DOI: http://doi.org/10.4038/sljpm.v2i1.34

Current Practice

Guideline on management of Persistent pulmonary hypertension (PPHN) of the newborn using inhaled Nitric Oxide therapy

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1. Introduction

This guideline is prepared based on the available evidence to provide optimum care for newborns with persistent pulmonary hypertension (PPHN) and ensure that inhaled nitric oxide (iNO) is used in a safe, effective, appropriate and cost-effective way for newborns with PPHN in the neonatal intensive care unit.

Persistent Pulmonary Hypertension is a failure of pulmonary vascular resistance to fall post natally at any gestation. It is characterized by right to left shunting of deoxygenated blood at atrial, ductal and pulmonary levels resulting in severe hypoxaemia.

Its aetiology may be classified by normal or abnormal pulmonary vasculature development.

- Conditions with normal pulmonary vasculature include meconium aspiration, asphyxia states and congenital pneumonia, which tend to respond more quickly to treatment and may tolerate more aggressive measures. Abnormal transition without parenchymal lung disease rarely requires inhaled nitric oxide.
- Conditions with abnormal pulmonary vasculature include chronic foetal hypoxia, oligohydramnios and congenital diaphragmatic hernia, which tend to be less responsive to pulmonary vasodilators and may benefit from lung protective ventilation strategies. Most cases of idiopathic PPHN probably belong to this group.

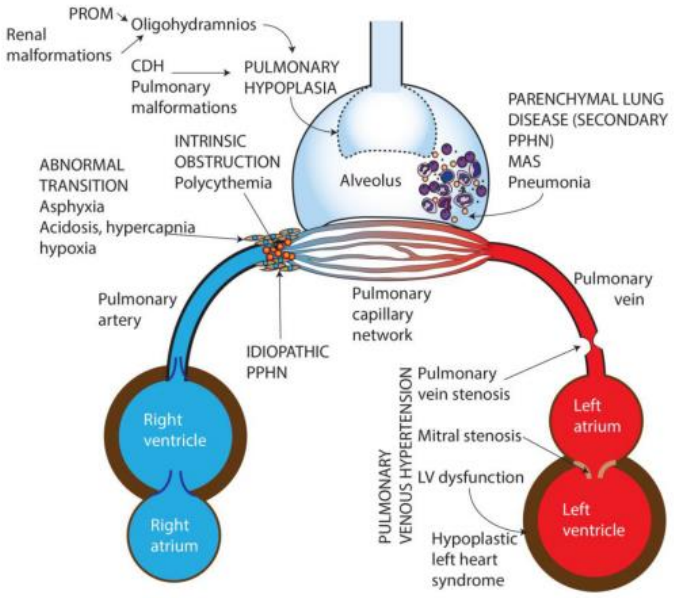


Figure 1. Causes of persistent pulmonary Hypertension in the newborn. PROM—Premature rupture of membranes, CDH—Congenital diaphragmatic hernia, MAS—Meconium aspiration syndrome, PPHN—Persistent pulmonary hypertension of the newborn, LV—Left ventricle. Copyright Mathew and Lakshiminurusimha, 2017

2. Key Clinical Features:

- Hypoxia despite 100% oxygen and structurally normal heart
- Hypoxia disproportionate to underlying lung disease
- Pre- and post-ductal saturation discrepancy (>5%, often 10-15%)

3. Investigations:

- Continuous central blood pressure and pre- and post-ductal saturation monitoring
- Serial arterial blood gases and calculation of Oxygenation Index (OI). (Severity of hypoxic respiratory failure: mild 40)
- CXR – rule out pneumothorax, atelectasis/pneumonia and provide adequate lung inflation

$$OI = \frac{FiO_2(\%) \times MAP\ (cm\ H_2O) \times 100}{PaO_2\ (kPa) x\ 7.5}$$

- Echocardiogram: establish cardiac anatomy and evidence of PPHN to guide treatment. Serial echo may guide treatment during the clinical course. If OI>20 and unresponsive to iNO, urgent formal assessment by Cardiology is required
- Screen and treat for sepsis
- Cranial ultrasound if considering ECMO
- Starting Prostaglandin E_2 is usually indicated in equivocal cases until definite diagnosis is established

4. Treatment Strategies:

4.1 General management principles - These points are very important and can prevent further unnecessary escalation of therapy.

- Ensure secure and well-positioned ETT, with leak 30%
- Central venous access and arterial access (ask for assistance if required)
- Correct metabolic acidosis with bicarbonate. Aim to keep pH 7.35-7.45 in the early phase of management.
- Aim for normal temperature unless cooling treatment is required
- Electrolyte correction
- Treat for sepsis
- Strict fluid balance and consider nutritional needs

(Refer Figure 2 for treatment sequence)

4.2 Optimize Ventilation/Oxygenation

CO_2, pH and O_2 are the most important determinants of pulmonary vascular resistance. Optimal lung inflation is essential when iNO is used.

- Early liberal oxygen use – wean when stabilized. The optimal saturation target range for patients with PPHN is not known. Targeting a lower limit of preductal SpO_2 of 92% provides a buffer to hypoxic pulmonary vasoconstriction and an upper limit of 97% ensures the optimal balance of pulmonary vasodilation and minimizes adverse effects from oxidative stress.
- Consider surfactant
- Optimize ventilation settings to achieve target $PaCO_2$ 4-6 kPa and PaO_2 8-12 kPa. Oxygenation is defined by mean airway pressure (MAP) and FiO_2. Higher PEEP and longer inspiratory time yields higher MAP in conventional ventilation.
- If high PIPs required (>28 cm H_2O), consider starting HFOV

- If using HFOV, repeat CXR to monitor inflation and guide MAP settings (aim diaphragms at 9 ribs). Term infants may require MAP >16 cmH_2O. Inform consultant if needing MAP >20 cmH_2O.
- Increased sedation and often muscle relaxation may be required for appropriate minute ventilation. Consider prone positioning.

4.3 Sedation

- Morphine or Fentanyl bolus and infusion for initial sedation
- Add Midazolam if required
- Muscle relaxation if ongoing difficulty with ventilation – Pancuronium bolus +/- Vecuronium infusion. Vecuronium infusion is preferred, as Pancuronium can cause tachycardia.
- Monitor blood pressure closely. give saline bolus if BP decreases with sedation.

4.4 Blood Pressure Support

- Aim for high-normal BP (MAP≥ 45-50 for term neonates).
- Consider starting inotropes early for hypotension.
- Dopamine first-line (max 10-15 mcg/kg/min to prevent tachycardia)
- Consider fluid resuscitation (max 20ml/kg 0.9% NaCl) if there is evidence of hypovolemia.
- Then consider Noradrenaline/ Adrenaline infusion followed by Hydrocortisone depending on echo finding or BP values if echo is not available:

  Adrenaline if echo demonstrates decreased LV function or when systolic BP is low with narrow pulse pressure on BP monitor.

  Noradrenaline if echo demonstrates relatively maintained LV function or when diastolic BP is low with wide pulse pressure on BP monitor. Consider Vasopressin in case of catecholamine resistant hypotension or when oxygenation significantly improves at higher BP values.

4.5 Pulmonary Vasodilators

- **Echo** prior to commencement if possible but treatment should not be delayed.

4.5.1 Inhaled Nitric Oxide: First line therapy (after general management steps)

- Exclusion criteria: Cyanosis secondary to congenital heart disease and preterm infants with hypoxic respiratory failure
- Contraindications to iNO therapy:

  Bleeding diathesis should be corrected prior to commencing iNO

Note: No clear benefit has been demonstrated in babies with diaphragmatic hernia

4.5.1.2 Starting treatment, maintenance and monitoring

- Consultant Neonatologist/ Paediatrician must decide on commencing iNO
- Start at 20ppm and slow wean when stabilized to prevent rebound hypoxemia
- Monitor for thrombocytopaenia and coagulopathy.
- Methhaemoglobin should ideally be monitored if facilities are available.
- Response must be assessed in 20-40 mins by ABG and calculation of OI or less preferably by response in pre- and post-ductal saturations and FiO_2 requirement. These must also be documented in notes.

- When the baby is stable on 20 ppm, start weaning of oxygen slowly.

4.5.1.3 Weaning iNO

- There is a high risk of rebound PPHN and therefore iNO should be weaned slowly, especially in infants with abnormal vasculature development or significant parenchymal disease
- Consider weaning iNO when clinical stability achieved and FiO_2 requirements ≤0.6
- Decrease iNO by 5ppm every 4 hours as tolerated, until 5ppm reached. Slower decrease by decrements of 1ppm every 4 hours until ceased.
- A faster wean (decrease iNO hourly) may be tolerated in low-risk infants.
- Stop and increase iNO back to last effective setting (≥5ppm) if signs of weaning failure.

Weaning failure if:

- FiO_2 requirement increases ≥0.2
- Pre- and post-ductal saturation difference >10%

- After stability re-achieved, attempt wean again more slowly
- If signs of recurrent weaning failure, consider adjunctive oral Sildenafil after discussion with Cardiology.
- Repeat echo soon after successful weaning from iNO to identify persistent signs of PPHN and right ventricular failure (as clinical features might be initially subtle).
- Discuss follow up and length of Sildenafil treatment with cardiology before discharge home.

4.5.1.4 Documentation

- The time of starting and stopping iNO therapy should be entered in the neonatal BHT. The prescribed dose of iNO with the duration for each dose should be entered in the monitoring chart.
- NO_2 and methhaemoglobin (if facilities available for measuring) concentration should be recorded).
- Summary of iNO therapy must be recorded in 'Neonatal Monthly Return H 1168'

4.5.2 Milrinone and Sildenafil

- Consider in consultation with Neonatologist or Cardiologist
- Milrinone has inotropic and vasodilator effects and is useful in myocardial dysfunction. Consider a saline bolus prior to commencement to prevent hypotension.
- Sildenafil (IV) may be useful in cases with good cardiac function. Oral Sildenafil is preferred during weaning of iNO.
- Prostaglandin E_2 (Dinoprostone): may be indicated to re-open the duct if RV failure on echo

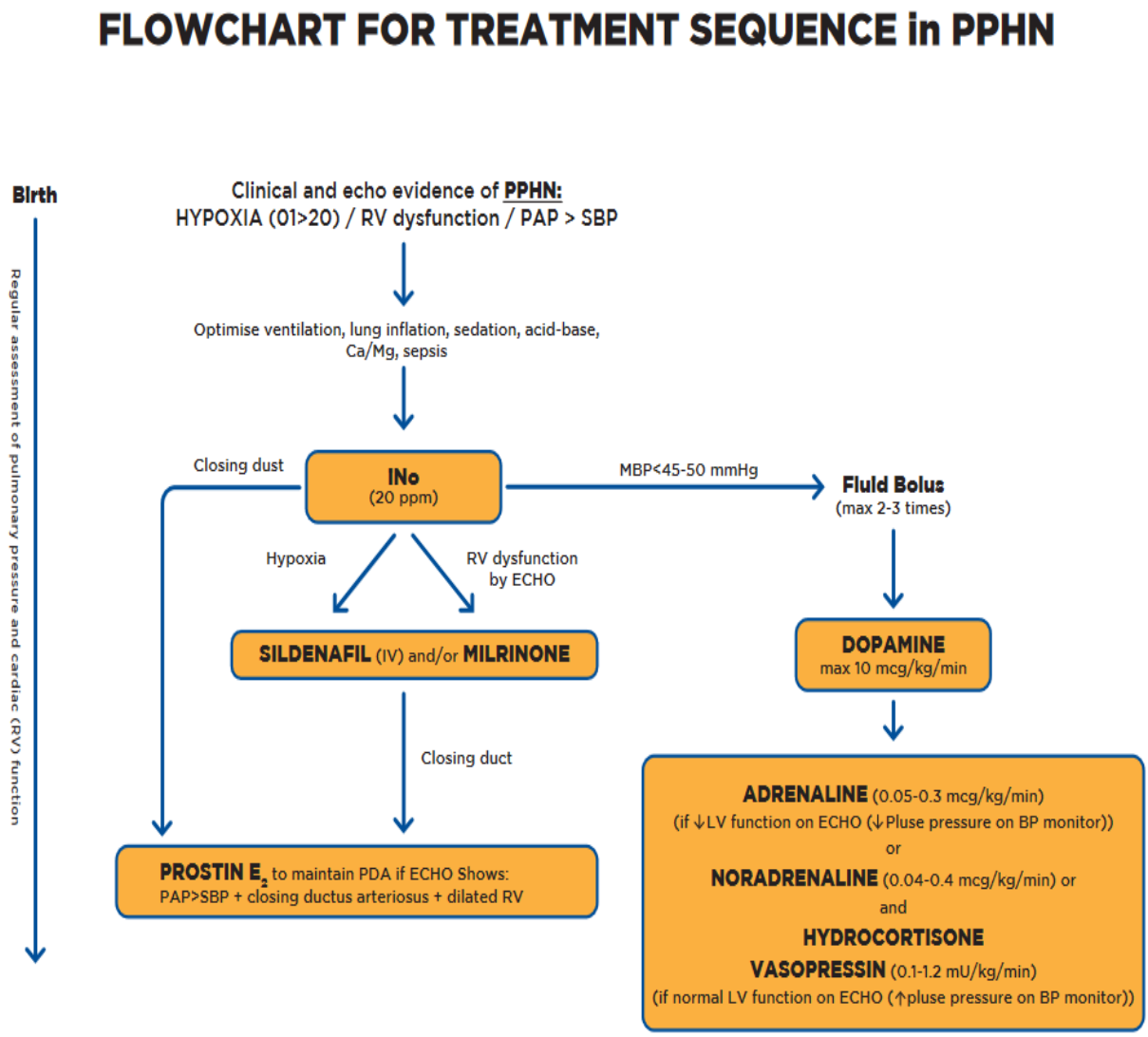
4.6 ECMO

- Eligibility
  term, reversible respiratory failure in absence of congenital abnormality and IVH

- Significant risks
  haemorrhage, mortality 20%, morbidity up to 46% in selected groups

5. Postoperative management of pulmonary hypertension associated with heart or lung surgery in infants

- The development of right ventricular failure secondary to pulmonary arterial hypertension is a serious postoperative complication in children.
- The selective pulmonary vasodilatation produced by inhaled nitric oxide is a therapeutic option in certain cardiac lesions.
- Such examples are obstructed Total Anomalous pulmonary venous return (TAPVD), Atrio-ventricular septal defects, and large Ventricular septal defects with Pulmonary hypertension



(Source: John Radcliffe Hospital, Oxford, UK)

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