East Midlands Neonatal
Operational Delivery Network

NETWORK GUIDELINE

Guideline:	**Persistent Pulmonary Hypertension of the Newborn (PPHN)**
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Risk Managed:	**Management of persistent pulmonary hypertension of the newborn**

This document is a guideline. Its interpretation and application remains the responsibility of the individual clinician, particularly in view of its applicability across the different Trusts in the East Midlands Neonatal Operational Delivery Network. Please also consult any local policy/guideline document where appropriate and if in doubt contact a senior colleague.

Caution is advised when using guidelines after a review date.

REVIEW AND AMENDMENT LOG

Version	Type of Change	Date	Description of Change
1	N/A	Jan 2019	N/A

Appendix 1 – Management of infant suspected with Persistent Pulmonary Hypertension of Newborn (PPHN) (adapted from (1, 2))

Suspicion of Persistent Pulmonary Hypertension of Newborn (PPHN)

Severe hypoxaemia disproportionate to other clinical findings or degree of hypercarbia

↓

Effective resuscitation and adequate oxygenation reduce risk of PPHN

General Management

*Monitoring (pre and postductal saturations, arterial blood pressure, heart rate, temperature)
*Insert central venous line and consider arterial line
*Antibiotics
*Minimal handling
*Maintain normothermia
*Monitor glucose and electrolyte

Investigations

*CXR + AXR (assess lung, exclude pneumothorax, confirm line and tube position)
*Bloods (FBC, UE, Ca, Mg, CRP, Coagulation, Blood culture, Blood gas)
*Echocardiogram (exclude congenital cyanotic heart disease, assess pulmonary pressure, guide inotrope and fluid therapy)

If echo not feasible, no improvement with conventional treatment and unable to exclude congenital cyanotic heart disease, consider Prostin & discussion with cardiology team

Respiratory

*Intubate and ventilate with targeted tidal volume 5-6 ml/kg and preductal saturations >95%

These infants should NOT be managed on nasal CPAP or high flow.

*If < 3 days old, consider additional surfactant at 200mg/kg
*BOLDPEEP to optimise conventional ventilation and manage deterioration (**Appendix 2**)
*CO_2 clearance issue - try faster rate, shorter Ti and lower PEEP
*Oxygenation issue - try longer Ti, higher PEEP
*Is there excessive chest movement? Reduce MAP as high MAP may impair venous return

Cardiovascular

*Systemic blood pressure support (early use of inotropes, cautious 10ml/kg 0.9% saline bolus)
*Correct anaemia, thrombocytopaenia and deranged coagulation
*Correct acidosis with bicarbonate

Neurology

*Commence sedation (e.g. morphine) and muscle relaxation (e.g. atracurium)
*Cerebral function monitoring if neurological concerns
*Cranial ultrasound scan

↓

Assess Oxygenation Index (OI) $= \frac{\text{Mean Airway Pressure (cm } H_2O\text{) X } FiO_2\ (\%)}{\text{PaO2 (kPa) X 7.5}}$

↓

Early discussion with tertiary neonatal unit via **CenTre (0300 300 0038)** to optimise treatment

↓ If **OI >25,**

*Consider iNO. CenTre neonatal transport service able to provide iNO
If iNO non-responsive PPHN, consider echo/cardiology opinion to rule out cyanotic heart defect
*Consider HFOV. **Infant CANNOT be transfered while ventilated on HFOV by CenTre**
*Consider conference discussion with **ECMO team in Glenfield (0300 300 3200)** and CenTre

Appendix 2 – BOLDPEEP table (adapted from (3))

B.O.L.D.P.E.E.P.	Common Findings
Bad RDS/lung disease	Significant lung disease on CXR History of worsening gases and rising oxygen Declining flow and volumes on trend waveform Flat V/P loop Minimal/no chest movement, Reduced/squeaky air entry bilaterally Improvement seen over 30 seconds with Neopuff at higher pressures (improved expansion and air entry)
Obstructed ETT	Possibly, history of secretions, blood in ETT or bad BPD Declining flow and volumes on trend waveform Blunted flows in real time, Flat V/P loop Minimal/no chest movement Reduced/squeaky air entry bilaterally Rising resistance (>200) Minimal improvement with Neopuff® at higher pressures, if the obstruction is partial Look for water in ventilator tubing Look for a response to suction
Long ETT	CXR evidence/previous use of dental rolls Asymmetrical air entry/chest expansion Agitated baby, never completely settled Improvement with easing ETT back
Dislodged ETT	Sudden change, sudden events Leak heard No chest movement with ventilator Gas flow in the stomach Agitated baby Ventilator registers leak-high flows to compensate and low VTe (make sure low VTe alarm is on and set) No improvement with Neopuff®
Pneumothorax	Bad / worsening lung disease (RDS/Meconium) No antenatal steroids No Surfactant or late surfactant Asymmetric chest shape Decreased expansion/possibly asymmetrical Asymmetrical air entry Volume/time waveform doesn't return to baseline V/P loop doesn't complete (subtle) 'Positive' Transillumination
Equipment problem	Water in the tubing? Pneumotach left out of circuit (no volume or flow data!!) Water in pneumotachograph? Kinked ETT due to the weight of pneumotach connection? Check waveforms, check alarm settings
Equipment/**P**atient interaction (sedation/paralysis)	Bad lung disease? Long ETT? Profound Acidosis? Consider use of more sedation or paralysis ONLY when you are clear what the underlying cause e.g. Bad RDS requiring higher pressures and control of pulmonary hypertension

1. Background

Persistent pulmonary hypertension of the newborn (PPHN) is a complex condition with a varied range of causes and severity. PPHN occurs when the neonatal circulation fails to adapt to extrauterine life and is a common endpoint of many different pathophysiological mechanisms.

1.1. Pathogenesis

At birth, the pulmonary vascular resistance and hence the pressure in the pulmonary circulation should fall. PPHN occurs when there is a failure of the normal fall in pulmonary pressures. This leads to right to left shunting at the level of atria and/ or ductus arteriosus causing severe hypoxaemia (Persistent Fetal Circulation).

PPHN can be primary or secondary. Idiopathic or primary PPHN is very rare. More commonly, PPHN is secondary to or associated with a variety of conditions including:-

- Hypoxia-ischaemia
- Severe lung diseases such as meconium aspiration syndrome or surfactant deficiency
- Congenital lung problems such as congenital diaphragmatic hernia, pulmonary hypoplasia or congenital cystic adenomatoid malformation
- Sepsis such as Group B streptococcus pneumonia
- Polycythaemia

1.2. Clinical Features

PPHN is usually a condition of term infants presenting in the first 12 hours of life. Primary PPHN presents subtly mimicking cyanotic congenital heart disease. In secondary PPHN, clinical features are those of the underlying clinical condition e.g. hypoxia-ischaemia, sepsis. As the underlying disease process and PPHN progresses, additional features like worsening hypoxia, acidosis, and hypotension may also be present. Respiratory distress is often mild (compared to the degree of hypoxia). Rare though precordial palpation may reveal parasternal heave. Careful auscultation may reveal soft systolic murmur secondary to Tricuspid regurgitation. It is characterised by:

- Severe hypoxaemia (SpO_2 <95% or PaO_2 <6kPa in FiO_2 of 1) which is disproportionate to findings expected from chest X-ray (CXR) and degree of hypercarbia.
- Evidence of right of left shunting at the level of atria or ductus arteriosus

Be aware that presentation of congenital cyanotic heart disease such as transposition of great arteries may mimic PPHN.

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

2. Assessment

2.1. Oxygenation Index (OI)

When PPHN is suspected, the oxygenation index (OI) needs to be calculated. The OI is a measure of the severity of hypoxaemic respiratory failure and should be monitored regularly in infants with respiratory failure. It has been used in several interventional studies to determine study entry for example for the UK extracorporeal membrane oxygenation (ECMO) trial (4). The maximum value of OI also correlates with outcome in terms of mortality in preterm infants (5).

$$\text{Oxygenation Index (OI)} = \frac{Mean\ Airway\ Pressure\ (cm\ H20) \times FiO2\ (\%)}{PaO2\ (kPa) \times 7.5}$$

(Note 1 kPa = 7.5 mmHg)

There is no reference range for OI but for most ventilated infants with mild or moderate respiratory distress syndrome, OI will be <10. Early discussion for advice may be held with a tertiary neonatal consultant if needed, facilitated by CenTre neonatal transport service (0300 300 0038). In the meantime, continue the assessment using clinical review, review of bedside observations, blood gas, CXR and echocardiography to assess whether additional therapies are required.

2.2. Blood gas

If there is hypoxaemia with low or normal CO_2, this implies that alveolar ventilation is not a significant problem and by inference intra or extrapulmonary shunting due to PPHN is more likely to be the problem. A high CO_2 along with hypoxaemia implies alveolar hypoventilation and primary parenchymal lung pathology. However, in most cases, the underlying disease causing PPHN will produce a mixed picture.

2.3. Chest X-ray

Chest X-ray (CXR) may produce a variety of findings depending on the underlying disease causing PPHN. Clear or minimal changes in the lung field may be seen in idiopathic or primary PPHN. Dense lung fields (whatever the cause) imply significant parenchymal lung disease. A careful review of CXR is needed to rule out pneumothorax. If abnormal shaped heart (such as boot shaped or 'egg on the side') or abnormal pulmonary vasculature such as oligaemic lung fields is seen on CXR, congenital cyanotic heart disease should be considered as its presentation may mimic PPHN.

2.4. Echocardiogram

If available, an early echocardiogram should be performed to:-

- exclude congenital cyanotic heart disease.
- assess pulmonary pressure. Tricuspid regurgitation (TR), right to left shunting at the level of intra-atrial or ductus arteriosus, dilatation of right heart and pulmonary regurgitation are features of extra-pulmonary shunting or raised pulmonary pressure. The absence of tricuspid regurgitation does not exclude PPHN (6).
- evaluate ventricular function.
- guide selection of inotrope/vasopressor/vasodilator and fluid therapy

If echocardiogram is not readily available, pre and postductal saturation measurements are also useful as a guide to whether there is shunting at ductal level. If in doubt, discuss with the tertiary neonatal consultant and consider specialist cardiology advice. Occasionally, the differentiation between PPHN and duct dependent cyanotic congenital heart disease is difficult and a diagnostic assessment in the cardiac centre may be needed to help with the further management including in decision making regarding the best unit to care for the baby.
Electrocardiogram (ECG) can also be useful in this situation. ECG is often normal but can show features of right ventricular hypertrophy such as tall R waves and upright T waves in V_1 and V_2 and right axis deviation.

3. Management of persistent pulmonary hypertension of the newborn

Risk of PPHN is reduced by effective resuscitation and adequate oxygenation. PPHN should be suspected if the infant has severe hypoxaemia which is disproportionate to other clinical findings or degree of hypercarbia. Once PPHN is suspected, the infant should be admitted to the neonatal unit for ongoing management and consultant neonatologist should be informed and involved in the care of the infant early on.

It is important in this situation to optimise initial intensive care management first as if this is done effectively no other treatments may be necessary. Flowchart of the management of PPHN can be found in **Appendix 1**.

3.1. General Management

- Monitor pre and postductal saturations, invasive blood pressure, heart rate and temperature.
- Insert central venous line (umbilical venous catheter (UVC) or a percutaneous long line) and strongly consider arterial line (umbilical arterial catheter (UAC) or peripheral arterial line). Limb perfusion must be monitored with arterial line use.
- Administer antibiotics to cover for sepsis
- Minimal handling if possible
- Monitor glucose and electrolyte. Correct as needed
- Maintain normothermia

3.2. Respiratory

- Infants with hypoxaemia can enter a spiral of PPHN very quickly.

Low threshold to intubate a term baby with an oxygen requirement. These infants should NOT be managed on non-invasive respiratory support such as nasal CPAP or high-flow.

- Conventional ventilation should be used initially with a targeted tidal volume of 5–6 ml/kg and preductal saturations of above 95%. Oxygen is a pulmonary vasodilator and is an important part of the management. The mnemonic **BOLDPEEP** may be helpful in gathering information and optimise conventional ventilation and managing deterioration of infant during mechanical ventilation (see **Appendix 2**).
- Is the main problem CO_2 clearance or oxygenation?
    - If CO_2 clearance is the problem, consider the following changes on the ventilator
        - faster rate
        - shorter inspiratory time (Ti)
        - lower PEEP
    - If oxygenation is the problem, consider the following changes on the ventilator
        - longer inspiratory time (Ti)
        - higher PEEP
- Consider whether the level of mean airway pressure is impairing venous return to the heart, especially when there is excessive chest movement. Does ventilation need turning down, rather than up?
- Additional dose of surfactant at 200mg/kg should be considered if **<3 days old** (see **section 4.1**).
- High frequency oscillation ventilation (HFOV) strategy may improve oxygenation further if poor response to optimal conventional ventilation (see **section 4.2**). If

required, advice can be sought from tertiary neonatal consultant facilitated by CenTre neonatal transport service (0300 300 0038).

However, please note that infant CANNOT be transferred on HFOV by the CenTre neonatal transport service. Infant needs to be on conventional ventilation for transfer.

3.3. Cardiovascular

- Maintain adequate perfusion as supporting the systemic circulation will reduce the right to left shunting seen in PPHN.
- Ensure blood pressure is adequate aiming for a normal mean arterial blood pressure and normal perfusion.
    - Early use of inotropes may be beneficial. If required, advice on choice of inotropes can be sought from tertiary neonatal consultant facilitated by CenTre neonatal transport service (0300 300 0038).
    - Consider using a bolus of 10ml/kg 0.9% saline if there is clinical or echocardiographic evidence of hypovolaemia.. However, the overzealous use of fluids can prove to be counterproductive.
    - Knowledge of the estimated pulmonary arterial pressure from an echocardiogram may be helpful in guiding management
- Correct any anaemia, thrombocytopaenia and deranged coagulation.
    - Aim for haemoglobin (Hb) > 140g/L, platelet count >30 $x10^6$ /mL and normal coagulation profile appropriate for infant's gestation.
- In the context of PPHN, severe metabolic acidosis may be seen. Normal pH values should be aimed for. Lactic acidosis typically improves as hypoxia and hypoperfusion improve.

3.4. Neurology

- Sedation and muscle relaxation using morphine and atracurium infusions should be considered
    - There may be hypoxic injury to the brain in these infants. Hence, cerebral function monitoring (CFM) should be considered if there are any neurological concerns.
- A cranial ultrasound scan should be performed especially if ECMO is being considered.

3.5. Pulmonary vasodilator

3.5.1. Inhaled Nitric Oxide (iNO)

Inhaled nitric oxide (iNO) is an effective pulmonary vasodilator in term infants (see **section 4.3**). For local neonatal units (LNU) and special care units (SCU) who do not have access to iNO locally, iNO can be offered by CenTre neonatal transport service (0300 300 0038) during the transfer to a tertiary neonatal unit. After discussion with tertiary or transport neonatal consultant, iNO should be considered in infants with respiratory failure with OI above 15 despite optimal management and evidence of pulmonary shunting. In circumstances of poor or unclear prognosis (e.g. severe pulmonary hypoplasia), iNO should be only considered if adequate CO_2 clearance can be achieved with ventilatory management. If in doubt, discuss with the tertiary neonatal consultant.

<u>Commencing iNO</u>

After discussion with tertiary or transport neonatal consultant, iNO should be commenced at a dose of 10ppm and increased at 30 minutes intervals of 5ppm increments to 20ppm depending upon response. Dose above 20ppm should only be used on tertiary neonatal consultant advice.

Monitoring while on iNO

In addition to usual intensive care monitoring, methaemoglobin (MetHb) levels should be monitored during iNO therapy.

- MetHb levels should be recorded at baseline, 1 hour and 6 hours after starting iNO. Thereafter, MetHb should be measured 6-12 hourly.
- The normal range of MetHb is 1-3%
    - If MetHb >3%, discuss with tertiary neonatal consultant. Increase monitoring frequency or reducing dose may be needed (7). Managing high Met Hb will need tertiary neonatal consultant input as there has to be a balance of sudden stopping versus reduction depending on levels of MetHb (7)

Weaning iNO

iNO switches off the body natural NO production. Hence, it is crucial to wean NO slowly to avoid rebound pulmonary hypertension. iNO should be weaned over 8-12 hours steps of 3-5ppm down to a minimum of 1-2ppm before switching off iNO.

Be vigilant of rapid fall in PaO_2 during weaning. If this occurs, a slower weaning regime is needed. Hence, weaning iNO can be very prolonged with the infant being sensitive to small decrease or brief disconnections from iNO.

3.5.2. Other Pulmonary Vasodilators

Until the advent of iNO, three drugs Tolazoline, prostacyclin (Epoprostenol) and magnesium sulphate were widely used. Increasingly, milrinone, vasopressin and sildenafil are used. There is anecdotal evidence from case series that these may be helpful but there is no evidence from controlled trials. The problem with all IV administered pulmonary vasodilators is that they inevitably will also have an effect on the systemic circulation causing systemic hypotension. In addition, even if they do cause pulmonary vasodilatation they will dilate segments of the lung that are perfused but not necessarily ventilated, potentially increasing any ventilation-perfusion mismatch.

The use of these intravenous pulmonary vasodilators is therefore not recommended unless iNO is unavailable and should always be discussed with a tertiary neonatal consultant and ECMO centre. If they are used, the blood pressure should be monitored carefully and inotropic support prepared.

3.6. Extracorporeal membrane oxygenation (ECMO)

ECMO should be considered in infants with severe and resistant respiratory failure secondary to persistent pulmonary hypertension of the newborn (PPHN) not responding to conventional management, following discussion with tertiary neonatal consultant and ECMO team. The level of OI at which these interventions should be used is controversial.

Consideration should be given to referral for ECMO if the OI is rising or above 25 (see **section 4.4**). This must be discussed with tertiary neonatal consultant beforehand via CenTre neonatal transport service (0300 300 0038). In term, at an OI that is persistently (2 blood gasses 30 minutes apart) of 25 or greater, and on optimal management as discussed above, early conference call with ECMO team should be considered.

To refer for ECMO, initially contact the ECMO co-ordinator at Glenfield Hospital, Leicester via CenTre ECMO line (0300 300 3200).

Criteria for considering ECMO include (if in doubt, discuss with tertiary neonatal consultant and ECMO centre):

- Term or near-term infants (≥ 34 weeks of gestation) or birthweight ≥ 2kg with PPHN
- Respiratory failure or OI above 25 despite optimal conventional ventilation including iNO, inotrope and/or HFOV
- Not maintaining blood pressure with 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)

The ECMO centre will need the following:

- Recent cranial ultrasound scan
- Full blood count and coagulation screen measured and corrected as appropriate prior to transfer
- Maternal blood sample
- Referral or Badger discharge letter
- Copies of hospital notes, drug chart and radiological images
- Sometimes, mobile ECMO may be considered prior to transfer. If so, check requirement from ECMO centre (e.g. diathermy unit or amount of packed red cell required).

The other possible interventions should be targeted to try to prevent a high OI and ECMO referral.

4. The evidence behind proposed management

4.1. Additional doses of surfactant

In preterm respiratory distress syndrome (RDS), giving multiple doses of surfactant reduces the incidence of pneumothorax (8-11). However, there is no evidence of benefit to using more than three doses (12). Surfactant therapy has also been found to be beneficial in term or late preterm infant with meconium aspiration syndrome, reducing the severity of the respiratory illness and the need for extracorporeal membrane oxygenation (ECMO) (13). Usage of surfactant therapy has not been investigated as thoroughly in other conditions and it is possible that further doses in pulmonary haemorrhage and pneumonia may be useful.

4.2. High frequency oscillation ventilation (HFOV)

The use of HFOV as rescue treatment has been investigated in both term and preterm infants. Unfortunately, there is insufficient data from randomised controlled trials to support the use of rescue HFOV in the term (14, 15) and preterm infants (16, 17) with severe respiratory failure. This is because studies in both these groups of infants have been small and insufficiently powered to show small but important differences in outcome. Furthermore, studies are complicated by the diverse disease pathology of respiratory failure and concurrent use of other interventions.

However, it seems reasonable to use this intervention at the same OI as iNO, depending on the type of hypoxaemia. There is some evidence that adding iNO to HFOV or vice versa may be beneficial (18). It may also be appropriate to use HFOV at lower levels of OI depending on the clinical circumstances and this should always be discussed with a tertiary neonatal consultant. HFOV in meconium aspiration syndrome may produce air trapping and over-distension. This may lead to deterioration or air leaks. So HFOV should only be used with caution.

4.3. Inhaled nitric oxide (iNO)

There are several randomised controlled trials of iNO in term infants (19). Most of these have enrolled babies with an OI of greater than 25 and they consistently show a reduction in the combined outcome of death or need for ECMO. Hence, the use of iNO in term infants with respiratory failure who have not responded to other methods of support improved survival and reduced the need for ECMO. However, the benefit of iNO in term infants with respiratory failure due to congenital diaphragmatic hernia is unclear at present based on data from a recent meta-analysis (19).

In preterm infants, a recent meta-analysis concluded that iNO does not appear to be effective as rescue therapy for preterm infant with respiratory failure (20). However, there are case reports of iNO being used in selected preterm infants, for example with pulmonary hypoplasia (21). Hence, further study is required to investigate the use of iNO in preterm infants, including its effect on long-term outcomes or even short-term morbidity. There may be individual preterm patients that may benefit from the use of iNO. Hence, the use of iNO in preterm babies below 36 weeks of gestation should only be done on advice by the consultant neonatologist.

4.4. Extracorporeal membrane oxygenation (ECMO)

The main study which has investigated the use of ECMO in a systematic way is the UK ECMO study (4). This and three other studies from the USA have been systematically reviewed and showed a decreased mortality with ECMO (RR 0.44; 95% CI 0.31 to 0.61), especially for babies without congenital diaphragmatic hernia (RR 0.33, 95% CI 0.21 to 0.53). In addition, ECMO decreased death or disability at one and four years (22).

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8. Audit Points

Use of nitric oxide and HFOV in term and preterm infants
Number of infants and timing of referral for ECMO
Use of additional doses of surfactant
Number of babies transported for tertiary care

9. Summary Box and Levels of Evidence

Summary	**Level of evidence**
Use of iNO in term infants with respiratory failure prevents referral for ECMO (19)	**A**
The benefit of iNO in term infants with respiratory failure due to congenital diaphragmatic hernia (19) and preterm infants is unclear at present (20)	**A**
Rescue HFOV in term with respiratory failure may improve ventilation (14)	**C**

Rescue HFOV in preterm infants with respiratory failure may improve ventilation (16)	**C**
If OI is > 40 in term infants ECMO improves survival (22)	**A**
Multiple doses of surfactant may decrease the risk of air leak (8, 9, 11, 13)	**A**
HFOV and NO together may have additive effects on improving oxygenation (18)	**B**