Management of Persistent Pulmonary Hypertension of newborn (PPHN)

For more detailed information, please read the complete guideline

Risk factors for Development of PPHN	
Term and near-term infants	**Preterm infants**
Male, African or Asian maternal race Maternal obesity, diabetes, and asthma C-section Chorioamnionitis Meconium-stained amniotic fluid Antenatal exposure to drugs (SSRI, COXi) Perinatal infection, Perinatal asphyxia Hypothermia, stress, pain stimuli Hypocalcemia, acidosis Polycythemia Trisomy 21	Severe BPD Lower GA, weight at birth Small for gestational age Pulmonary hemorrhage Sepsis Oligohydramnios and anhydramnios Prolonged duration of invasive respiratory support Increased length of stay in hospital

Primary PPHN

In response to in-utero conditions or drug exposure
Cyanosis + oligemic lungs on CXR
Pure intracardiac R>>L shunt

Secondary PPHN

Pneumonia, sepsis
MAS, surfactant deficiency
Abnormal CXR
Both extra/intracardiac R>>L shunt

PPHN and lung disease

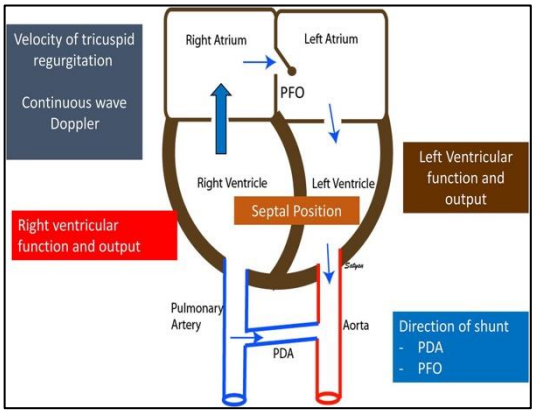
Pulmonary hypoplasia, CHD, Alveolar capillary dysplasia

Diagnosis:

- Severe hypoxemia within 72h of birth
- Pre/post ductal SatO2 > 10% difference
- Pre/Post ductal PaO2 > 10-20 mmHg difference
- Absence of cyanotic CHD
- Echocardiogram findings

Echocardiogram findings:

- To exclude CHD
- R-to-L shunt at PDA/PFO
- Flattening of IVS
- Tricuspid regurgitation
- R & L ventricular function



Stabilisation & Management

- Support A&B
  - If HFNC or NIV failure proceed to intubate and ventilate
  - Supplemental O2 – aim PaO2 > 8kPa and SatO2 > 92%
  - Aim for pH >7.35 and PaCO2 < 6-7kPa
  - Consider cuffed ETT if high pressure required
  - Monitor pre/post ductal saturations
- Optimise lung volume-recruitment
  - On CXR aim for 8-9 posterior ribs
  - Consider HFOV if high pressures required (> 25-30 cmH20)
  - Consider surfactant (200 mg/kg)
- Optimise O2 delivery
  - Invasive BP monitoring is advisable (aim SBP> Pulm pressure)
  - Optimise intravascular volume and consider inotropic support (adrenaline if impaired RV/LV function on echo)
  - Correct low Ca2+ (aim ionised Ca2+ > 1)
  - In inotropic resistant shock consider hydrocortisone IV bolus
- Pulmonary Vasodilators
  - Use supplemental O2 (FiO2>60%)
  - Inhaled NO 20 ppm
  - Calculate Oxygenation Index (OI)
  - Consider MgSO4 IV bolus if BP allows (aim Mg2+> 1)
- Supportive care
  - Aim normothermia & normoglycemia
  - Sedation and paralysis, CR USS (if ECMO considered)
  - Treat for systemic infection as appropriate

$$OI = \frac{(MAP\ (cmH_2O) \times FiO_2(0.21\text{-}1) \times 100)}{(PaO_2\ (kPa) \times 7.5)}$$

Indications for ECMO

- Weight > 2kg, GA > 34 w
- OI > 25 despite full medical therapy
- Refractory hypoxemia and low cardiac output despite inotropic support
- Persistent air leak despite drainage

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Management Of Persistent Pulmonary Hypertension Of The Newborn (PPHN)

1. SCOPE

For use within the Paediatric and Neonatal Decision Support and Retrieval Service (PaNDR) for the East of England.

2. PURPOSE

To provide, safe, efficient, and practical guidance for the management of neonates and young children with persistent pulmonary hypertension during stabilisation and transfer.

To provide guidance to deliver nitric oxide during stabilisation and transfer by the paediatric and neonatal transport team.

3. DEFINITIONS AND ABBREVIATIONS

PPHN	Persistent Pulmonary Hypertension of the Newborn
PDA	Patent Ductus Arteriosus
PFO	Patent Foramen Ovale
ASD	Atrial septal defect
SVR	Systemic vascular resistance
PVR	Pulmonary vascular resistance
HFOV	High Frequency Oscillatory Ventilation
MABP	Mean Arterial Blood pressure
ECMO	Extracorporeal Membrane Oxygenation
OI	Oxygenation index (see Appendix 1 for calculation)

MAS	Meconium Aspiration Syndrome
RDS	Respiratory distress syndrome
ETT	Endotracheal tube
iNO	Inhaled nitric oxide
IVH	Intraventricular haemorrhage
NICU	Neonatal Intensive Care Unit
MAP	Mean Airway Pressure
PH	Pulmonary Hypertension
BPD	Bronchopulmonary dysplasia
V/Q Mismatch	Ventilation-perfusion mismatch
PPROM	Pre-term, pre-labour rupture of membranes
SSRI	Selective serotonin re-uptake inhibitors
COXi	Cyclooxygenase inhibitors

4. INTRODUCTION

Persistent pulmonary hypertension of the newborn (PPHN) occurs when there is failure of the pulmonary circulation to change from the foetal (high pulmonary vascular resistance) to a stable postnatal (low resistance) state.

It is characterised by central cyanosis – increased pulmonary vascular resistance leads to shunting of deoxygenated blood from the pulmonary to the systemic circulation (via right to left shunting across the PDA and/or PFO).

Its incidence has been reported as 1.9 per 1,000 live births (0.4–6.8 per 1,000 live births) in the United States and 0.43 to 6 per 1,000 live births in the United Kingdom, with mortality rates ranging from 4% to 33%.

It is associated with an increased risk of an adverse outcome – five-year survival is approximately 90% and neurologic impairment occurs in 15-25%.

5. PATHOPHYSIOLOGY

The fetal circulation is characterised by high PVR and right-to-left shunt through the foetal channels (PFO/PDA), with gas exchange occurring in the placenta.

A series of circulatory events take place at birth to ensure a smooth transition from fetal to extrauterine life. Clamping of the umbilical cord removes the low-resistance placental circulation, increasing systemic arterial pressure. Various mechanisms operate simultaneously to rapidly reduce PVR and increase pulmonary blood flow. The most important stimulus appears to be ventilation of the lungs and an increase in oxygen tension. An 8-fold increase in pulmonary blood flow occurs, which raises left atrial pressure, closing the foramen ovale. Because PVR decreases lower than systemic vascular resistance, flow reverses across the ductus arteriosus (from the aorta to the pulmonary artery or left-to-right). The increase in arterial oxygen saturation leads to closure of the ductus arteriosus and ductus venosus. Also, rise in SVR is also promoted by catecholamine surge (associated with birth) and exposure to relatively cold extra-uterine environment.

Conditions that affect these factors can interfere with the normal postnatal fall of PVR/SVR ratio and result in PPHN. In addition to maladaptation processes, excessive muscularisation of lung vasculature or hypoplastic vasculature, such as seen in congenital diaphragmatic hernia can result in PPHN.

- **If PVR remains high after birth, blood shunts right-to-left through the PDA and PFO, resulting in systemic hypoxaemia**
- **The degree of hypoxaemia in 'PPHN' reflects the proportion of blood shunting across the fetal channels without passing through the lungs**

I. PRIMARY PPHN

- Due to a primary failure of adaption from fetal to postnatal circulation in a lung which is otherwise normally developed, and in the absence of secondary triggers such as sepsis or aspiration of meconium at birth
- In response to in utero fetal stress/hypoxia/pulmonary hypertension (e.g. premature Ductus Arteriosus closure secondary to maternal NSAID exposure)
- Babies with primary PPHN classically present with
    - profound cyanosis
    - markedly oligaemic lung fields on CXR (usually normal lung compliance)
    - Hypoxaemia is purely due to R>>L shunting through the fetal channels

II. SECONDARY PPHN

PPHN can also occur in response to a range of pulmonary insults which cause the pulmonary vasculature to 'flip' back to its foetal state, even if PVR had initially started to fall at birth:

- Pneumonia
- Early neonatal systemic sepsis
- Meconium Aspiration Syndrome (MAS)
- Surfactant deficiency
- Pulmonary hemorrhage

Most babies with secondary PPHN have

- reduced lung compliance
- Hypoxemia is mainly due to shunting R>>L through fetal channels, but there is additional element of intrapulmonary shunting due to pulmonary parenchymal disease – this is caused by a ventilation-perfusion (V/Q) mismatch.

III. PPHN and Structural Lung Disease

A third group of babies with structural lung abnormalities can be described in whom baseline pulmonary artery pressures are high due to a poorly developed or 'hypoplastic' pulmonary vascular bed.

- Pulmonary hypoplasia
- Congenital diaphragmatic hernia (CDH)
- Alveolar capillary dysplasia

IV. Late onset Pulmonary Hypertension

There is also late-onset pulmonary hypertension. This may occur in preterm babies who have developed bronchopulmonary dysplasia (BPD). They develop alveolar diffusion impairment and abnormal vascular remodeling, leading to increased pulmonary hypertension. Incidence increases with the severity of BPD.

6. Risk factors for Development of PPHN

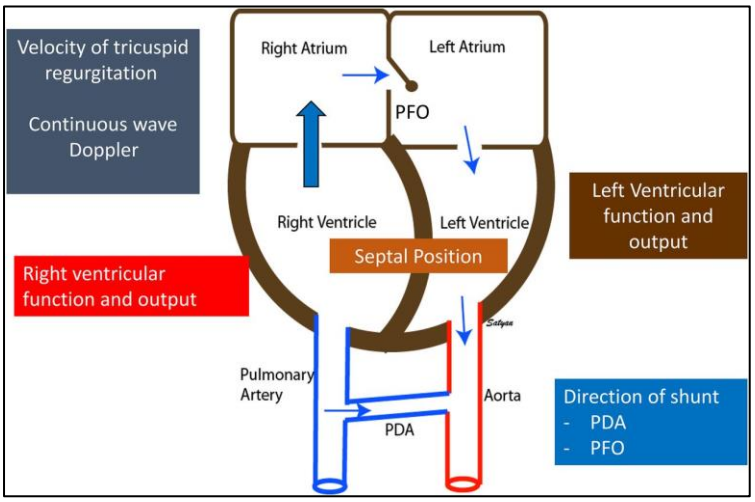
Term and near-term infants	Preterm infants
• Male gender, African or Asian maternal race • Maternal morbidity (obesity, diabetes, and asthma) • caesarean section • Chorioamnionitis • Meconium-stained amniotic fluid • Antenatal exposure to (SSRI), (COXi), certain "medications" (Chinese herbs) • Perinatal infection, Perinatal asphyxia • Hypothermia • Metabolic derangements (hypocalcemia and acidosis) • Stress, pain stimuli • Polycythemia • Trisomy 21	• Severe bronchopulmonary dysplasia • Lower gestational age at birth • Lower birth weight • Small for gestational age • Pulmonary hemorrhage • Sepsis • Oligohydramnios and anhydramnios • Prolonged duration of invasive respiratory support • Increased length of stay in hospital

7. DIAGNOSIS

- A newborn - mostly within 72hrs after birth - presenting with persistent **severe hypoxemia not responding to oxygenation (FiO_2 1.0 (100% O_2))**
- **Differential cyanosis**
    - Absence of Critical left heart-sided obstruction (ie Coarctation Aorta) or other ductal-dependent congenital heart defect

- If the PDA is open, saturations in the lower limbs are more than 5%–10% lower than the right upper limb
- PaO_2 difference >10 to 20 mm Hg between right upper limb and lower limbs
- If the PDA is closed and the shunt is exclusively at the PFO level, the degree of cyanosis is similar in both the upper and lower limbs

- **Echocardiography**:
  - Gold standard to confirm the diagnosis and to monitor the efficacy of specific therapeutic interventions in PPHN
  - Essential **to exclude congenital heart disease** as a cause of cyanosis (eg. TGA, pulmonary atresia) or pulmonary oedema (obstructed pulmonary venous drainage)
  - Echo findings should include:
    - Right to left shunting through PDA +/- PFO
    - Flattening or left deviation of the interventricular septum
    - Right ventricular systolic pressures by peak velocity of tricuspid regurgitation
    - Evaluation of right and left ventricular function to guide the choice of appropriate pulmonary vasodilator and inotropic support



Echocardiographic features of PPHN: tricuspid regurgitation (TR) and deviation of the interventricular septum to the left. The presence of R to L shunt at PFO and PDA is commonly observed in infants with severe PPHN. Impaired right and left ventricular function is associated with poor outcome in PPHN (From: Neoreviews. 2015 Dec; 16(12): e680–e692)

8. INITIAL STABILISATION AND ONGOING MANAGEMENT

A. Intubation if not done, especially when oxygen therapy and NIV have failed

- checking the ETT level on CXR (ideally at level of T2).
- Consider need for cuffed ETT, specially in term babies when PPHN is likely secondary to pulmonary disease (high ventilatory pressures likely to be needed)
- Suction the airway if required (avoid unnecessary ETT disconnections)
- **Supplemental O2 therapy – aim for PaO_2 > 8 kPa** and **Pre ductal** oxygen saturations **> 92%**
- Monitor pre- & post-ductal saturations (right hand and either foot) aiming for <5% difference

B. Optimize lung volume-recruitment:

- Review CXR - **Aim for 8- to 9 posterior-ribs** on an inspiratory chest x-ray (avoid overdistension)
- Rule out pneumothorax and treat if required
- Consider **surfactant therapy (200mg/kg)** – improves oxygenation and reduces the need for ECMO when PPHN is secondary to parenchymal lung disease such as RDS, pneumonia/sepsis or MAS
- Consider HFOV (if available) when peak inspiratory pressures > 25 - 28 cm H_2O or tidal volumes > 6 mL/kg are required to maintain a PaCO2 < 7-8 kPa on conventional ventilation
- Decompress the stomach using an NG/OG
- Calculate oxygenation index (OI) regularly – see ECMO section below.

C. Optimize O2 delivery

- If local expertise, perform an ECHO
- **Monitoring invasive BP** is important (UAC or peripheral arterial line)– **aim for MABP above estimated pulmonary pressures**
- Obtain central vascular access, remembering that sampling from a UAC is sampling from the post-ductal circulation
- Optimize **intravascular volume**, which may also require blood products
- Consider **inotropes** early (see table below), to maintain good cardiac output and adequate MABP
    - Use Noradrenaline infusion to increase SVR and revert right-to-left shunt
    - Use Adrenaline infusion – to support impaired RV and/or LV function
- If two inotropes are required, consider giving IV hydrocortisone as a bolus (2.5mg/kg IV)
- Correct hypocalcaemia aiming for an ionized calcium >1.1.

Assessment / Inotrope	Poor contractility	Peripherally vasodilated "warm shock"	Peripherally vasoconstricted "shut down" / "cool shock"	Tachycardia
Dopamine 5-10 mcg/kg/min	✓		✓	×
Dopamine 10-20 mcg/kg/min	✓	✓	×	
Noradrenaline 0.1-1.0 mcg/kg/min		✓ ✓	× ×	
Dobutamine 5-20 mcg/kg/min	✓ ✓	× ×	×	× ×
Adrenaline 0.03-0.1 mcg/kg/min	✓	×	✓	
Adrenaline 0.1-1.0 mcg/kg/min		✓	×	×

✓ – likely to be useful
✓✓ – very likely to be useful
× – risk of worsening picture
× × – likely to worsen picture

D. Use of Pulmonary vasodilators

- **Oxygen FiO_2 1.0 (100% O_2)**
- **Inhaled Nitric Oxide**:
  - Licensed for ≥34 weeks' gestation
  - Can be considered in <34 weeks' gestation in discussion with PaNDR Consultant – some evidence successful use in extremely preterm infants with PPHN secondary to lung hypoplasia/sepsis due to PPROM.
  - **Start at 20 ppm when OI > 15 despite optimal alveolar recruitment**
  - Adjust nitric oxide range between 5-20 ppm to keep methaemoglobin <5%
  - Combination HFOV and iNO results in the greatest improvement in oxygenation in PPHN associated with diffuse parenchymal lung disease
- Magnesium sulphate ($MgSO_4$) slow infusion (0.4 mmol/kg) – aim for Mg^{2+} > 1 mmol/L
- Other pulmonary vasodilators (such as sildenafil or milrinone) – to be discussed with PaNDR Consultant

E. Supportive care:

- Aim for normothermia unless neurological concerns to start cooling (see separate guideline)
- Aim for normoglycemia (blood sugar >3mmol/L)
- Avoidance of stress – covering eyes and ears and maintaining a low-noise environment
- Handling with **sedation and analgesia infusions +/- muscle relaxation** is mandatory to reduce physiological lability (discuss with PaNDR Consultant appropriate regimes)

- Cranial USS scan must be done and rule out any intracranial bleed if ECMO is being considered
- Investigate and **treat for systemic sepsis** as appropriate
-

F. Avoid metabolic / respiratory acidosis:

- Aim **to maintain pH > 7.35** (ideally 7.4-7.45). Sodium bicarbonate may be helpful in cases of severe metabolic acidosis where normalising the pH may improve response to inotropes. The risks/benefits of this treatment should be discussed with the PaNDR consultant
-
- Aim for **normal to low $PaCO_2$** (ideally 4-5 kPa) but do not induce hypocarbia ($PaCO_2$ <4 kPa) as this is associated with worse long-term neurodevelopment outcome.

9. ECMO REFERRAL (see "Management of ECMO referrals" guideline)

a. Indications for ECMO:
   - Weight >2kg
   - Gestation >34 weeks
   - **OI > 25** despite full medical therapy (HFOV if available and inhaled Nitric Oxide)
   - Refractory hypoxemia and low cardiac output states despite full medical therapy with a potentially reversible cause (including as a bridge to transplant)
   - Persistent air leak despite appropriate drainage

b. In discussion with the PaNDR Consultant, if ECMO advice is required, contact PaNDR on 01223 274274. Organize a conference call between the referring

team, the PaNDR Consultant and the ECMO/CICU Consultant. If GOSH the unit on take, call to ECMO Consultant to be arranged via CATS.

c. The baby may potentially be considered for an ECMO center even if they do not immediately require ECMO.

10. TRANSPORT CONSIDERATIONS:

In addition to the above management:

a. Set up nitric delivery circuit following the operational manual instruction

- Set ventilator to the required settings, with the dummy lung attached
- Set up the iNO to initially deliver 20ppm
- Start the infant on iNO therapy through the transport ventilator; this can be done before the infant is moved into the transport incubator/babypod or trolley
- If using modes of ventilation that consume higher gas flows, such as 'Active PEEP' on the Babypac ventilator, the iNO flow may also need to be modified to provide the same concentration of iNO

b. Transfer into the transport incubator and journey

- Prior to moving, check ETT and other lines are well-secured.
- All SpO_2 and ETCO2 monitoring must be continued
- Both the PaNDR nurse and doctor should transfer infant into the transport incubator/trolley. After moving re-check the ETT position and air entry. For those babies on $ETCO_2$ ensure there are still waveforms present
- Continue sedation and muscle relaxant infusions during the journey
- Perform a blood gas once the baby has been stable in the transport ventilator for 15-20 minutes
- Continue pre- and post-ductal SpO_2 monitoring during transfer
- Record observations every 15 minutes

- Update on-call PaNDR Consultant and update parents
- Consider planning to stop the ambulance in a safe place to check a blood gas if the transfer is anticipated to be >1.5 hours and/or the gases have been very unstable.

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APPENDIX 1: OXYGENATION INDEX

Oxygenation Index (OI) = (Mean Airway Pressure (cmH_2O) x FiO_2(0.21-1)x 100) / (PaO_2 (kPa) x 7.5)

- Note: FiO_2 is a value between 0.21 (= 21% O_2) and 1.0 (= 100% O_2)
- If PaO_2 is expressed in kPA, then multiply by 7.5 as per the calculation above (this converts the kPa result into mmHg so that the correct result is obtained). If the PaO_2 is already expressed in mmHg, there is no requirement to multiple by 7.5 (e.g. at Lakenheath, their gas machine will provide PaO_2 in mmHg).
- An OI > 25 is associated with a 50% risk of requiring ECMO or mortality
- For OIs between 25-40 despite optimal management, referral should be made to the ECMO team on the basis of failure to respond to standard therapies

12 Monitoring compliance with and the effectiveness of this document

The PaNDR team will periodically monitor that the guideline is being adhered to and the results will be presented to the senior team at a governance meeting.

13 Equality and diversity statement

This document complies with the Cambridge University Hospitals NHS Foundation Trust service equality and diversity statement**.**

14 Disclaimer

It is **your** responsibility to check against the electronic library that this printed out copy is the most recent issue of this document.

Document management

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