### Nottingham Neonatal Service Clinical Guidelines

**Guideline B6**

**Nottingham Children’s Hospital**

**PPHN AND NITRIC OXIDE GUIDELINE**

<table>
<thead>
<tr>
<th>Title of Guideline (must include the word “Guideline” (not protocol, policy, procedure etc))</th>
<th>Hypoxaemic Respiratory Failure, Persistent Pulmonary Hypertension and use of inhaled Nitric Oxide guideline (B6)</th>
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</thead>
<tbody>
<tr>
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<tr>
<td>Directorate &amp; Speciality</td>
<td>Neonatal Intensive Care Unit, Family Health</td>
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<td>Date of submission</td>
<td>December 2018</td>
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<td>Explicit definition of a patient group to which it applies (e.g. inclusion and exclusion criteria, diagnosis)</td>
<td>Infants admitted to the Neonatal Unit with hypoxaemic respiratory failure</td>
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<td>Version</td>
<td>2</td>
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<td>If this version supersedes another clinical guideline please be explicit about which guideline it replaces including version number.</td>
<td>Hypoxaemic Respiratory Failure / Failure of Conventional Ventilation in Term and Preterm Infants version 1</td>
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<tr>
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<td>2a, 2b, 3a, 3b, 4, 5, 6</td>
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<tr>
<td>1</td>
<td>NICE Guidance, Royal College Guideline, SIGN (please state which source).</td>
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<tr>
<td>2a</td>
<td>meta analysis of randomised controlled trials</td>
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<td>2b</td>
<td>at least one randomised controlled trial</td>
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<td>3a</td>
<td>at least one well-designed controlled study without randomisation</td>
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<td>3b</td>
<td>at least one other type of well-designed quasiexperimental study</td>
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<td>4</td>
<td>well –designed non-experimental descriptive studies (ie comparative / correlation and case studies)</td>
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<td>5</td>
<td>expert committee reports or opinions and / or clinical experiences of respected authorities</td>
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<td>6</td>
<td>recommended best practise based on the clinical experience of the guideline developer</td>
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<td>Ratified by:</td>
<td>Neonatal Guideline Task and Finish Group</td>
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<td>Date:</td>
<td>January 2019</td>
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<td>Target audience</td>
<td>The staff of the Nottingham Neonatal Service</td>
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<tr>
<td>Review Date: (to be applied by the Integrated Governance Team)</td>
<td>January 2024</td>
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A review date of 5 years will be applied by the Trust. Directorates can choose to apply a shorter review date, however this must be managed through Directorate Governance processes.
This guideline should be read in conjunction with guidelines covering early care (A8), mechanical ventilation (B1), congenital diaphragmatic hernia (B4), surfactant therapy (B5), high frequency oscillation ventilation (B9), inhaled nitric oxide (B10), meconium aspiration syndrome (B16), red cell transfusion (E1), cardiovascular support (E2), Central Venous Line (G3) and Umbilical Venous and Arterial Catheter (G5).

KEY POINTS:

1. Persistent pulmonary hypertension of the newborn (PPHN) should be suspected if infant has severe hypoxaemia which is disproportionate to findings expected from chest X-ray and degree of hypercarbia. The main differential diagnosis in this context would be congenital cyanotic heart disease.

2. A step-wise approach to address hypoxaemia and PPHN is presented.

3. An additional dose of surfactant may decrease the risk of air leak.

4. ECMO should be considered in infants above 34 weeks of gestation or above 2kg if oxygenation index is >30 or rapidly rising despite interventions. Consider early discussion with ECMO team.

5. Monitor and document Methaemoglobin levels (on a gas machine).

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<th>Description</th>
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<tr>
<td>ABG</td>
<td>Arterial Blood Gas</td>
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<tr>
<td>BOLDPEEP</td>
<td>Pnemonic: B: Bad RDS/ lung dis; O: Obstructed ETT; L: Long ETT; D: Dislodged ETT; P: Pneumothorax; E: Equipment problems; EP: Equipment Patient interaction</td>
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<tr>
<td>BP</td>
<td>Blood Pressure</td>
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<td>CDH</td>
<td>Congenital Diaphragmatic Hernia</td>
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<td>CFM</td>
<td>Cerebral Function Monitoring</td>
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<td>CO₂</td>
<td>Carbon Di-oxide</td>
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<tr>
<td>CPAM</td>
<td>Congenital Pulmonary Airway Malformation</td>
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<tr>
<td>CXR</td>
<td>Chest X-ray</td>
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<tr>
<td>ECG</td>
<td>Electrocardiogram</td>
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<tr>
<td>ECMO</td>
<td>Extracorporeal membrane oxygenation</td>
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<tr>
<td>ETT</td>
<td>Endotracheal Tube</td>
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<tr>
<td>FFP</td>
<td>Fresh Frozen Plasma</td>
</tr>
<tr>
<td>FiO₂</td>
<td>Fraction of inhaled O₂</td>
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<tr>
<td>Hb</td>
<td>Haemoglobin</td>
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<tr>
<td>HFOV</td>
<td>High Frequency Oscillatory Ventilation</td>
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<tr>
<td>iNO</td>
<td>inhaled Nitric Oxide</td>
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<tr>
<td>kPa</td>
<td>kilo Pascals</td>
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<tr>
<td>MAP</td>
<td>Mean airway pressure</td>
</tr>
<tr>
<td>MetHb</td>
<td>Methaemoglobin</td>
</tr>
<tr>
<td>iNO</td>
<td>Nitric oxide</td>
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<tr>
<td>O₂</td>
<td>Oxygen</td>
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<tr>
<td>OI</td>
<td>Oxygenation Index</td>
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<tr>
<td>PaO₂</td>
<td>Arterial partial-pressure of oxygen</td>
</tr>
<tr>
<td>PaCO₂</td>
<td>Arterial partial-pressure of carbon di-oxide</td>
</tr>
<tr>
<td>PEEP</td>
<td>Peak End-Expiratory Pressure</td>
</tr>
<tr>
<td>PIP</td>
<td>Peak Inspiratory Pressure</td>
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<tr>
<td>PPHN</td>
<td>Persistent Pulmonary Hypertension of Newborn</td>
</tr>
<tr>
<td>PPROM</td>
<td>Preterm Prolonged Rupture of Membranes</td>
</tr>
<tr>
<td>RDS</td>
<td>Respiratory Distress Syndrome</td>
</tr>
<tr>
<td>Ti</td>
<td>Time of inspiration</td>
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<tr>
<td>UVC</td>
<td>Umbilical Venous Catheter</td>
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</table>
FLOWCHART 1: PPHN Management in Term/ Near-term Babies: 7 Steps to use Nitric Oxide treatment

**Step 1:**
- **OXYGENATION:**
  - Optimise mean airway pressure (Guideline B1), CXR
  - Optimal monitoring and access: Pre and post ductal Sats, Arterial and central lines
  - Consider Surfactant therapy (Guideline B5), HFOV (Guideline B9)
  - Monitor Oxygenation Index (OI)
  - Optimise analgesia, consider muscle relaxation (See Step 6)

**Step 2:**
- **VENTILATION:**
  - Optimise Minute Ventilation, aim for normal PaCO$_2$ (Guideline B1)
  - Consider HFOV (Guideline B9)
  - Consider BOLDPEEP (Appendix 2)
  - Acceptable PaCO$_2$ crucial if considering Nitric Oxide therapy

**Step 3:**
- **HAEMODYNAMIC MANAGEMENT:**
  - Assessment of vital signs including arterial BP; blood gases including Lactate; Haemoglobin; Echocardiographic assessment; exclude cong heart disease
  - Correct anaemia, consider inotropes (Guideline E2) guided by echo; aim for normal BP

**Step 4:**
- **pH:**
  - Aim for normal pH (7.35–7.45) with normal PaCO$_2$
  - With respiratory and haemodynamic management, pH should improve
  - Discuss with consultant about Sodium Bicarbonate if pH still acidotic

**Step 5:**
- **SEPSIS:**
  - Treat sepsis with appropriate antibiotics (Sepsis guideline C6)

**Step 6:**
- **NEUROLOGY:**
  - Adequate analgesia with Morphine (Neonatal pain guideline G9)
  - Minimise handling
  - Consider paralysis with Atracurium to gain full control if deteriorating

**Step 7:**
- **START NITRIC OXIDE:**
  - If despite above interventions, poor/worsening OI (see text) but good PaCO$_2$ response: Discuss with consultant about starting Nitric Oxide
1. Introduction and Background

The mainstay for management of respiratory disease requiring ventilatory support in the newborn infant is volume targeted, conventional time cycled pressure limited ventilation with the use of surfactant in most situations (see Neonatal Guidelines B1 Mechanical Ventilation and B5 Surfactant Therapy). However, there are circumstances when conventional treatment is failing and additional treatments may become necessary.

1.1 Persistent Pulmonary Hypertension of the Newborn (PPHN)

PPHN is one of the common differential diagnoses considered in an infant with hypoxaemic respiratory failure. 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. At birth, the pulmonary vascular resistance and hence the pressure in the pulmonary circulation should fall in relation to the systemic circulation. PPHN occurs when there is a failure of the normal fall in pulmonary pressures. This leads to right to left shunting at the atrial (patent foramen ovale)/ ductus arteriosus level with blood flow bypassing the lungs as well as intrapulmonary shunting. This inadequate pulmonary blood flow leads to refractory systemic arterial hypoxaemia and acidosis.

The prevalence of PPHN is around 1.9 per 1000 live births and is associated with a considerable mortality and morbidity including chronic lung disease and neurodevelopmental sequelae(1). PPHN is a common endpoint of several different pathophysiological mechanisms(2). It is characterised by a structurally normal heart and(2):

- Severe hypoxaemia e.g. PaO$_2$ of <6kPa in an FiO$_2$ of 1.0 (with IPPV as needed)
- Hypoxaemia disproportionate to the radiological, clinical and acid-base abnormalities
- Evidence of right-left shunting (on echocardiogram or a persistent pre and post-ductal O$_2$ saturation difference of >5%)

1.1.1 Aetiology

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 condition including:

- Perinatal hypoxia-ischaemia
- Severe lung diseases such as meconium aspiration syndrome or surfactant deficiency
- Congenital lung problems such as congenital diaphragmatic hernia (CDH), pulmonary hypoplasia or congenital pulmonary airway malformations (CPAM)
- Sepsis such as Group B streptococcus sepsis/ pneumonia
- Polycythaemia

1.1.2 Clinical Features

PPHN is usually a condition of term infants presenting in the first 12 hours (rarely after 24 hours) of life. (Pulmonary hypertension is not uncommon in babies with established chronic lung disease which can worsen with exacerbations, for example, with late onset viral or bacterial sepsis). Primary PPHN presents subtly mimicking cyanotic congenital heart disease. Secondary PPHN, clinical features would be those of the underlying condition e.g. Hypoxia-ischaemia, RDS, 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). Careful auscultation may reveal a murmur may be because of Tricuspid regurgitation(2) but congenital heart disease is an important differential diagnosis to exclude.

Be aware that presentation of congenital cyanotic heart disease such as transposition of great arteries may be very similar to PPHN.
2. Patient Group / Indications
Ventilated term and preterm infants requiring high (typically >50%) or rising FiO\textsubscript{2} with disproportionately low arterial PaO\textsubscript{2} (typically < 6.5 kPa). The common causes of severe hypoxaemia ± PPHN are:
- Respiratory distress syndrome (Guidelines A8, B1, B5, B9)
- Hypoxia-ischaemia (Network HIE guideline)
- Meconium aspiration syndrome (Guideline B16)
- Congenital diaphragmatic hernia (Guideline B4)
- Sepsis/ Congenital pneumonia (Risk factors for sepsis guideline)
- CPAM
- Pulmonary hypoplasia
- Polycythaemia
- Idiopathic (rare)
Please refer to the appropriate guidelines. For conditions like CDH, CPAM, and prolonged preterm rupture of membranes (PPROM) from early pregnancy, there may be multi-disciplinary plans made by fetal medicine, paediatric surgery and neonatal team. Please review the alert folder and review these plans. If in doubt, discuss with the duty neonatal consultant.

The following section focusses on PPHN in term and late preterm babies born at gestation of 34wks and above. The principles of management for more preterm babies are similar though an approach with permissive hypercapnia and tolerance of lower pH is used. iNO is rarely used and only on consultant advice.

3. Initial Treatment and Assessment (see Flowchart 1)

It is important in this situation to optimise initial intensive care management first as if this is done effectively no further treatments may be necessary (see Neonatal Guidelines A8, B1 and B5). Therefore, assess the following:

3.1 General Management
- These patients must have continuous monitoring including vital signs, pre and post-ductal saturations
- Aim for pre-ductal saturations >93% and a PaO\textsubscript{2} of ≥10kPa. Once stabilised, the gap between pre and post-ductal saturations should be <5%
- Arterial access should be obtained if possible for invasive blood pressure (BP) and arterial blood gases (ABG) (Guidelines G3 and G5). Limb perfusion must be monitored with arterial line use.
- Insert central venous line (umbilical venous catheter (UVC) or a per-cutaneous long line)
- Minimal handling and avoid stimulation where possible.
- Maintain glucose and electrolytes within normal limits. (Hypoglycaemia- Guideline D1 and fluid and electrolytes Guideline D2)
- Maintain normothermia unless receiving active cooling therapy. Rarely, babies with refractory hypoxaemia may need rewarming. Early rewarming is ALWAYS a consultant decision.

3.2 Seven Steps to Nitric Oxide:
A stepwise approach ensures that conventional care is optimised before need/ consideration of Nitric Oxide (NO).

3.2.1: Step 1 Oxygenation
Refer to mechanical ventilation guideline B1.
Monitor: Pre and post ductal saturations, arterial PaO\textsubscript{2}, vital signs, Oxygenation Index (OI)
Review: Chest x-ray, nursing observation charts, ventilator graphics, cold light to exclude Pneumothorax
Optimise MAP with consideration to PIP, PEEP, Ti, and slope. Consider HFOV mode of ventilation.
- Oxygenation Index (OI)
The oxygenation index (OI) is a measure of the severity of hypoxaemic respiratory failure and should be monitored regularly in infants with respiratory failure.

\[
\text{Oxygenation Index (OI)} = \frac{\text{Mean Airway Pressure (cm H2O)} \times \text{FiO2} (\%)}{\text{PaO2} (\text{kPa}) \times 7.5}
\]

(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.

If the OI is less than 15, then continue current management. No additional interventions are required. If the OI is greater than 15 or rising rapidly, then continue the assessment using clinical review, review of bedside observations, blood gas, chest X-ray (CXR) and echocardiography to assess whether additional therapies are required.

This assessment is to determine whether the primary problem is parenchymal lung disease or extra-pulmonary shunting due to pulmonary hypertension. Parenchymal lung disease may benefit from additional surfactant replacement if the lung disease is surfactant responsive (RDS, meconium aspiration) and/or HFOV. Extra-pulmonary shunting unresponsive to ventilator management is probably best treated with an early inhaled nitric oxide (iNO)(3). However, parenchymal lung disease and extra-pulmonary shunting can often coexist. Hence it is important to optimise the respiratory, haemodynamic, metabolic (acidosis) and neurological (adequate sedation and muscle relaxation) management before escalating to iNO.

- Blood gas
A high CO₂ along with hypoxaemia implies alveolar hypoventilation and primary parenchymal lung pathology. If the CO₂ is low or normal, this implies that alveolar ventilation is not a significant problem and by inference intra or extrapulmonary shunting is more likely to be the problem.

- Chest X-ray (CXR)
Review the previous x-ray(s) and consider repeating the x-ray to assess lung inflation, look for parenchymal changes, air leaks and heart size/shape. Dense lung fields (irrespective of cause) imply significant parenchymal lung disease. Clear lung fields imply extra-pulmonary shunting is more likely. Overdistension of lungs can impair venous return and an increase in pulmonary vascular resistance. Reducing the MAP in such situations can improve oxygenation(4). If an abnormal shaped heart (such as boot shaped or ‘egg on the side’) or abnormal pulmonary vasculature such as oligaemic lung fields is seen on chest X-ray, congenital cyanotic heart disease should be considered as its presentation may mimic PPHN.

### 3.2.2: Step 2 Ventilation

- The mnemonic BOLDPEEP (Appendix 2) may be helpful in gathering information, optimising conventional ventilation and managing deterioration of the infant during mechanical ventilation (see section 2.5 page 11 of Neonatal Guideline B1).
  - Optimise Minute Ventilation
  - Assess for HFO ventilation strategy (see Neonatal Guideline B9)
3.1.3 Step 3: Haemodynamic management

- Monitor: vital signs, invasive BP, urine output, Lactate
- Maintain adequate perfusion as supporting the systemic circulation may reduce the right to left shunting seen in PPHN (refer to section 1.1).
- Ensure blood pressure is adequate aiming for a normal mean arterial blood pressure and normal perfusion guided by vital signs, skin perfusion, urine output and lactate.
  - Early use of inotropes may be beneficial (see Neonatal Guideline E2)
  - Fluid boluses should be avoided. Consider giving fluid bolus only when there is evidence of hypovolaemia (clinically or on echocardiogram). If necessary, use colloids like fresh frozen plasma (FFP)/ Cryoprecipitate as guided by coagulation results (guideline E8) in preference to 0.9% sodium chloride (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.
  - Aim for haemoglobin (Hb) > 140g/L (see Neonatal Guideline E1 Red Cell Transfusion)

Echocardiogram
An echocardiogram is generally done to(2,5):
- Exclude congenital cyanotic heart disease.
- Assess pulmonary pressures (refer to unit echo teaching manual).
- Evaluate ventricular function and guide selection of inotrope/vasopressor/vasodilator and fluid therapy

Please discuss all out-of-hours echocardiograms with the Consultant Neonatologist on call before requesting an echo to ensure the request is clear, reaches the right resource (Echo arrangements are different at City and QMC campus, and may not be readily available out-of-hours) and will inform the next management stages.

Where an echocardiogram is not readily available, pre and postductal saturation measurements are also useful as a guide to whether there is shunting at ductal level. An electrocardiogram (ECG) can sometimes 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 V₁ and RV₃ and right axis deviation. Note that upright T waves in V₁ and RV₃ may be normal in the first few days of life.

Summary of assessment
Investigations and suggested therapeutic options*

<table>
<thead>
<tr>
<th>CO₂</th>
<th>CXR</th>
<th>Echo</th>
<th>Initial additive treatment</th>
</tr>
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<tbody>
<tr>
<td>Low / normal</td>
<td>Clear</td>
<td>Right to left shunting</td>
<td>Nitric Oxide</td>
</tr>
<tr>
<td>High</td>
<td>Dense</td>
<td>Left to right flow</td>
<td>Additional Surfactant and/or HFOV</td>
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* Often both strategies are needed and should be used sequentially

3.1.4 Step 4: pH
Severe metabolic acidosis may be seen in PPHN. Normal pH values (7.35-7.45) should be targeted.
Acidosis can worsen pulmonary hypertension, therefore, priority should be given to treating hypoxaemia and improving perfusion, which will lead to an improvement in lactic acidosis. A slow infusion of 4.2% Sodium Bicarbonate (0.5-1mmol/kg/hr) may be used in select cases to improve pH. Discuss with consultant.
3.1.5 Step 5: Sepsis

- Administer antibiotics to cover for sepsis (Risk factors for sepsis guideline). Addition of Aciclovir should be considered in presence of abnormal transaminases/ coagulopathy or atypical presentation. If in doubt, discuss with the consultant.

3.1.6 Step 6: Neurology

- Adequate analgesia and sedation helps by reducing the pulmonary vascular resistance. Muscle relaxation is not essential in mild cases but may be considered if hypoxaemia not responding.
  - If muscle relaxation being used, consider using cerebral function monitoring (CFM) if there are any neurological concerns. Document the neurological assessment prior to starting muscle relaxation.
- A cranial ultrasound scan should be performed especially if ECMO referral is being considered.

3.1.7 Step 7: Inhaled Nitric oxide

See below

3.2 Escalation of Management

3.2.1 Inhaled Nitric Oxide (iNO)

Inhaled nitric oxide (iNO) is an effective pulmonary vasodilator in term infants(3). After discussion with the consultant neonatologist, iNO should be considered in infants with respiratory failure with OI above 15 despite optimal management (section 3.2) and evidence of PPHN. In circumstances of poor or unclear prognosis (e.g. severe pulmonary hypoplasia), iNO should be only considered if adequate CO₂ clearance can be achieved with ventilatory management.

Training on set-up and use of Nitric oxide is periodically arranged. Please make sure you attend the teaching session.

Commencing iNO

Discuss with the duty consultant if you are considering iNO therapy. iNO is usually commenced at a dose of 10ppm and increased at 30 minute intervals of 5ppm increments to 20ppm depending upon response. Dose above 20ppm should only be used on consultant neonatologist advice.

Monitoring while on iNO

In addition to usual intensive care monitoring, following monitoring should be considered during iNO therapy:

- Methaemoglobin (MetHb)
  - MetHb levels are 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 consultant neonatologist. If persistent or worsening, a reduction in iNO dose may be required.
    - Values of MetHb >10% may need discontinuation of iNO and active treatment with methylene blue 1-2mg/kg IV(6,7). Discuss with the consultant neonatologist and on-call pharmacist.
Weaning iNO

iNO switches off the body’s natural NO production. Hence, it is crucial to wean NO slowly to avoid rebound pulmonary hypertension. iNO should be weaned over 8-12 hours in steps of 3-5ppm down to a minimum of 1-2ppm before switching off. Typically, NO of 1-2ppm if kept for 12-16 hours before stopping.

Be vigilant of rapid fall in PaO₂ during weaning. If this occurs, a slower weaning regime may be needed. Hence, weaning iNO can be very prolonged with the infant being sensitive to small decrease or brief disconnections from iNO.

3.2.2 Extracorporeal membrane oxygenation (ECMO)

Consideration should be given to referral for ECMO if the OI is rising or above 30 persistently (2 blood gasses 30 minutes apart) infants should be discussed with ECMO team(8). To refer for ECMO, initially contact the ECMO co-ordinator at Glenfield Hospital, Leicester (0116 287 1471). This must be discussed with the Consultant Neonatologist beforehand.

Criteria for considering ECMO include (if in doubt, discuss with consultant neonatologist and ECMO centre, early discussion with ECMO team is important):

- Term or near-term infants (≥ 34 weeks of gestation) or birthweight ≥ 2kg with PPHN
- Respiratory failure or OI above 30 despite optimal conventional ventilation including iNO, inotrope and/or HFOV
- Not maintaining blood pressure with inotropes
- No significant improvement or progression in 24-48 hours

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

- Term or near-term infants (≥ 34 weeks of gestation) or birthweight ≥ 2kg with PPHN
- Oxygenation index (OI) above 40 (refer section 3.2 Assessment)
- Reversible lung disease
- No lethal congenital malformation (e.g. lethal chromosomal abnormality, major intracranial haemorrhage, major cardiac malformation or severe encephalopathy)

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).

3.2.3 Other Pulmonary Vasodilators

They are rarely used and only on advice of consultant neonatologist or consultant cardiology.

Sildenafil

Sildenafil is a Phosphodiesterase type 5 inhibitor. There is a lack of evidence for the use of both IV and oral sildenafil for acute PPHN. It may be used in individual cases especially in PPHN associated with CDH on direction of consultant neonatologist or on consultant cardiologist(9).
Milrinone
Milrinone is a Phosphodiesterase type 3 inhibitor. In selected cases, it may improve OI or inotropic requirement (10,11). Dosage regimen varies from 0.25microgram/kg/min to maximum of 0.75microgram/kg/min by continuous infusion. Loading dose preceding infusion should not be used in sick infants to avoid hypotension. It should only be used in discussion with the duty consultant taking into account the echocardiogram findings.

Magnesium sulphate
Magnesium decreases the influx of extracellular calcium into smooth muscle cells in blood vessels causing vasodilation. However, it is not selective and can lead to systemic hypotension. A recent meta-analysis found no evidence for its use (12). Hence, the current recommendation is to maintain normal levels of magnesium especially in infants with PPHN where high normal levels (closer to 1mmol/L) should be maintained.

Prostacyclin
Prostacyclin (Epoprostenol) has also been used in this situation (13). Again there is no trial data and a trial in the USA was terminated because of severe hypotension. Its use in an aerosolised form has been reported with anecdotal success.

Vasopressin
After discussion with ECMO centre, low dose arginine vasopressin may be considered to cause selective vasodilatation in pulmonary, cerebral, renal and coronary vasculature under hypoxic condition through its action on V1 receptors. Similarly, there are only very few published case series showing vasopressin as a potential effective adjunct in infants with PPHN with refractory systemic hypotension and hypoxaemia (14).

Tolazoline
The most commonly used of these in the past was Tolazoline (15). Its use was commonly associated with severe systemic hypotension and it is therefore no longer used.

Bosentan
It is an endothelin receptor antagonist (ETA and ETB receptors). There are a handful of case report in infants (16) though has shown to reduce pulmonary pressures in adults.

4. Audit Points
Use of nitric oxide and HFOV in term and preterm infants
Number of infants and timing of referral for ECMO
Use of Nitric oxide prescribing form

5. Related Guidelines
- Neonatal Guideline A8 Early Care
- Neonatal Guideline B1 Mechanical Ventilation
- Neonatal Guideline B4 Congenital Diaphragmatic Hernia
- Neonatal Guideline B5 Surfactant Therapy
- Neonatal Guideline B9 High Frequency Oscilation Ventilation
- Neonatal Guideline B16 Meconium Aspiration Syndrome
- Neonatal Guideline E1 Red Cell Transfusion
- Neonatal Guideline E2 Cardiovascular Support
- Neonatal Guideline G3 Central Venous Line
- Neonatal Guideline G5 Umbilical Venous and Arterial Catheter
6. Summary Box and Levels of Evidence

<table>
<thead>
<tr>
<th>Summary</th>
<th>Level of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Use of iNO in term infants with respiratory failure prevents referral for ECMO</td>
<td>A</td>
</tr>
<tr>
<td>The benefit of iNO in term infants with respiratory failure due to congenital diaphragmatic hernia and preterm infants is unclear at present</td>
<td>A</td>
</tr>
<tr>
<td>Rescue HFOV in term with respiratory failure may improve ventilation</td>
<td>C</td>
</tr>
<tr>
<td>Rescue HFOV in preterm infants with respiratory failure may improve ventilation</td>
<td>C</td>
</tr>
<tr>
<td>If OI is &gt; 40 in term infants ECMO improves survival</td>
<td>A</td>
</tr>
<tr>
<td>Repeat doses of surfactant may decrease the risk of air leak</td>
<td>A</td>
</tr>
<tr>
<td>HFOV and NO together may have additive effects on improving oxygenation</td>
<td>B</td>
</tr>
</tbody>
</table>

References


### APPENDIX 1 – BOLDPEEP table (Neonatal Guideline B1 Mechanical Ventilation)

<table>
<thead>
<tr>
<th>B.O.L.D.P.E.E.P.</th>
<th>Common Findings</th>
</tr>
</thead>
</table>
| **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 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/Patient 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 |
APPENDIX 2: Setting up Nitric Oxide

How to set up Inhaled Nitric Oxide

Set up guide for the use of the INOmax with both the Dräger Ventilator.

Teaching package updated by:
Julie Hitchcox
Revised by Clare Brown 2017

How to set up and attach a patient to Nitric Oxide

- The content of this folder has been prioritised such that the emphasis is about building, testing and attaching a nitric circuit.

- Information about the machine functions and controls including alarm limits has been pushed further back within the folder.

- The Nitric team on both sides of town are:
  - GMC: Clare Brown
  - City: Clare Brown
  - Kirsty Spencer
  - Hannah Warman
  - Michelle Wilcoxson
  - Banida Orbita

- If you have any problems whilst using the INOmax Dslr machine there is a trouble shooting number which can be used at any time of day or night this is:

  0800 917 4024
INOmax setup book contents:

- Section 1: Setting up and testing the INOmax
- Section 2: Connecting the Neo puff to the INOmax
- Section 3: Connecting INOmax to Dräger Ventilator
- Section 4: Purging the system
- Section 5: Swapping the nitric cylinders
- Section 6: Changing the nitric cylinders
- Section 7: Documents

Section 1:

Setting up and testing the INOmax
iNOmax Pre-Use procedures

7 Steps:

1. Plug in the iNOmax and switch on
2. Perform a high pressure leak test
3. Perform a low range calibration
   –Build test circuit whilst calibration stabilising
4. Purge the system
5. Perform the back up delivery test
6. Complete the performance test
7. Complete the blender test
8. Convert test circuit to patient circuit and attach to ventilator

1. Plug into the mains and switch on.

• Connect the iNOmax to electric supply and switch on the iNOmax. (It should be always on, do not turn off the electric supply while not using)

The water trap is a single patient use only. Always discard after patient use, ensure a new trap is in place.
2. Do a system high pressure leak test

- Turn both cylinders on and off one at a time.
- Checking the cylinder top goes green on the screen
- Watch the pressure gauge for any falling pressure for 30 seconds.

3. Do a low range calibration

- Access the menu screen
- Press the Low Cal button
- Press the second Low Cal button
- Once the calibration is complete all of the lines will become green.
- Go back to the main screen X2
1. Set up test circuit.

2. Connect this circuit to the iNOmax system

4. Purge the system

- Ensure both iNOmax cylinders are turned off
- Connect the oxygen tubing to the wall oxygen
- Turn the wall oxygen to 10 litres
- Set the iNOmax dose to 40 ppm
- You should hear and see a "cylinder valve closed" alarm.
Now you should also hear the “low NO/N₂:Pressure” alarm

Open one of the cylinder valves

Turn the iNOmax dose down to zero, you will see “Set dose is zero, close cylinder valve” alert, however ignore this. Do not close the valve.

5. Backup Delivery Test

Ensure your wall oxygen supply is still at 10L

Turn on the backup delivery system

“Backup ON” should alarm

Ensure the values you can see are
- NO 14-26 ppm
- NO₂ ≤1.0 ppm

Backup test completed turn off backup
6. Complete the performance test

- Ensure the wall oxygen is still at 10L
- Set the main iNOmax dose to 40 ppm
- Ensure the values you can see are
  - NO 35-45 ppm
  - NO2 <1.5 ppm
  - FiO2 95% ± 3%
- Turn the iNOmax dose to zero

7. Perform iNOblender test

Remove the O2 tubing from the flow meter and connect to the iNOblender. Ensure that the white oxygen hose from the inovent is attached to the wall outlet.

Set at 8L/hr

Remove the injector module from the Pre-Use set up and reconnect the adapters.
• Connect the iNOmax oxygen port to the wall oxygen supply.

• Set the iNOmax dose to 40 ppm on the iNOblender and turn the O2 flow to 8L/min

• Ensure the values are
  – NO 32-48 ppm

• Turn the dose and flow to zero and remove all of the pre use test set.

NB the blender dial is stiffer than you think!

• The iNOmax system is now ready to connect to the patient.

• Follow the next steps to connect to either the Dräger or Stephanie ventilator

• If the system is not going to be used within ten minutes please purge the cylinders leaving the grey hose disconnected.

• If the system is left longer than 10 hours please purge the system as above and perform another low range calibration.
Patient Identity

- Click on the picture of the patient
- Input their name and identification number

This will save your patients details as well as calculate the number of nitric hours used, which will save us money and is more precise.

Checklist
Complete before attaching to baby

Trouble shooting!
☐ Made sure the sample line is connected to the water trap?
☐ Ran 20 – 40 PPM of nitric whilst doing the device check?

Have you:
☐ Check that water chamber on iNOmax is empty.
☐ Entered a meter reading prior to therapy on the charging form.
☐ Collected an Nitric Observation Form.
☐ Collected a Nitric Clinical Datasheet.
Things to ensure whilst using the iNOmax:

• Ensure Met Hb is done after 1 hour & ‘INOmax Use’ form is filled in

• Ensure observation charts are used

• Document all changes of cylinders and the amount of time they have been used

• If iNOmax is not used within 5-10 minutes of doing pre-use checks NO2 may start to build up again – purging the iNOmax before attaching to baby should clear this

• Ensure the water trap is emptied regularly this is done whilst the iNOmax is still connected to the patient

• The neopuff is always connected to the iNOmax and when use turned up to 8 litres on the flow meter.

Section 2:

Connecting the Neo puff to the iNOmax
Connect Neo puff tubing to iNOmax machine

The green tubing of the Neo puff is connected to the outlet port marked NO/NO2, rather than to wall oxygen and is then used in exactly the same manner to provide manual breaths with prescribed NO dose.

Neo puff Flow Meter

When using the neo puff connected to the iNOmax you must ensure that the flow meter on the side is turned up to 8 litres to ensure that pressures on the neo puff are correct.
Section 3:
Connecting iNOmax to Dräger Ventilator

4 Steps:

1. Swing the humidifier arm out to the side of the ventilator
2. Connect the injection module before the humidifier to the inlet side.
3. Connect iNO/NO2/O2 monitoring (sampling port) line to Inspiratory limb.
4. Connect Neo puff unit to back of iNOmax — green tubing connects to silver connector marked ‘NO/NO2’
1. Connect the Injection module before the humidifier

- Ensure the arrow on the Injection module and the one way valve point down towards the humidifier.

2. Connect iNO/NO2/O2 monitoring (sampling port) line to Inspiratory limb

- Insert the luer lock connector (clear and blue) into the inspiratory limb (blue tubing) next to the temperature line.
- The sample line connects to circuit on clear luer-lock connector

• Once this has been completed and the baby is being Neo puffed the ventilator will need to have the breathing circuit test re-done.
Section 4:

Purging the system

Purging the System

1. Disconnect the grey hose from the back of the iNOmax by pushing in on the silver connector.

2. Push the grey hose in to the pin in the back of the iNOmax (you will hear a hissing noise)

3. Reconnect the grey hose into the iNOmax machine.
Section 5:
Swapping Nitric Oxide Cylinders

Swappin the INOmax cylinders

The cylinders in use must be changed when they reach 200ppm (red line).

1. Disconnect the spare unused cylinder (remove the grey hose from the sliver connector from the rear of the machine)

2. Whilst disconnected turn on the unused cylinder then off again immediately. The gauge at the front should rise showing the cylinder is full.

3. Purge the cylinder to remove the unused gas from the tubing (section 5).

4. Reinsert the black hose in to the back of the INOmax machine.

5. Turn on and off the cylinder to ensure there is gas in the cylinder watching the gauge rise.
Section 6:

Changing Nitric Oxide Cylinders

1. Once your cylinder is empty, turn it off and purge the black hose (section) leave this hose disconnected.

2. Unscrew the black adapter from the empty cylinder and attach the sliver screw top.

3. Remove the empty cylinder from the iNOmax.

4. Remove the new cylinder from the new box found in the old transport room QMC or gas room CHN.

5. Attach the black adaptor on to the new cylinder leaving the black hose disconnected.

6. Turn on the new cylinder and off again ensuring the pressure rises on the from of the iNOmax and purge the system (section 5).

6. Reconnect the black hose to the back of the iNOmax and keep the new cylinder turned off.
7. Reconnect the black hose to the back of the iNOmax and keep the new cylinder turned off.

8. Locate the empty white box (if this wasn’t with the new cylinder the porters can bring you a new one).

9. remove the barcode label and stick it on to the white box above.

10. Place the cylinder in the box and call the porter they will bring a new cylinder and a new empty white box.

Section 7:
Documents

REMEMBER daily low range calibration test to be performed daily during therapy.
APPENDIX 3: INOMAX Competency Document (Sample copy)

<table>
<thead>
<tr>
<th>INOmax DS IR</th>
<th>Verified Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Make</td>
<td>Ino Therapeutics</td>
</tr>
<tr>
<td>Model</td>
<td>INOmax DSIR</td>
</tr>
<tr>
<td>Category</td>
<td>37266</td>
</tr>
</tbody>
</table>

Nottingham University Hospitals NHS

Title
Surname
Fname
Dept / Ward

Directorate:

Verification of competence is undertaken by assessment against the following statements:
These statements are designed to indicate competence to use this device. Responsibility for use remains with the user, so if you are in any doubt regarding your competence to use the device, you should seek education to bring about improvement. Do not perform any additional procedures until you are confident you are competent. You must be able to score "Y" to all the questions before being considered competent. If you are not competent, initiate learning and then a repeat assessment.

1. Explain correct Visual check of the INOMAX
2. Explain and demonstrate how to change cylinders on the machine
3. Explain how to clean / decontaminate the device
4. Explain how to shut down and switch off the device
5. Explain how to store the device safely
6. Explain the documentation required for the patient and nitric oxide calculation

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</table>

Authorised Trainer

Signature: Date:

Please ensure this form is in your personal portfolio or training record. Give your manager a copy of the form and check that details of your training/competence have been recorded on OUM and/or ePortfolio.

Date Issued: April 2015
Review Date: April 2017

Nottingham Neonatal Service Clinical Guidelines
Guideline B6