Persistent Pulmonary Hypertension of the Newborn: Management Guideline

Persistent pulmonary hypertension of the newborn (PPHN) is a syndrome caused by failure of the pulmonary vascular resistance (PVR) to decrease at birth. The normal cardio-pulmonary adaptation can fail due to a variety of conditions, including retention of fetal lung liquid, surfactant deficiency, aspiration of meconium/blood/amniotic fluid, pneumonia/sepsis, and congenital anomalies that interfere with the establishment of ventilation at birth (Congenital Diaphragmatic hernia, Pulmonary hypoplasia, Oligohydramnios, etc).

**General management of PPHN:**

Optimum response to pulmonary vasodilator therapy requires

- Adequate lung expansion
- Proper acid–base balance
- Sufficient preload for the left heart
- Optimum cardiac performance
- Avoidance of hyperoxia

1. **Use of Surfactant:**

According to recent Level 1A evidence, early surfactant therapy rapidly improves oxygenation, optimizes response to iNO and decreases the level of ventilator support needed for lung recruitment for parenchymal lung disease secondary to RDS, pneumonia or perinatal aspiration syndrome. Infants treated with surfactant have decreased need for ECMO. Best responses are seen when surfactant is given early in respiratory failure, at an oxygenation index (OI) of 15–25. Surfactant deficiency is a major component of parenchymal lung disease, occurring either as the primary deficiency in respiratory distress syndrome (RDS) or a secondary loss from inactivation (meconium), injury (pneumonia, inflammation), or dilution (excess fluid in transient tachypnea of newborn-TTN).

Based on the strength of this data, **we recommend that any late preterm or term neonate requiring intubation and mechanical ventilation for hypoxic respiratory failure secondary to parenchymal lung disease should be given surfactant, early in the course of illness.** A consistent need for FiO2 >40% on positive pressure support should trigger an evaluation of underlying lung disease and lung expansion to assess the need for surfactant therapy. Remember “Surf early to higher tides”.

2. **High Frequency Ventilation**

The ventilator strategy should target recruitment of the atelectatic segments while avoiding over distension which leads to lung injury and increased resistance to pulmonary blood flow. **A lung recruitment strategy with the application of HFOV or HFJV, with its safer means to provide higher Mean Airway Pressure, leads to better responses to iNO, when PPHN is secondary to parenchymal lung disease.** Infants with primary PPHN (in absence of parenchymal lung disease or “Black Lung PPHN”) respond to iNO equally whether given with conventional mechanical ventilation (CMV) or HFV.

3. **Optimum Oxygen targeting**

While achieving a normal PaO2 of 60–90 torr is important for restoring postnatal adaptation, there is no evidence that a PaO2 >100 causes a greater reduction in PVR. Current evidence suggests 91-97% O2 saturation as an appropriate goal as long as there is evidence of adequate oxygen delivery to the tissues (perfusion, capillary refill, NIRS, urine output, acid-base balance). Failure to wean due to higher PaO2 or
O2 saturation targeting risks prolonged exposure to 100% FiO2 which may exacerbate lung injury, vascular dysfunction and blunt the response to pulmonary vasodilators. **While hypoxia is bad, hyperoxia isn’t good either!**

4. **Inhaled Nitric Oxide**

We recommend initiation of iNO therapy when respiratory failure progresses and OI reaches 15–20 on at least two blood gases. iNO requires sufficient alveolar surface area to diffuse across to the pulmonary vasculature in order to effectively lower the PVR. Therefore, lung recruitment and keeping the majority of alveoli open are important prerequisites to optimize response to iNO. Note that iNO is contraindicated in neonates with (1) Congenital Heart disease with ductal-dependent systemic blood flow (2) Total Anomalous Pulmonary Venous Return (3) CDH with Left ventricular Dysfunction. It is essential to obtain an echocardiogram not only to document pulmonary hypertension but to also rule out structural cardiac anomalies for which iNO could be detrimental. Methemoglobin (MethHb) is monitored daily. Exposure to iNO even for a brief period can sensitize the pulmonary circulation to rebound vasoconstriction during discontinuation of iNO therapy, hence weaning should be cautiously performed in steps (refer to iNO guidelines). iNO may be initiated without an echocardiogram if obtaining an echocardiogram is not feasible (e.g. CDH patient in the delivery room), however an echocardiogram should be obtained as soon as possible. (For more details, refer to iNO Initiation and weaning guideline)

5. **Sildenafil**

There are 2 randomized controlled trials (RCTs) comparing sildenafil with placebo for PPHN infants in resource-constrained settings lacking iNO and ECMO. Both RCTs showed improvement in oxygenation in sildenafil-treated infants 6–12 hours after the first dose. Systemic hypotension was not observed with oral sildenafil. An open label trial of IV Sildenafil showed improved OI beginning 4 hours after Sildenafil initiation. Since hypotension has been reported with IV sildenafil, we recommend oral/enteric therapy first even if the patient is not receiving enteral feeds. IV route is recommended when oral administration is not practical (i.e. CDH). Hypotension, if noted, responds well to volume infusion and vasopressor support. Giving a loading dose over a few hours (as indicated below) reduces possibility of hypotension.

**Sildenafil Dosing:**

**Oral:** 0.5–2 mg/kg/dose every 6 hours OG. Consider starting at the lower end and escalating up if no significant hypotension.

**Intravenous:** Loading 0.14 mg/kg/h over 3 hours followed by 0.07 mg/kg/h. Consider central access with multiple lumens since there are few compatibility studies.

IV-PO conversion: Bioavailability of enteral sildenafil is ~40%, keep this in mind if/when transitioning route of administration. Unlike BPD-PAH, there is no reason to gradually wean off sildenafil in PPHN. It can simply be stopped once hypoxemia has resolved clinically. Steinhorn et al used Sildenafil IV for a range of 2–7 days.

6. **Prostacyclins (PGI2) Iloprost**

There is limited data on PGI2 use in PPHN in neonates and is primarily based on retrospective studies and expert opinion. The vasodilatory effects of inhaled PGI2 can be complementary to iNO, and are due to potentiation of cAMP in pulmonary vascular smooth muscles. PGI2 may be more effective in neonates with PPHN secondary to CDH or alveolar capillary dysplasia. There are various formulations available, and the medication can be given as IV or inhalation. In the ACH NICU for patients with PPHN, we recommend **inhalation over IV route** since aerosolization allows for (1) direct delivery of medication closer to the
alveoli and pulmonary vasculature, (2) minimizes the systemic effects of hypotension, and (3) does not require a dedicated lumen for access like IV formulations (Epoprostenol “Flolan”) do.

**Inhaled Iloprost (Brand name: Ventavis)** is a synthetic PGI2 with a half life of 20-30 mins and can be given up to 6-9 times a day through a nebulizer.

Iloprost Dosing: 0.5–2 µg/kg/dose every 2–4 hours as inhalation. Inhalation Device: Aeroneb - uses vibrating mesh electronic micro pumping technology. The nebulizer is placed between the ETT and circuit with both conventional and HFOV. Each treatment takes approximately 5 minutes and the therapeutic effects should be noted shortly after and last about 30-60 mins.

7. **Phosphodiesterase Inhibitors (Milrinone)**

A PDE-3 inhibitor, milrinone increases the bioavailability of cAMP and may indirectly increase cGMP levels in PPHN. Observational studies have demonstrated decrease in pulmonary artery pressure and right to left shunts and improvement in left and right ventricular output by echocardiography. In neonates with CDH with PPHN and poor LV function, the combination of its pulmonary vasodilator and inotropic effects are beneficial. Be cautious when using sildenafil and milrinone simultaneously due to the potential for hypotension associated with blocking both PDE isoforms in the vascular smooth muscle.

**Milrinone Dosing:**

IV: Loading: 50 µg/kg/minute over 60 minutes. Not recommended in the setting of systemic hypotension.

Maintenance: 0.25–0.75 µg/kg/minute continuous infusion.

Table 1 Summary of key points regarding pulmonary vasodilators in PPHN

<table>
<thead>
<tr>
<th>Drug</th>
<th>Administration route/dose</th>
<th>Mechanism of action</th>
<th>Use in PPHN</th>
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<tr>
<td>Oxygen</td>
<td>To achieve PaO2 60–80 mmHg or SpO2 91%–97%</td>
<td>Generates ATP in circulation, enhances NO formation from endothelium</td>
<td>• First line of treatment&lt;br&gt;• Avoid hyperoxia - Worsens pulmonary vascular dysfunction and lung injury</td>
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<tr>
<td>Nitric Oxide</td>
<td>Inhalation: 20 ppm (For more info, refer to iNO Initiation and weaning guideline)</td>
<td>Produced in the vascular endothelium; causes vasodilation through increase in intracellular cGMP in the smooth muscle cells</td>
<td>• Standard treatment for PPHN&lt;br&gt;• Selective pulmonary vasodilator&lt;br&gt;• Need to monitor methemoglobin</td>
</tr>
<tr>
<td>Drug</td>
<td>Route</td>
<td>Details</td>
<td>Side Effects</td>
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| PGI2 (Iloprost) | Inhalation: 0.5–2 µg/kg/dose q2–4 hours as inhalation | Produced from arachidonic acid; causes vasodilatation by increasing intracellular cAMP in lung smooth muscle | • Vasodilatation through alternative and complementary pathway  
• May enhance NO action  
• Nonspecific pulmonary vasodilator  
• May have systemic effects |
| Sildenafil    | PO/NG (Preferred): 0.5–2 mg/kg/dose q6 h  
IV: Loading 0.14 mg/kg/h for 3h followed by 0.07 mg/kg/h | Inhibitor of phosphodiesterase enzyme type V (responsible for cGMP degradation) | • It may potentiate nitric oxide  
• Safe and easy to administer  
• May worsen oxygenation due to vasodilation of unventilated areas |
| Milrinone     | IV: loading: 50 µg/kg over 60 min (Avoid in the setting of systemic hypotension)  
Maintenance: 0.25–0.75 µg/kg/ min OR continuous infusion only at 0.25-0.75 µg/kg/min | Inhibitor of phosphodiesterase enzyme type III (responsible for degradation of cAMP) | • May potentiate the action of prostaglandins  
• Improves right cardiac output by reducing afterload |

8. **Sedation/Paralysis**

In PPHN, episodes of pulmonary vasoconstriction can be induced by external stimuli. Hence, these infants should be nursed in an environment with **minimal stimulation and provided adequate sedation** with fentanyl/morphine. Routine neuromuscular paralysis is discouraged.

9. **Cardiovascular support**

It is a common practice to increase systemic blood pressure to supraphysiological levels above pulmonary arterial pressures to prevent right-to-left shunting and desaturation. Iatrogenic systemic hypertension does not improve oxygen delivery to the brain or myocardium (peductal), but may increase stress on an already failing right ventricle. See below algorithm to determine approach to cardiovascular support in PPHN.
Theoretically, an infant should be placed on extracorporeal membrane oxygenation (ECMO) when the danger of mechanical ventilation (CMV/HFV + iNO and/or other adjuvant therapies) is insufficient to support the patient or outweighs the risks of extracorporeal support. Unfortunately, it is never possible to absolutely determine when that moment occurs, so most centers use some form of numerical scoring (e.g. OI). For neonates deemed ECMO candidates, notify the ECMO team early whenever clinical suspicion for worsening PPHN is high. However, care should be individualized with focus on the entire cardiopulmonary status paying attention to indicators of oxygen delivery, and not necessarily only one blood gas or OI. In general, a patient with severe cardiac dysfunction, significant hypotension with PPHN or acute deterioration would need ECMO sooner. In conditions where cardiac function seems reassuring and the main issue is oxygenation, optimize ventilator management, consider surfactant administration, consider pulmonary vasodilators and hemodynamic support as outlined in Table 1 prior to ECMO. In those instances, if the infant’s cardiac performance is acceptable and there is fair oxygen delivery and organ function, allowing 12-24 hours for agents like Sildenafil, Milrinone and Iloprost to complement iNO and lung recruitment, seem like prudent management strategy. Communicate treatment goals and failure criteria clearly to all team members (APRN, RN, RT, ECMO coordinators, family).
**Follow-up**

Studies report a significant risk of hearing loss and neuro-developmental impairments among survivors of PPHN. Late onset hearing loss has been identified in infants that initially pass their hearing screen prior to discharge from the NICU. These data demonstrate a need for close follow-up of survivors of PPHN as they remain at a high risk for adverse outcomes. Infants with a history of severe PPHN (even the ones going home with no respiratory support or medications) should be followed up in the High-Risk Newborn Clinic to identify long-term deficits. Infants with a history of ECMO, discharged home on oxygen or Sildenafil secondary to PPHN are typically followed up in Complex-Care Clinic.