Guideline for the management of Persistent Pulmonary Hypertension of the Newborn in Term Infants

- Persistent Pulmonary Hypertension of the Newborn (PPHN) has an incidence of 1-2/1000 live births.
- PPHN occurs secondary to lung hypoplasia or mal-adaptation at birth of the pulmonary vessels (often secondary to acidosis and hypoxia e.g. asphyxia, meconium aspiration, sepsis and RDS).
- It is characterised by marked pulmonary hypertension due to increased pulmonary vascular resistance causing profound hypoxemia secondary to right to left shunting of blood through the foramen ovale, ductus arteriosus and intrapulmonary shunts.
- PPHN should be considered in the differential diagnosis of cyanosis.

Diagnosis
The perinatal history is very important and will often give clues to the underlying diagnosis. Clinical examination will reveal cyanosis, nearly always with respiratory distress. A >10% difference between pre-ductal (right arm) and post-ductal saturations (foot) is also frequently observed. An echocardiogram is helpful in distinguishing cyanotic heart disease from PPHN, and also indirectly measures the pulmonary arterial pressure and level/direction of shunting. The oxygenation index (OI) is a calculation that gives an overall assessment of the severity of the respiratory disease and is helpful in monitoring patient progress.

Oxygenation index: \( \text{Mean airway pressure} \times \text{FiO}_2\ (\text{eg Air }=0.21) \times 100 \)
\( \text{PaO}_2\ (\text{mmHg}) \)

1 Kpa = 7.5mmHg

Management
The aims of treatment are to reduce the pulmonary vascular resistance and to maintain a systemic blood pressure higher that the pulmonary arterial pressure (estimated by echo). Aim for \( \text{SaO}_2 >95\% \), arterial \( \text{PaO}_2 >7kPa \), a Ph around 7.4 and \( \text{PaCO}_2\ ) in the normal range. Wean oxygen according to blood gases rather than \( \text{SaO}_2\ ).

Correct any underlying abnormalities such as hypothermia, acidosis, polycythaemia (central venous haematocrit (Hct) >65%) hypoglycemia, hypocalcaemia or hypomagnesaemia.

First line treatment includes ventilation, oxygenation and maintenance of systemic blood pressure. Second line treatments such as high frequency ventilation and nitric oxide can be tried if the patient is not improving and ECMO is the last resort for PPHN.

These patients are often very sick, and their management should always be discussed with the consultant.

Respiratory support
1. Use conventional ventilation initially. Avoid hyperventilation, as although hypocapnia has been shown to decrease the need for ECMO, it increases the risk of long term neurological disability and in particular sensori-neural deafness.
2. Consider early surfactant, as it can reduce the requirement for ECMO.
3. If conventional ventilation is failing, HFOV should be considered as it has been shown to rescue >60% of patients failing conventional ventilation.
4. If there is no improvement and worsening OI start inhaled nitric oxide (iNO) at 20ppm. If there is no improvement following iNO and or OI >40, consider ECMO. Nitric oxide is known to reduce mortality and the need for ECMO in >60% of patients with PPHN.

Circulatory support
1. Aim to maintain systemic BP above pulmonary pressures. Repeated fluid boluses are often required to maintain adequate filling volume. Pulmonary pressure may be estimated by echocardiography,
however, if there is a large ductus the systemic and pulmonary pressures will be the same. A pragmatic approach is to set a high/normal target systemic mean blood pressure, (please see the hypotension guideline).

2. Consider early inotropic support (please see hypotension guideline).

3. Milrinone works by inhibition of phosphodiesterase 3 in vascular smooth muscle and may be a useful adjunctive inotrope as it potentiates the effects of NO, causes pulmonary vasodilatation and improves diastolic function.

   **Milrinone Dose:** initially 50-75mcg/kg over 30-60 minutes, then 30-45mcg/kg/hr as a maintenance dose.

### Sedation

1. Ensure minimal handling as these patients are very labile and can deteriorate following minor stimulation.

2. Sedate with morphine (some patients will require > 20mcg/kg/hr).

3. Use of muscle relaxants remains controversial as it may be associated with increased mortality and deafness. However if patients are “fighting the ventilator” or have asynchronous ventilation it may be useful.

### Alternate therapies

a) These are experimental and would usually be considered after discussion with ECMO centers. Adenosine infusions have been demonstrated to improve oxygenation in small trial of 9 infants with proven PPHN on iNO. It acts by increasing cAMP in vascular smooth muscle resulting in vasodilatation. Systemic hypotension is a complication. However larger studies are needed before it can be recommended for routine use in management of refractory PPHN.

   **Adenosine dose:** continuous intravenous infusion at 50mcg/kg/min.

b) Sildenafil is a selective phosphodiesterase inhibitor that enhances NO mediated vasodilatation. Mainly used as a weaning adjunct, and should be avoided if PPHN is caused by lung pathology as it worsens VQ mismatch. It is administered orally.

   **Sildenafil dose:** start at 0.2mg/kg/dose every 6 hours and increase to a maximum of 1mg/kg/dose 4 hourly.

c) Magnesium sulphate has been shown to improve OI in 5 small uncontrolled trials in 40 ventilated infants. The vasodilatation is short lived and associated with profound hypotension. However a Cochrane review concluded that in the absence of good quality trial Magnesium sulphate cannot be recommended for treatment of PPHN

### References


