PERSISTENT PULMONARY HYPERTENSION OF THE NEWBORN (PPHN) NEONATAL CLINICAL GUIDELINE

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.

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 gasses.

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.

**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.
- There is significant difference in pre and post ductal PaO2 (>2.5 kPa) or 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:**
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
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.

Specific measures:
Oxygenation & Ventilation:
• Optimise ETT position and size.
• Aim for no leak.
• Aim for saturation of above 95%
• Always start with 100% oxygen and reduce the FiO₂, rather than starting on lower and increasing. In the short term there is no risk to a term baby using such measures.
• Avoid overexpansion of lungs (aim <9 ribs posteriorly).
• Normo-ventilation i.e. pO₂ 8-12 kpa is acceptable if baby stable, and pCO₂ 5-7 kpa if this can be achieved.
• Use of HFOV, particularly in combination with inhaled Nitric Oxide, has been shown to reduce the need for ECMO.
• If HFOV unavailable, conventional ventilation with high PEEP (8-10) may improve oxygenation whilst reducing requirement for high PIP.
• Consider use of Surfactant- may be useful in Meconium Aspiration and GBS Sepsis.
• Alkalinise with sodium bicarbonate or THAM to maintain pH >7.35 if gas exchange permits.
• Consider low dose 24 hour maintenance sodium bicarbonate through the UAC.

Pulmonary Vasodilators:
Inhaled nitric oxide (iNO) is the vasodilator of choice.
Use if Oxygenation Index (OI) >15 or Difference in pre to post-ductal SaO₂ >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. Refer to iNO guideline

Magnesium Sulphate may be used in refractory cases. Consider a magnesium bolus of 50mg/kg over 30 min if MAP maintained (watch for hypotension). This may be repeated as tolerated if effective, or administered as an infusion (suggested maximum serum Mg level of 5.5mmol/l)

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 5-10 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 considered in refractory cases – see hypotension guideline.
Sedation:
- Adequate sedation with I.V. Morphine Sulfate and minimal handling approach.
- I.V. Midazolam if adequate sedation unobtainable with Morphine. Use with caution.

Muscle Relaxants:
- Have a low threshold for paralysis with sedation
- Use I.V. Vecuronium Bromide I.V infusion at 1-2 micrograms/kg/minute (refer to Neonatal Formulary) to maintain longer muscle relaxant effect.
- Use I.V. Pancuronium Bromide @100 micrograms/kg/dose PRN (refer to Neonatal Formulary) Use as bolus if access limited.
- Beware: above medications may mask clinical seizures and consider CFM

Correct Metabolic Acidosis:
- Maintain pH between 7.35 to 7.45
- Half or full correction with Sodium Bicarbonate or THAM 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

Avoid Hyperventilation:
- Respiratory alkalosis by hyperventilation causes as many problems as it solves. It is no longer recommended.

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.

ECMO
- Consider ECMO if Oxygenation Index (OI) is >25
- Or use formula: OI = Mean Airway Pressure (cmH2O) x FiO2 x 100 / Post-ductal PaO2 (kPa) x 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

<table>
<thead>
<tr>
<th>Element to be monitored</th>
<th>Key changes to practice</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lead</td>
<td>Dr. Paul Munyard.</td>
</tr>
<tr>
<td>Tool</td>
<td>Audit</td>
</tr>
<tr>
<td>Frequency</td>
<td>As dictated by audit findings</td>
</tr>
<tr>
<td>Reporting arrangements</td>
<td>Child Health Directorate Audit and neonatal Clinical Guidelines Group.</td>
</tr>
<tr>
<td>Acting on recommendations and Lead(s)</td>
<td>Paul Munyard. Consultant Paediatrician and Neonatologist</td>
</tr>
<tr>
<td>Change in practice and lessons to be shared</td>
<td>Required changes to practice will be identified and actioned within 3 months. A lead member of the team will be identified to take each change forward where appropriate. Lessons will be shared with all the relevant stakeholders</td>
</tr>
</tbody>
</table>

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, Diversity & 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>
<thead>
<tr>
<th>Document Title</th>
<th>Persistent Pulmonary Hypertension of the Newborn (PPHN) – Neonatal Management. Clinical Guideline</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Date Issued/Approved:</strong></td>
<td>22 January 2015</td>
</tr>
<tr>
<td><strong>Date Valid From:</strong></td>
<td>22 January 2015</td>
</tr>
<tr>
<td><strong>Date Valid To:</strong></td>
<td>22 January 2018</td>
</tr>
</tbody>
</table>
| **Directorate / Department responsible (author/owner):** | Dr. Nagendra Venkata  
Dr. Mohammed Buhary  
Dr. Paul Munyard  
Child Health Directorate. Neonatal. |
| **Contact details:** | 01872 252667 |
| **Brief summary of contents** | Management of a newborn infant with Persistent Pulmonary Hypertension of the Newborn (PPHN) in the acute hospital setting |
| **Suggested Keywords:** | Persistent Pulmonary Hypertension of the Newborn . PPHN. Neonatal. Clinical |
| **Target Audience** | RCHT | PCH | CFT | KCCG |
| | ✓ | | | |
| **Executive Director responsible for Policy:** | Executive Director |
| **Date revised:** | 22:01:2015 |
| **This document replaces (exact title of previous version):** | New Document |
| **Approval route (names of committees)/consultation:** | Neonatal Guidelines Group  
Child Health Directorate Audit  
Consultant approval |
| **Divisional Manager confirming approval processes** | Sheena Wallace |
| **Name and Post Title of additional signatories** | Not Required |
| **Signature of Executive Director giving approval** | {Original Copy Signed} |
| **Publication Location (refer to Policy on Policies – Approvals and Ratification):** | Internet & Intranet | ✓ Intranet Only |
| **Document Library Folder/Sub Folder** | Neonatal. Clinical. Child Health |
| **Links to key external standards** | none |

**Related Documents:**

References:
8. CATS PPHN guidelines.
10. Cardiff PICU Cardiac guidelines.
11. Auckland PPHN guidelines.

**Training Need Identified?** No
<table>
<thead>
<tr>
<th>Date</th>
<th>Version</th>
<th>Summary of Changes</th>
<th>Changes Made by</th>
</tr>
</thead>
<tbody>
<tr>
<td>22:01:15</td>
<td>V1.1</td>
<td>Formatted and Approved by Neonatal Guidelines Group</td>
<td>Approved by Dr Paul Munyard. Consultant Paediatrician.</td>
</tr>
</tbody>
</table>

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 on Document Production. 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 (hereafter referred to as policy) (Provide brief description):</th>
<th>Persistent Pulmonary Hypertension of the Newborn (PPHN) – Neonatal Management. Clinical Guideline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Directorate and service area:</td>
<td>Child and Women’s Health. Neonatal</td>
</tr>
<tr>
<td>Name of individual completing assessment:</td>
<td>Dr. Paul Munyard</td>
</tr>
<tr>
<td>Telephone:</td>
<td>01872 252667</td>
</tr>
<tr>
<td>Is this a new or existing Policy?</td>
<td>New</td>
</tr>
<tr>
<td>1. Policy Aim*</td>
<td>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).</td>
</tr>
<tr>
<td>2. Policy Objectives*</td>
<td>As above</td>
</tr>
<tr>
<td>3. Policy – intended Outcomes*</td>
<td>Audit</td>
</tr>
<tr>
<td>4. *How will you measure the outcome?</td>
<td>audit</td>
</tr>
<tr>
<td>5. Who is intended to benefit from the policy?</td>
<td>Neonatal patients. Medical and Nursing staff</td>
</tr>
<tr>
<td>6a) Is consultation required with the workforce, equality groups, local interest groups etc. around this policy?</td>
<td>No. Neonatal Guideline Group Consultant approved guideline</td>
</tr>
<tr>
<td>b) If yes, have these *groups been consulted?</td>
<td></td>
</tr>
<tr>
<td>C). Please list any groups who have been consulted about this procedure.</td>
<td></td>
</tr>
</tbody>
</table>

---

Persistent Pulmonary Hypertension of the Newborn (PPHN) – Neonatal Management. Clinical Guideline

Page 9 of 13
### 7. The Impact

Please complete the following table.

<table>
<thead>
<tr>
<th>Equality Strands:</th>
<th>Yes</th>
<th>No</th>
<th>Rationale for Assessment / Existing Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Sex (male, female, trans-gender / gender reassignment)</strong></td>
<td></td>
<td>x</td>
<td></td>
</tr>
<tr>
<td><strong>Race / Ethnic communities /groups</strong></td>
<td></td>
<td>x</td>
<td></td>
</tr>
<tr>
<td><strong>Disability -</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>learning</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>disability, physical</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>disability, sensory</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>impairment and</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mental health</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>problems</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Religion / other beliefs</strong></td>
<td></td>
<td>x</td>
<td></td>
</tr>
<tr>
<td><strong>Marriage and civil partnership</strong></td>
<td></td>
<td>x</td>
<td></td>
</tr>
<tr>
<td><strong>Pregnancy and maternity</strong></td>
<td></td>
<td>x</td>
<td></td>
</tr>
<tr>
<td><strong>Sexual Orientation,</strong></td>
<td></td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>Bisexual, Gay, heterosexual, Lesbian</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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 service redesign or development
### 8. Please indicate if a full equality analysis is recommended.

| No |

### 9. If you are not recommending a Full Impact assessment please explain why.

No area indicated

<table>
<thead>
<tr>
<th>Signature of policy developer / lead manager / director</th>
<th>28:02:2015</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paul Munyard</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Names and signatures of members carrying out the Screening Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
</tr>
<tr>
<td>2.</td>
</tr>
</tbody>
</table>

---

**Keep one copy and send a copy to the Human Rights, Equality and Inclusion Lead,**

c/o Royal Cornwall Hospitals NHS Trust, Human Resources Department, Knowledge Spa, Truro, Cornwall, TR1 3HD

A summary of the results will be published on the Trust’s web site.

Signed ____________ Kim Smith __________

Date ____________ 28:02:2015 __________
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 gives 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
\[ OI = \text{MAP} \times \text{FiO2 \%} \]
\[ \text{PO2 mm/hg (kpa x 7.5)} \]
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 iT ime 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

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.

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

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
Thoracocentesis/Chest drain
Pleural effusions
Pericardial effusions
Congenital Diaphragmatic Hernia
Hypothermia
Hypoglycaemia
Sepsis