



**PEDIATRIC NEWBORN MEDICINE CLINICAL  
PRACTICE GUIDELINES**

**Diagnosis and Management of the Infant  
with Suspected or Known Pulmonary  
Hypertension of the Newborn**



## **Clinical Practice Guideline: Diagnosis and Management of the Infant with Known or Suspected Persistent Pulmonary Hypertension of the Newborn (PPHN)**

### **Points of Emphasis/Primary Changes in Practice:**

- PPHN is a constellation of clinical signs that reflect one or more of a number of underlying pathophysiologic mechanisms involving the heart, lungs, and pulmonary and/or systemic vasculature.
- PPHN should be considered in any infant with marked hypoxemia, especially if he/she is of late-preterm or term gestation or is a growth restricted preterm infant.
- For each patient with suspected PPHN, thorough evaluation of potential pathophysiological contributors and confirmation of PPHN is key to individualizing and optimizing the therapeutic approach for the individual infant.
- Therapeutic interventions aim to optimize pulmonary, cardiac, and pulmonary and systemic vascular resistance to enhance pulmonary gas exchange, relax systemic vascular resistance, enhance cardiac output, and support systemic blood pressure. This can be accomplished by therapies that:
  - Reverse hypoxemia and respiratory acidosis by providing adequate respiratory support to the infant with neonatal lung disease and respiratory failure
  - Provide cardiac support to the infant with myocardial dysfunction
  - Relax pulmonary vascular resistance when it is abnormally elevated
  - Enhance systemic vascular resistance when it is inadequate

**Rationale for change: This is a new guideline intended to make care of infants with PPHN optimized and standardized.**

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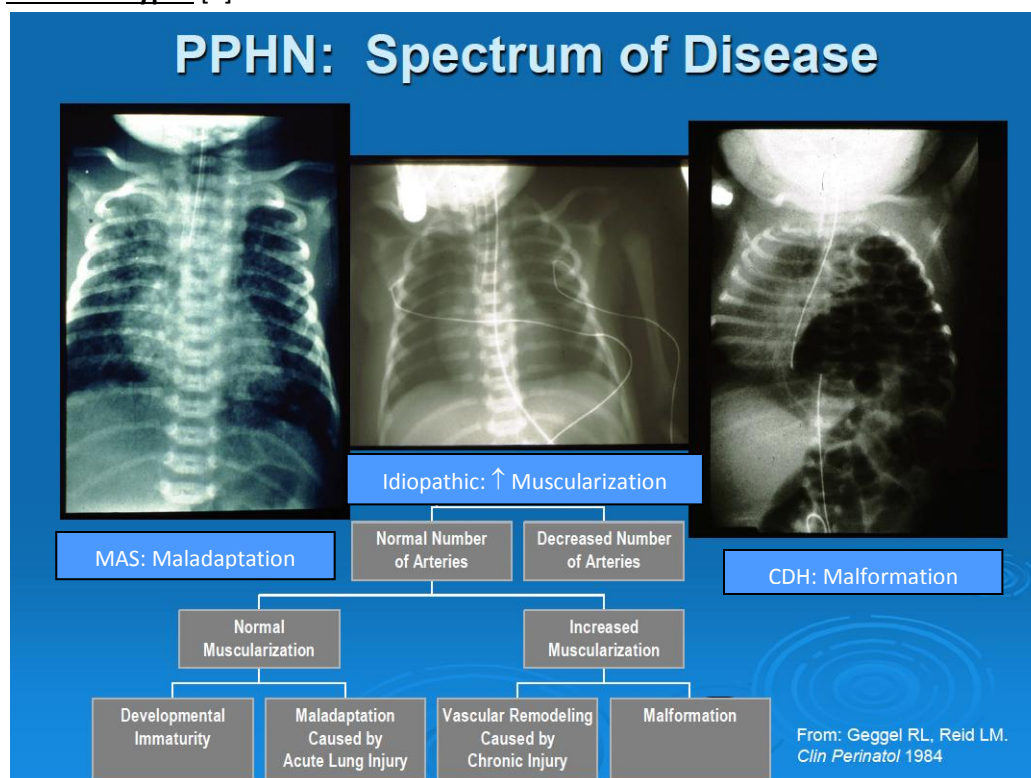
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This is a clinical practice guideline. While the guideline is useful in approaching the care of the infant with persistent pulmonary hypertension, clinical judgment and / or new evidence may favor an alternative plan of care, the rationale for which should be documented in the medical record.

### Brief Description of PPHN

PPHN is a clinical syndrome that represents a common final pathway whose origins might be idiopathic or the product of one or more distinct antecedents, including perinatal depression, meconium aspiration syndrome (MAS), pneumonia, sepsis, surfactant deficiency, or pulmonary hypoplasia due to congenital diaphragmatic hernia (CDH, Potter Syndrome or other conditions that impair fetal lung growth)[1, 2]. All fetuses have high pulmonary vascular resistance (PVR) and, in some infants, idiopathic pulmonary hypertension, characterized by excessive pulmonary arteriolar muscularization, begins before birth[3], sometimes associated with pregnancy exposures such as maternal diabetes, maternal obesity, salicylate exposure, or other factors and leads to remodeling of the fetal pulmonary vasculature [4-6]. Several distinct PPHN subtypes exist, each of which is influenced by the number, muscularity and reactivity of pulmonary vessels[7]. Diagnostic approaches such as careful clinical exam and radiographic and echocardiographic imaging are needed to determine the physiological aberrations that will guide optimal PPHN management for the particular infant.

### PPHN Subtypes [7]



## Management of the Infant with PPHN

Therapeutic interventions aim to optimize pulmonary gas exchange, enhance cardiac output, and thereby relax systemic vascular resistance and support systemic blood pressure. This can be accomplished by therapies that:

- Reverse hypoxemia and respiratory acidosis by providing adequate respiratory support to the infant with neonatal lung disease and respiratory failure
- Provide cardiac support to the infant with myocardial dysfunction
- Relax pulmonary vascular resistance when it is abnormally elevated
- Enhance systemic vascular resistance when it is inadequate

### Respiratory Management: General

Respiratory management should be guided by the specific type of pulmonary parenchymal disease, if any.

- **Mechanical Ventilation**
  - Each patient's oxygen and ventilation requirements should be optimized prior to beginning inhaled Nitric Oxide (iNO) therapy. The specific approach to mechanical respiratory support should be guided by the infant's underlying lung disease, if any.
  - If the baby has pulmonary parenchymal disease and would benefit from lung recruitment, respiratory support via HFV is recommended:
    - Suggest: HFOV for severe surfactant deficiency (primary or secondary) or homogeneous low volume lung disease, or meconium aspiration that has progressed to an ARDS appearance consistent with secondary surfactant deficiency.
    - Suggest: HFJV for meconium aspiration accompanied by air-trapping, pulmonary parenchymal disease associated with airleak (e.g., pulmonary interstitial emphysema or pneumothorax), or aspiration with high lung volume or very heterogeneous lung disease
- **Surfactant**
  - Administration of intratracheal surfactant is indicated for primary or secondary surfactant deficiency. Secondary surfactant deficiency can occur as a consequence of meconium aspiration, sepsis, or pneumonia[8, 9].
- **Oxygenation**
  - To enhance oxygenation (and pulmonary vasodilation) and avoid the dual hazards of hypoxia and hyperoxia, each of which can raise PVR, we recommend keeping post-ductal SpO<sub>2</sub> levels in the 90-95% range.
- **Nitric Oxide**
  - In the presence of documented pulmonary hypertension without complicating structural heart disease, inhaled Nitric Oxide (iNO) is indicated.

## Inhaled Nitric Oxide (iNO)

When administered via the inhaled route, Nitric Oxide (NO) is a selective pulmonary vasodilator and therefore affects vascular resistance only near ventilated alveoli. iNO offers several potentially beneficial effects to infants with cardiorespiratory failure, including bronchodilation and pulmonary vasorelaxation. The mechanism by which iNO accomplishes selective improvement in blood flow to ventilated alveoli is by increasing cyclic GMP in pulmonary vascular smooth muscle. Inhaled nitric oxide has little effect on the systemic vascular resistance because hemoglobin has a high affinity for NO, binds it when it reaches the circulation, and thereby effectively inactivates any potentially adverse iNO-induced systemic vasodilation. The use of iNO in treatment of infants with PPHN has been shown to reduce the composite outcome death or need for extracorporeal membrane oxygenation (ECMO)[10-12].

- **Responsibility:** NICU Respiratory Care Department administers and is responsible for inhaled Nitric Oxide (iNO) therapy, under the direction of the attending neonatologist.
  
- **Indications**
  - Infant  $\geq$  34 weeks gestation with hypoxic respiratory failure.
  - Diagnosis of Persistent Pulmonary Hypertension (PPHN) diagnosed by pre/post differential and confirmed via Echocardiogram (Echo) and the absence of congenital heart disease accompanied by hypoxic respiratory failure.
    - In the presence of clinical signs of PPHN, an Echo is not required for the initiation of iNO however it should be obtained as soon as possible to confirm the diagnosis of PPHN and to rule out congenital heart disease.
  - Oxygen Index (OI)  $> 25$  or in the presence of very rapid deterioration in the presence of OI  $> 15$ 
    - $OI = (MAP \times F_{iO_2} \times 100) / PaO_2$
  
- **Contraindications**
  - Infants with most forms of cyanotic congenital heart disease
    - Caveat: If the baby has CHD, consultation with Cardiology should occur, ideally before using iNO
  - Infants born  $< 34$  weeks of gestation
  
- Caveat: In preterm infants with documented acute PPHN and severe hypoxic respiratory failure, iNO may be considered after reviewing the potential risks and benefits, informing parents, and seeking their consent [13].

- **NO Dosing**
  - **The recommended starting dose of iNO is 20 ppm.**
    - Doses above 20 ppm have not been found, in most infants, to achieve better therapeutic response and are associated with increased risk of toxicity.
    - The desired response is a rapid improvement in oxygenation and an elimination of or significant decrease in the gradient between pre- and post-ductal SpO<sub>2</sub> levels, accompanying reduced pulmonary vascular resistance and right-to-left hemodynamic shunting.
    - If there is a moderate response, the lungs may be under-inflated or the hemodynamics might have changed.
- **Monitoring**
  - Obtain ABG after 15 minutes on iNO therapy.
    - Avoid any manipulation or stresses during this time.
  - Ensure MetHb was obtained at 24 hours of therapy and every 24 hours thereafter.
  - If OI remains > 25 within 2-3 hours of initiating NO therapy and ventilator therapy/adjunctive therapies are optimized, strong consideration should be given to transferring the infant to Boston Children's Hospital (BCH) for **Extracorporeal Membrane Oxygenation (ECMO)**.
    - The baby should remain on iNO throughout the transport to BCH
- **Weaning Strategy**
  - Tapering or 'weaning' of the iNO dose can be commenced once the F<sub>I</sub>O<sub>2</sub> is ≤ 0.60 with a PaO<sub>2</sub> > 60 mmHg and SpO<sub>2</sub> > 92%.
  - From 20 ppm wean NO to 15 ppm and ventilator MAP per clinical assessment.
  - Subsequent weans in iNO dose should occur no sooner than 4 hours apart.
    - iNO should be weaned by gradually dropping the dose if tolerated (20 ppm to 15 ppm, 15 ppm to 10 ppm, 10 ppm to 5 ppm
    - From 5 ppm, the taper is in smaller steps: from 4, 3, 2, to 1 ppm.
  - Unsuccessful Wean: If, after performing an iNO wean, the SpO<sub>2</sub> drops by > 5% and SpO<sub>2</sub> is reading < 92% on > 0.60 F<sub>I</sub>O<sub>2</sub> the wean is considered unsuccessful.
    - In the case of an unsuccessful wean, the baby should be returned to the previous iNO dose (ppm) and/or F<sub>I</sub>O<sub>2</sub> can be adjusted.
  - Establish parameters: SpO<sub>2</sub> 92-97% with PaO<sub>2</sub> ≥ 60mmHg and F<sub>I</sub>O<sub>2</sub> ≤ .60.
    - Hemodynamics and lung volume, as assessed by chest radiograph, should be monitored closely and standard measures taken to optimize oxygenation and ventilation, while avoiding excessive ventilation (PCO<sub>2</sub> <40).

- **Final Wean:**
  - Once the infant is at 1ppm and requiring  $F_{iO_2}$  0.40 or less and has a  $SpO_2 > 92\%$ , a trial off iNO may be attempted.
  - Clinicians may increase the  $F_{iO_2}$  as high as 0.60, if needed, to make this transition.
  - Thereafter, oxygen should be tapered, as tolerated, to keep  $SpO_2$  92-97%
  - If, after one hour,  $F_{iO_2} > 60\%$ ,  $SpO_2$  is labile or if ventilator setting rise, restarting NO at 1ppm should be considered.
    - Another wean can again be attempted in 4-8 hours.
  
- **Hazards and Cautions:** There are several aspects of therapy and potential complications to consider when using iNO therapy. These include:
  - **Interruption of iNO Therapy**
    - Nitric oxide therapy should not be abruptly discontinued.
    - If necessary, to wean rapidly (e.g., in the case of a strict contraindication to iNO):
      - Obtain physician order to wean 2ppm every 10-15 minutes until 0 ppm.
      - Document wean, time,  $SpO_2$ ,  $F_{iO_2}$  and every stage of the dose taper.
  - **$NO_2$  Toxicity:** an undesirable by-product of mixing Oxygen and Nitric Oxide.
    - $NO_2$  should never exceed 1.5 ppm.
    - $NO_2$  levels are likely to be  $<1ppm$  and more negligible as the  $F_{iO_2}$  decreases when used with most neonatal continuous-flow ventilators.
  
  - **Methemoglobinemia:** When NO crosses from the alveoli to the pulmonary bed and binds with hemoglobin, it produces Methemoglobin (MetHgb), interfering with the oxygen-carrying capacity of hemoglobin. The higher the dose of NO the greater the likelihood for an elevated methHgb. This is a more significant concern when iNO exceeds 40 ppm and is less likely to occur at levels in the current recommended range of 20 ppm or less.
    - Monitoring for Methemoglobinemia: MetHgb level is sent 24 hours after iNO is started and every 24 hours thereafter to monitor. If the baby demonstrates unexpected desaturation or other clinical deterioration, MetHgb levels can be sent as clinically necessary.
    - Potential toxic levels are rare during iNO treatment.
    - Concentrations of  $> 5\%$  are treated by:
      - Methylene blue - 1mg/kg IV x 1 – recommended first-line treatment
      - Other Potential Treatments
        - Vitamin C - 500 mg/kg IV x1
        - Blood transfusion
      - Tapering of iNO dose should be considered (see section below on Weaning Strategy for guidance)

- **Rebound Effect:** Because inhaled NO inhibits the endogenous production of NO by the endothelial cells in the blood vessels, when iNO is tapered, a sudden drop in SpO<sub>2</sub> can occur associated with a spike in pulmonary vascular resistance with resultant pulmonary hypertension and resumption of right to left hemodynamic shunting. For this reason, we recommend a very gradual tapering of the iNO dose.
  - **Ventilator:** The respiratory therapist must refer to instructions and guidelines for the specified ventilator use with iNO to determine required precautions, equipment and placement to assure accurate delivery and measurement.
- **Assessment of Outcome:**
  - Outcome assessment is based on oxygenation, Oxygen Index, and trend in Echo findings.
  - An inadequate response may be due to under-recruited lungs, acidemia, or systemic hypotension.
    - In cases of severe pulmonary parenchymal disease, addition of high frequency ventilation (HFV) - (high frequency oscillatory ventilation (HFOV) or high frequency jet ventilation (HFJV)) is likely to optimize delivery of iNO to the alveoli.

### Other Pulmonary Vasodilators

- Although the most well established pulmonary vasodilator therapy for PPHN is inhaled Nitric Oxide (iNO), other therapies that have been reportedly used successfully with PPHN in a limited number of cases include intravenous pulmonary vasodilators (prostacyclin, sildenafil, alprostadil, milrinone), oral phosphodiesterase-5 inhibitors (sildenafil and tadalafil), and an endothelin receptor antagonist (bosentan), although a recent randomized clinical trial showed no benefit of bosentan in PPHN treatment[14].
- Of these agents, the only agent that has been subjected to clinical trial in newborns is **oral sildenafil**. Three small clinical trials were conducted among a total of 77 subjects across the three studies. The data currently are deemed insufficient to warrant routine use. The Cochrane Collaborative has called for larger clinical trials targeting both pulmonary and neurological outcomes [15].
- Clinical trials of modest size support enteral sildenafil for the treatment of PPHN [16]. There also are limited observational data suggesting that **intravenous sildenafil** [17, 18] and **milrinone** (see Vasopressor Section) [19-22], work synergistically with iNO to improve oxygenation but no clinical trial evidence documenting a benefit in mortality or morbidity associated with PPHN.
- Other general vasodilators, including tolazoline and magnesium sulfate have been shown not to be of consistent benefit.



## Inotrope and Vasopressor Management

The goal of inotrope and vasopressor treatment of infants with PPHN is to optimize oxygenation by reducing right-to-left hemodynamic shunting. This is accomplished by directly targeting the underlying hemodynamic disturbances contributing to hypoxemia. In most instances, the primary hemodynamic aberration is abnormally elevated pulmonary vascular resistance; however, systemic hypotension due to poor cardiac output or low systemic vascular resistance also can contribute. The infant's underlying pathophysiology is critically important in determining the appropriate inotrope(s) and/or vasopressor(s).

There are no clinical trials showing an outcome benefit to infants with PPHN of any single or combination of vasopressor or inotropic agents. These medications are best used as supportive therapy of observed physiologic abnormalities complicating PPHN.

Goals of therapy guide the choice of inotropic and vasoactive medications, as noted.

### Improved Cardiac Contractility

**Dobutamine**, a synthetic catecholamine, has been traditionally utilized for cardiac dysfunction in the setting of PPHN. It has predominantly beta<sub>1</sub> adrenergic effects followed by β beta<sub>2</sub> adrenergic effects. It is effective in increasing cardiac contractility and thus may be useful in the setting of PPHN accompanied by decreased cardiac contractility, as often is seen in PPHN in the setting of perinatal depression with. It might be preferred initially for its rapid onset of action, facilitating optimization of alternative inotropes such as milrinone. Because of its beta<sub>1</sub> adrenergic effects, dobutamine is associated with tachycardia and increases myocardial oxygen consumption. Because it has the potential for peripheral vasodilatory effects through beta<sub>2</sub> activity, it has potential to lower systemic blood pressure, especially in PPHN associated with 'warm' septic shock in which peripheral vasodilation is a major contributor to hypotension.

### Improved Cardiac Contractility and Pulmonary Vasodilation

**Milrinone**, a selective phosphodiesterase-3 inhibitor, has both inotropic and vasodilatory properties and modest chronotropic effects. It is associated with less tachycardia than some other agents. It enhances lusitropy, i.e., diastolic filling of the heart, which in turn increases stroke volume and cardiac output. As a phosphodiesterase-3 inhibitor, it reduces the breakdown of cyclic AMP and can act synergistically with cyclic GMP promoters, such as iNO. Milrinone (0.33 to 1 mcg/kg/minute) may be combined with iNO to augment pulmonary vasodilation as well as independently increase right ventricular systolic performance.[19, 20] Systemic vasodilation is the most common, dose-limiting adverse effect. Milrinone should be considered in neonates with PPHN refractory to 100% oxygen and iNO (assuming optimization of ventilatory support, sedation, etc.) with evidence of poor cardiac function on echocardiogram. Milrinone has also been used in extremely low birth weight preterm or growth-restricted infants with acute pulmonary hypertension without adjunctive iNO.[23]

### Improved Cardiac Contractility and Systemic Vasoconstriction

**Dopamine** acts as a dose-dependent renal and mesenteric vasodilator (at low doses via dopaminergic receptors), inotrope (at moderate doses via  $\beta_1$  adrenergic receptors), and vasoconstrictor (at high doses via  $\alpha_1$  adrenergic receptors). Vasoconstrictive effects at high doses on the labile pulmonary vascular bed may counteract the beneficial effects of inhaled vasodilators.[24] Dopamine is a potent constrictor of venous beds and, as such, increases cardiac return.

**Epinephrine** acts as a dose-dependent inotrope (at low doses via  $\beta_1$  and  $\beta_2$  adrenergic receptors) and vasoconstrictor (at high doses via  $\alpha_1$  and  $\alpha_2$  adrenergic receptors). When compared with dopamine in preterm neonates, epinephrine has similar effect on mean arterial pressure, but produces more tachycardia, hyperglycemia, and lactic acidosis.[25] Therefore, epinephrine should generally be reserved for patients with hypotension refractory to dopamine.

Although these non-specific agents may be preferable in the setting of unclear or mixed pathophysiology, clinical data may inform utilization of one or more of the specific therapies discussed below:

### Systemic Vasoconstriction

Because of the need to reverse extra-pulmonary right-to-left hemodynamic shunts that contribute to hypoxemia in the setting of PPHN, vasopressor therapy in infants with PPHN has traditionally been associated with improved oxygenation.

**Norepinephrine** (0.05 to 1 mcg/kg/minute) is a potent alpha adrenergic agent that stimulates both  $\alpha_1$  and  $\alpha_2$  adrenergic receptors (as well as  $\beta_1$  receptors), raising SVR disproportionately to PVR. Data advocating the use of norepinephrine in neonates is limited. One observational study suggests it might improve oxygenation in some infants with PPHN; the same study showed no effect or worsening in other infants [26]. Its strong alpha adrenergic effects cause vasoconstriction and whether the pulmonary vascular bed will be affected more, less or the same as the systemic system is unpredictable. Norepinephrine causes less tachycardia than epinephrine and, therefore, might prove useful in the subset of infants with tachycardia and marked peripheral vasodilation (e.g., warm shock) however should be used with caution and with careful attention to the infant's pulmonary vascular response and oxygenation.

**Arginine vasopressin (AVP)**, a  $V_1$  receptor agonist, selectively vasodilates coronary, cerebral, pulmonary, and renal vascular beds while causing vasoconstriction in other systemic vascular beds.[27] There are few published studies of the use of AVP in neonates. Limited observational data suggest that low-dose AVP (0.1 milliunits/kg/minute to 1.2 milliunits/kg/minute) might improve blood pressure, urine output, and oxygenation index in some infants with PPHN.[27-29] AVP may be the preferred vasopressor in neonates with PPHN who are hypotensive as a result of peripheral vasodilation, such as septic shock because it inhibits excessive endogenous nitric oxide release that occurs in septic shock. However, in decreasing production of cGMP, pulmonary nitric oxide production also might be affected. [REF] Another known complication of AVP is fluid retention and associated hyponatremia.

	Dose	Primary Receptor Effects	Indications	Potential Side Effects
<b>Primary Goal:</b>				
<b>Increase Cardiac Output</b>				
Dobutamine	5 – 20 mcg/kg/min	$\beta_1, \beta_2$	Cardiac dysfunction requiring rapid resolution	Tachycardia (++) Systemic vasodilation
<b>Increase Cardiac Output and Decrease Pulmonary Vascular Resistance</b>				
Milrinone	0.33 – 1 mcg/kg/min	PDE <sub>3</sub> inhibition	Cardiac dysfunction Pulmonary vasodilation	Systemic hypotension
<b>Increase Both Cardiac Output and Systemic Vascular Resistance</b>				
Dopamine*	0.5 – 2 mcg/kg/min	Dopaminergic	Poor urine output	Tachycardia (++) Pulmonary vasoconstriction
	2 – 6 mcg/kg/min	$\beta_1$ , dopaminergic	Cardiac dysfunction	
	> 6 mcg/kg/min	$\alpha_1, \beta_1$ , dopaminergic	Hypotension	
Epinephrine*	0.05 – 0.1 mcg/kg/min	$\beta_1, \beta_2$	Cardiac dysfunction	Tachycardia (+++) Lactic acidosis Hyperglycemia
	0.1 – 0.5 mcg/kg/min	$\alpha_1, \alpha_2, \beta_1, \beta_2$	Hypotension refractory to dopamine	
<b>Increase Systemic Vascular Resistance</b>				
Norepinephrine	0.05 – 0.5 mcg/kg/min	$\alpha_1, \alpha_2, \beta_1$	Hypotension	Tachycardia (+) Pulmonary vasoconstriction
Vasopressin	0.1 – 1.2 mU/kg/min	V <sub>1</sub> , V <sub>2</sub>	Hypotension	Hyponatremia
*Dose ranges based on limited evidence and vary between patients				

## **Extracorporeal Membrane Oxygenation**

Extracorporeal Membrane Oxygenation (ECMO) is reserved for infants with PPHN who fail to respond to maximal medical management and meet criteria, including achieving an Oxygenation Index (OI) of >30 on two arterial blood gases obtained at least 30 minutes apart.

- If an infant is at or approaching ECMO criteria, consultation should be sought with the Medical Intensive Care Unit (MICU) attending intensivist and surgeon-of-the-day at Boston Children's Hospital.
- Whenever possible, the infant should be transferred for ECMO when neonatologist and intensivist and surgeon agree that ECMO is indicated and before the infant is in extremis.

## **Management of Pain, Discomfort, and Agitation**

Because catecholamine release activates pulmonary  $\alpha$ -adrenergic receptors, thereby potentially raising PVR, every effort should be made to minimize pain, discomfort, and overstimulation of infants with PPHN.

### ***Nonpharmacologic Pain Management:***

Measures to enhance the infant's comfort and lower his/her stress include lowering light levels and background noise. In addition, comfortable positioning of the infant, addition of circumferential 'nest', and minimizing tactile stimulation and loud talking also are helpful. Most babies with PPHN will be NPO, however, they can receive mouthcare with sucrose 20% oral solution or breastmilk on a cotton swab to provide potential nonpharmacological comfort.

### ***Pharmacologic Pain Management:***

An opioid analgesic that minimizes pain and might reduce adrenergic output, such as fentanyl (1 to 4  $\mu\text{g}/\text{kg}/\text{hour}$  infusion), is a useful adjunct therapy in PPHN management. Morphine sulfate (0.05 to 0.1  $\text{mg}/\text{kg}/\text{hour}$  infusion) is an alternative analgesic for infants who are not hypotensive.

### ***Management of Agitation:***

Agitation may complicate PPHN management, especially in achieving synchrony with mechanical ventilation. The first line in management of agitation is to ensure adequate analgesia and that mechanical issues (e.g., misplaced endotracheal tube) are not contributing. Addition of Midazolam (0.2  $\text{mg}/\text{kg}$  IV x1, per BWH NICU DAG) adds synergy with analgesia. If ongoing non-opioid sedation is required, Midazolam (0.06  $\text{mg}/\text{kg}/\text{hr}$  infusion) also may be useful, in the absence of systemic hypotension. Infants with PPHN rarely require continuous muscle relaxation via neuromuscular blockade. Although not routinely recommended, brief neuro-muscular relaxation occasionally is needed to achieve respiratory synchrony with mechanical ventilation. Treatment with Rocuronium (0.6  $\text{mg}/\text{kg}$  IV x1, per BWH NICU DAG) may be used to achieve neuromuscular relaxation and respiratory synchrony when combined with an IV infusion of analgesic and other measures to ensure control pain and discomfort.



### **Other Therapeutic Considerations**

**Metabolic Management:** Biochemical abnormalities might contribute to right-to-left shunting by impairing cardiac function. Maintenance of normal glucose and ionized calcium levels is important in treating infants with PPHN in order to provide adequate substrates for myocardial function and appropriate responses to inotropic agents.

Acidemia should be treated by identifying and treating the underlying cause (e.g., respiratory, underperfusion, volume depletion, cardiac dysfunction). The use of agents such as sodium bicarbonate or THAM is discouraged [30-35].

**Avoiding Polycythemia:** Hyperviscosity, associated with polycythemia, increases PVR and is associated with release of vasoactive substances through platelet activation. Partial exchange transfusion to reduce the hematocrit to 50% to 55% should be considered in an infant with PPHN whose central hematocrit exceeds 65%.

### **PPHN Among Infants with Encephalopathy Receiving Therapeutic Hypothermia**

Infants undergoing therapeutic hypothermia also might have coinciding clinical conditions (e.g., meconium aspiration syndrome) that place them at risk for PPHN. A recent Cochrane Database review reported on the effect of hypothermia on PPHN. There were four trials (614 patients) that included this outcome. These data showed no increased risk of PPHN or need for iNO therapy in patients receiving therapeutic hypothermia [36]. Therefore, hypothermia should be continued in patients with PPHN. Blood gas analysis must be corrected for the infant's degree of hypothermia.

Morphine is routinely used in patients undergoing therapeutic hypothermia. However, it is administered at low doses because of cumulative effects in the setting of hypothermia, which can lead to hypotension. Therefore, increased morphine dosing is not recommended and fentanyl should be considered as the primary drug of choice for sedation in patients undergoing therapeutic hypothermia who are being treated for PPHN.



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