the clinical findings and blood gases.

2.2. **Pathogenesis:**

Failure to achieve expected fall in PVR (Pulmonary Vascular Resistance) and therefore failure of oxygenation of the pulmonary venous blood returned to the heart is described by the term Persistent Pulmonary Hypertension of the Newborn (PPHN).

In utero only 10-15% of the cardiac output reaches the lungs via the pulmonary circulation. After delivery, inflation of the lungs and increased PaO2 are the principle factors promoting pulmonary vasodilatation, reduced pulmonary vascular resistance (PVR) and improved pulmonary perfusion.

2.3. **Primary (Idiopathic) PPHN:**

- Degree of hypoxia disproportionate to degree of hypercarbia, maybe in response to utero-fetal stress.
- Echocardiogram: structurally normal heart (may show right ventricular hypertrophy), right-to-left or bidirectional shunt at PFO and/or Patent Ductus Arteriosus (PDA).

2.4. Secondary PPHN:

- Severe lung disease: meconium aspiration (MAS), surfactant deficiency
- Perinatal asphyxia
- Infection: Group B streptococcal (GBS) pneumonia - via Strep polysaccharide toxins.
- Structural abnormalities: pulmonary hypoplasia, congenital diaphragmatic hernia, A-V fistula Congenital Cystic Adenomatoid Malformation (CCAM). Alveolar Capillary Dysplasia
- Maternal drugs: aspirin, non-steroidal anti-inflammatory drugs, SSRIs
- Polycythaemia and hypocalcaemia may contribute similarly.

2.5. Diagnosis

This is essentially one of exclusion of significant Cyanotic Congenital Heart disease and severe Parenchymal lung disease. However, PPHN may coexist with significant parenchymal lung disease.

Have a high index of suspicion for the "at risk' group" in a term baby with respiratory distress and cyanosis, particularly if there has been a history of intrauterine hypoxia and meconium exposure or birth asphyxia.

2.5.1. Differential Diagnosis

- The hyperoxic test may play a role in diagnosis if 2D echocardiography is not available. However, severe PPHN is likely to produce a similar result to cyanotic CHD.
- Congenital heart disease, including transposition of the great arteries, total and partial anomalous pulmonary venous connection, tricuspid atresia, and pulmonary atresia with intact ventricular septum
- Primary parenchymal lung disease such as bronchopulmonary dysplasia (BPD), neonatal pneumonia, respiratory distress syndrome, pulmonary sequestration, and pulmonary hypoplasia
- Sepsis
- Alveolar capillary dysplasia
- Surfactant protein B deficiency

2.6. Clinical Features:

- The most important clinical feature is difficulty in oxygenating the neonate with a persistently low O2 saturations, despite increasing FiO2 and ventilatory support.
- The blood gas (arterial) is likely to show severe hypoxemia PaO2 <8kpa.
- There is significant difference in pre and post ductal O2 saturations (5-10%).
- A prominent right ventricular impulse may be noted and murmurs due to tricuspid regurgitation or pulmonary regurgitation may be heard.
- Signs of heart failure may be present.
2.7. Investigations:

- Sepsis screen: FBC, CRP, Blood Cultures
- Serial Arterial blood Blood Glucose, U&E, LFT, Bone Profile
- Chest X ray
- Echocardiogram if available - to exclude Congenital Heart disease, estimate Pulmonary arterial pressure and myocardial contractility. See Appendix 3
- Cranial USS when considering ECMO.

2.8. Management:

2.8.1. Aims of Management

- Lower pulmonary vascular resistance.
- Maintain systemic blood pressure higher than pulmonary pressures
- Reverse right-to-left shunting.
- Improve arteriolar oxygen saturation and oxygen delivery to the tissues
- Minimise barotrauma
- Ensure adequate sedation and pain relief

2.8.2. General measures:

- Ensure adequate sedation and pain relief
- Minimal handling, nurse in quiet environment
- Secure arterial and central venous access.
- Maintain normal temperature, biochemistry and fluid balance
- Give antibiotics (sepsis particularly GBS is difficult to exclude)
- Surfactant may be beneficial in MAS or GBS sepsis, discuss with consultant
- If perfusion poor, fluid bolus (10 mL/kg of 0.9% sodium chloride or if coagulopathy, fresh frozen plasma)
- Liaise early with Consultant-on-call and Regional Level 3 Neonatal Unit.

2.8.3. Specific measures:

2.8.3.1. Oxygenation & Ventilation:

- Optimise ETT position and size, Aim for no leak.
- Hyperoxia is important first step (Administering 100% Oxygen) at the outset of suspicion is important. Hyperoxia may play a role in the diagnosis if 2D echocardiography is not available. However, severe PPHN is likely to produce a similar result to cyanotic congenital heart disease. There is no risk associated with this step in a short term with term baby give 100% O2 until CHD proven
- Aim for saturation of above 98%
- Use SIMV as the first line mode of ventilation with a high PIP, high PEEP, long Inspiratory Time and slow rate. Tidal volumes up to 10ml/kg may be at times required. In an infant >2kg settings of 24/7, Ti 0.6 and rate 25 are an appropriate starting point
- Avoid overexpansion of lungs (aim <9 ribs posteriorly).
- Normo-ventilation i.e. pO\textsubscript{2} 8-12 kpa is acceptable if baby stable, and pCO\textsubscript{2} 5-7 kpa if this can be achieved.
- Consider use of Surfactant- may be useful in Meconium Aspiration and GBS Sepsis.
- Alkalainise with sodium bicarbonate to maintain pH >7.35 if gas exchange permits.
- Consider low dose 24 hour maintenance sodium bicarbonate (discuss with PHNT Consultant)

2.8.3.2. **Pulmonary Vasodilators:**

*Inhaled nitric oxide* (iNO) is the vasodilator of choice- discuss with Derriford first except in exceptional circumstances. Use if Oxygenation Index (OI) >15 or Difference in pre to post-ductal SaO\textsubscript{2} >5% in the absence of CHD ( +/- Evidence of significant pulmonary hypertension on echo). iNO should be started at 20ppm and reduced to 5ppm as able, according to response and stability.

*Magnesium Sulphate* correct magnesium if <0.8 as per NNF treatment of hypomagnesemia. Be aware magnesium can cause hypotension so ensure BP is optimal before commencing infusion.

2.8.3.3. **Blood Pressure:**

- Aim to keep the mean arterial pressures above 60mm Hg in term infants or higher if RV pressure calculated to be greater than this.
- Use volume (initially normal saline) and inotropic support: Dopamine and / or Dobutamine, both starting at 10 mcg/kg/min. If the systemic pressure increases and pulmonary pressure stays the same, R-L shunt will diminish.
- Adrenaline infusions may be indicated if there is severe myocardial dysfunction.
- Hydrocortisone should be given as per hypotension guideline.

2.8.3.4. **Sedation:**

- Adequate sedation with I.V. Morphine Sulphate and minimal handling approach.
- Fentanyl 2microgram/kg if additional boluses are required for achieving sedation under ventilation. This could at times cause muscle rigidity and can be reversed by use of muscle relaxant as rescue (as per neonatal formulary)

2.8.3.5. **Muscle Relaxants:**

- Have a low threshold for paralysis with sedation
- Use I.V. Vecuronium Bromide I.V infusion at 60-120micrograms/kg/hour (refer to NNF book) to maintain longer muscle relaxant effect.
- Beware: above medications may mask clinical seizures and consider CFM
2.8.3.6. Correct Metabolic Acidosis:
- Maintain pH between 7.35 to 7.45
- Half or full correction with Sodium Bicarbonate for metabolic acidosis.
- If repeated corrections are needed consider maintenance I.V. Bicarbonate infusions (which can be given via UAC)
- Liberal bicarbonate use may result in hypernatraemia and hypokalaemia

2.8.3.7. Avoid Hyperventilation:
- Respiratory alkalosis by hyperventilation causes as many problems as it solves. It is no longer recommended - maintain PaCO2 4.5-5.5 kpa.

2.8.3.8. Maintain adequate Fluid & Electrolyte balance:
- Careful monitoring and maintenance of normal adequate fluid volume, blood glucose, calcium, and electrolytes is essential.
- Careful attention to baby’s nutritional requirement must be adhered to.
- Consider TPN if available, particularly in growth restricted babies.

2.8.3.9. Echocardiography
- Telemedicine link equipment and echo machine available on Gwithian unit if Neonatal Transport team wish to use telemedicine link for discussion with Bristol Paediatric Cardiology. This can be brought to NNU. The step by step details of how to set up telemedicine link is available on shared folder

S:\RCH-WCSH\Child Health\Medical\Telemedicine
This can be done from nursery 1, nursery 2, nursery 5 and nursery 6
Log in details for echo machine
OPERATOR: ADM
PASSWORD: ulsadm

2.8.3.10. ECMO
- Consider ECMO if Oxygenation Index (OI) is >25
- Calculate OI by clicking here:
  Neomate
- Or use formula: 
  \[
  OI = \frac{\text{Mean Airway Pressure (cmH2O)} \times \text{FiO2} \times 100}{\text{Post-ductal PaO2 (kPa)} \times 7.5}
  \]

Inclusion Criteria for ECMO:
- Baby born ≥34 weeks or ≥2 kg with PPHN
- Oxygenation index >25
- Reversible lung disease (<10 days high pressure ventilation)
- No lethal congenital abnormalities

Exclusion Criteria for ECMO
- Major intracranial haemorrhage
- Irreversible lung injury or mechanical ventilation >10 days
- Lethal congenital or chromosomal anomalies
- Severe encephalopathy
- Major cardiac malformation
3. Monitoring compliance and effectiveness

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<td>Dr. Chris Bell</td>
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4. Equality and Diversity

4.1. This document complies with the Royal Cornwall Hospitals NHS Trust service Equality and Diversity statement which can be found in the 'Equality, Inclusion & Human Rights Policy' or the Equality and Diversity website.

4.2. Equality Impact Assessment
The Initial Equality Impact Assessment Screening Form is at Appendix 2.
Appendix 1. Governance Information

<table>
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<th>Persistent Pulmonary Hypertension of the Newborn (PPHN) Neonatal Clinical Guideline V2.0</th>
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<td>08 August 2019</td>
</tr>
<tr>
<td>Date Valid From:</td>
<td>August 2019</td>
</tr>
<tr>
<td>Date Valid To:</td>
<td>August 2022</td>
</tr>
<tr>
<td>Directorate / Department responsible (author/owner):</td>
<td>Dr. Chris Bell</td>
</tr>
<tr>
<td>Contact details:</td>
<td>01872 252667</td>
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<td>Management of a newborn infant with Persistent Pulmonary Hypertension of the Newborn (PPHN) in the acute hospital setting</td>
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<td>Persistent Pulmonary Hypertension of the Newborn . PPHN. Neonatal. Clinical</td>
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<td>Medical Director</td>
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<tr>
<td>Date revised:</td>
<td>August 2019</td>
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<td>Persistent Pulmonary Hypertension of the Newborn (PPHN) – Neonatal Management. Clinical Guideline V1.1</td>
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<td>Approval route (names of committees)/consultation:</td>
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<tr>
<td>Care Group General Manager confirming approval processes:</td>
<td>Debra Shields</td>
</tr>
<tr>
<td>Name and Post Title of additional signatories</td>
<td>Not Required</td>
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<tr>
<td>Name and Signature of Care Group/Directorate Governance Lead confirming approval by specialty and care group management meetings</td>
<td>Name: Caroline Amukusana</td>
</tr>
<tr>
<td>Signature of Executive Director giving approval</td>
<td>{Original Copy Signed}</td>
</tr>
<tr>
<td>Publication Location (refer to Policy on Policies – Approvals and Ratification):</td>
<td>Internet &amp; Intranet ✓ Intranet Only</td>
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References:
8. CATS PPHN guidelines.
10. Cardiff PICU Cardiac guidelines.
11. Auckland PPHN guidelines.

Training Need Identified? No

Version Control Table

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<td>V1.1</td>
<td>Formatted and Approved by Neonatal Guidelines Group</td>
<td>Approved by Dr Paul Munyard. Consultant Paediatrician. Formatted by Kim Smith. Staff Nurse</td>
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<tr>
<td>08:08:19</td>
<td>V2.0</td>
<td>Full review Updated with tertiary advice Addition of flow chart Re-formatted</td>
<td>Dr Chris Bell, Consultant Paediatrician</td>
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All or part of this document can be released under the Freedom of Information Act 2000

This document is to be retained for 10 years from the date of expiry. This document is only valid on the day of printing

Controlled Document
This document has been created following the Royal Cornwall Hospitals NHS Trust Policy for the Development and Management of Knowledge, Procedural and Web Documents (The Policy on Policies). It should not be altered in any way without the express permission of the author or their Line Manager.
Appendix 2. Initial Equality Impact Assessment Form

<table>
<thead>
<tr>
<th>Name of the strategy / policy / proposal / service function to be assessed</th>
<th>Persistent Pulmonary Hypertension of the Newborn (PPHN) Neonatal Clinical Guideline V2.0</th>
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<tr>
<td>New or existing document:</td>
<td>Existing</td>
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<tr>
<td>Name of individual completing assessment:</td>
<td>Dr C Bell</td>
</tr>
<tr>
<td>Telephone:</td>
<td>01872 252667</td>
</tr>
</tbody>
</table>

1. **Policy Aim***
   *Who is the strategy / policy / proposal / service function aimed at?*
   This guideline is aimed at all clinical staff responsible for the acute care of newborn infants with suspected Persistent Pulmonary Hypertension of the Newborn (PPHN).

2. **Policy Objectives***
   As above

3. **Policy – intended Outcomes***
   Consistent and safe management of newborn infants with suspected Persistent Pulmonary Hypertension of the Newborn (PPHN).

4. **How will you measure the outcome?**
   Audit

5. **Who is intended to benefit from the policy?**
   Neonatal patients.
   Medical and Nursing staff

6a. **Who did you consult with**

   b). Please identify the groups who have been consulted about this procedure.
   
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   Please record specific names of groups
   Neonatal Guideline Group

   What was the outcome of the consultation?
   guideline approved

7. **The Impact**
   Please complete the following table. **If you are unsure/don’t know if there is a negative impact you need to repeat the consultation step.**

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Persistent Pulmonary Hypertension of the Newborn (PPHN) Neonatal Clinical Guideline V2.0
Page 12 of 16
Are there concerns that the policy could have differential impact on:

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<th>Equality Strands</th>
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You will need to continue to a full Equality Impact Assessment if the following have been highlighted:

- You have ticked “Yes” in any column above and
- No consultation or evidence of there being consultation- this excludes any policies which have been identified as not requiring consultation. or
- Major this relates to service redesign or development

8. Please indicate if a full equality analysis is recommended.   | Yes | No | x |
9. If you are not recommending a Full Impact assessment please explain why.

Not indicated
This EIA will not be uploaded to the Trust website without the approval of the Policy Review Group.

A summary of the results will be published on the Trust’s web site.
Appendix 3: Echo cardiographic assessment of Pulmonary Hypertension:

1. Tricuspid regurgitation:
   - Right Ventricular pressure can be calculated from TR jet (4 X V^2 + estimated right atrial pressure)
   - Ensure the Doppler envelope is complete
   - Interpret in the context of systemic BP

2. Atrial shunting and other shunts:
   - Some degree of right-to-left atrial shunting through the patent foramen ovale is common, although it is rare for this to be purely right-to-left (Pure right-to-left flow indicates total anomalous pulmonary venous connection (TAPVC) until proved otherwise).
   - Bowing of the interatrial septum to the left is commonly seen.
   - Right-to-left atrial shunting reflects right atrial filling (diastolic) pressure
   - If a VSD is present, bidirectional shunting may be noted.

3. Ductal flow:
   The direction and velocity of ductal blood flow can give useful information on PAP.
   - Pure right-to-left flow indicates Pulmonary arterial pressure is higher than the aortic pressure throughout the cardiac cycle.
   - Bidirectional flow occurs when the aortic and pulmonary arterial pressures are approximately equal. Flow is left-to-right during diastole and right-to-left, in systole (as the pulmonary arterial pressure wave reaches the duct before the aortic pressure wave).
   - Bidirectional flow is common in healthy babies in the first 12 hours but changes to pure left-to-right when aortic pressures become higher than pulmonary pressures.

4. Cardiac function
   - There may be enlargement of Right atrium, Right ventricle and main pulmonary artery.
   - There may be flattening (RV: LV pressure >0.5) and or even bowing (RV: LV pressure ≥1.0) of interventricular septum to the left as RV pressure rises.
   - Quantitative assessment of cardiac function may assist with decisions and assessments of the roles of inotropes and inhaled nitric oxide.
   - If the LA and LV appear under-filled, it is critical to exclude TAPVD. Demonstration of left to right shunt at atrial level essentially excludes TAPVD.
Appendix 4: PPHN Guidelines Royal Cornwall Hospital
Overview Flowchart

Infants with refractory hypoxaemia and no evidence of lung disease should be considered to have possible duct dependent cyanotic congenital heart disease.

Evaluate for PPHN
Lack of response to 100% FiO2
No obvious cardiac abnormality
Term baby
Early discussion with consultant on-call
Early discussion with Regional Level 3 NICU

Calculate oxygenation index $OI = MAP \times fiO2 \%$
$PO2 \text{ mm/hg (kpa x7.5)}$
$OI >25$ Start iNO
$OI >40$ ECMO

Ventilation
Intubate and ventilate after muscle relaxants and sedation.
Early x-rays to confirm optimum positions of ETT. NO 4-hour wait for X-rays.
Target pO2 >8kpa
Target Saturations >95%
Liberal use of O2
Consider pulmonary vasodilators-iNO
Optimal Trial NO (transfer)

Optimise ventilation
200mg/kg of Surfactant
Try higher PEEP, titrate up from 5 to 8 (try reduced PEEP if CXR suggests air trapping)
lengthen iTime to max 0.8 to 1 sec
Wean up peak pressure to 28 cms
alternatively volume ventilate 4ml Kg with max 34cm, then consider HFOV

Optimise circulation
Adequate I.V.Fluids
Target mean invasive BP 50 mmhg
Early inotropes:
First line: Dobutamine then dopamine
Second line: Adrenaline/Noradrenaline
Strict Input/Output monitoring

Circulation
Early IV access
Insert UAC/UVC
Early x-rays to confirm optimum positions of lines.
ECHO to rule out Congenital Cardiac lesions, if available.

Miscellaneous
Cover for Sepsis: 1st line: I.V.Benzyl Penicillin and Gentamicin Sedate & Paralyse Morphine with Vecuronium Midazolam if high Morphine requirement Maintain normothermia unless associated HIE Correct acid-base deficits Avoid Polycythaemia Cranial USG

Rule out co-morbidities
Pneumothorax-Needle Thoracentesis/Chest drain Pleural effusions Pericardial effusions Congenital Diaphragmatic Hernia Hypothermia Hypoglycaemia Sepsis