PERSISTENT PULMONARY HYPERTENSION OF THE NEWBORN (PPHN)

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A) Introduction :

Neonatal respiratory failure affects 2% of all live births and is responsible for more than one third of all neonatal deaths. Persistent pulmonary hypertension of the newborn (PPHN) is a frequent complication of respiratory disease in neonates. PPHN complicates the course of approximately 10% of infants with respiratory failure and can lead to severe respiratory distress and hypoxemia associated with considerable mortality and morbidity[1]. Recent estimates suggest an incidence for PPHN of 1.9/1000 live births[1]. Newborns with PPHN are at risk for severe asphyxia and its complications, including death, chronic lung disease, neurodevelopmental sequelae, and other problems.

B) Definition:

PPHN is a cardiopulmonary disorder characterized by labile systemic arterial hypoxemia secondary to elevated pulmonary vascular resistance (PVR) in relation to systemic vascular resistance (SVR) with resultant right-to-left shunting through persistent fetal channels such as the ductus arteriosus and foramen ovale, bypassing the lungs. Inadequate pulmonary blood flow leads to refractory hypoxemia, respiratory distress, and finally acidosis.

C) **Pathophysiology**: The pathophysiology of PPHN can be discussed under 3 subheadings – changes in pulmonary vasculature, lung and heart (figure 1).

a. **Pulmonary vasculature**: During fetal life, pulmonary blood flow (Qp) is low (5-10% of combined ventricular cardiac output [CO] from both ventricles in lambs and 13-21% in humans). This is due to high PVR and the presence of shunts (foramen ovale, ductus arteriosus) which permit blood to bypass the pulmonary vascular bed (figure 1). At birth, PVR decreases significantly, Qp increases to 100% of right ventricular output and, by 24 hours after birth, pulmonary artery pressure (PAP) typically decreases to about 50% of systemic arterial pressure. In infants with PPHN, pulmonary vascular transition is not successful resulting in persistently elevated PVR. In cases of severe PPHN, pulmonary vasculature demonstrates increased muscularization of

pulmonary arteries and peripheral extension of vascular smooth muscle cell layer.

b. **Lungs**: PPHN is classified as secondary when there is associated lung disease (figure 2) such as meconium aspiration syndrome (MAS), respiratory distress syndrome (RDS), pneumonia or sepsis, transient tachypnea of newborn (TTN) and congenital diaphragmatic hernia (CDH). In these conditions, the lung parenchymal pathology leads to PPHN. If there is no underlying lung disease and PPHN is predominantly due to vascular changes, it is referred to as primary, idiopathic or black-lung PPHN (absence of lung disease and less vascularity makes the lungs look black on chest X-ray).

c. **Cardiac changes**: Extrapulmonary right-to-left shunting of blood secondary to high PVR is the hallmark of PPHN. Right-to-left or bidirectional shunt is commonly seen at the level of patent foramen ovale (PFO, from right atrium to left atrium) or across the patent ductus arteriosus (PDA, from pulmonary artery to aorta). Elevated pulmonary arterial pressure can also result in pulmonary insufficiency, right ventricular hypertrophy (and dysfunction), tricuspid regurgitation, bowing of the inter-ventricular septum to the left and left ventricular dysfunction. The absence of structural heart disease and presence of some of the above findings on echocardiogram confirms the diagnosis of PPHN.

D) **HEMODYNAMIC CHANGES (figure 1)** –

a. Elevated PVR results in shunting of poorly oxygenated blood across the PDA and PFO. If right-to-left shunt occurs predominantly at the ductal level, differential cyanosis (the lower extremities are more cyanotic with lower pulse oximeter readings compared to the head and upper extremities) is present. It is important to evaluate patients with suspected PPHN by dual pulse oximetry. The preductal pulse oximetry should always be placed on the right upper extremity as the left subclavian artery may be postductal in some infants. If the shunt across the PFO is the primary cause of hypoxemia, both upper and lower extremities will have similar low oxygen saturations by pulse oximetry (SpO_2).

b. Relatively low systemic blood pressure and systemic vascular resistance (SVR) are commonly observed in PPHN especially in the presence of sepsis. Low SVR enhanced right-to-left shunting in the presence of high PVR (figure 3). Maintaining normal systemic blood pressure is important during management of PPHN. However, elevating systemic blood pressure to supraphysiologic values using vasoconstrictor medications to limit shunting in the presence of elevated PVR is likely to be counterproductive for the following reasons.
    i. Most vasoconstrictor medications such as dopamine are not selective to systemic vasculature and cause significant pulmonary vasoconstriction further elevating PVR.
    ii. Very high SVR can result in left ventricular strain and dysfunction.
    iii. PDA and PFO act as pop-off valves in the presence of high PVR. Attempts to limit shunt and increase Qp in the presence of a constricted pulmonary vascular circuit is likely to lead to pulmonary endothelial dysfunction and exacerbation of PPHN. Increasing Qp in PPHN should preferably be achieved by dilating the pulmonary vascular bed.

E) **Mechanism of PPHN:** Based on etiology PPHN can be characterized as one of four types (figure 4):

a. ***Maladaptation*** : Secondary to lung parenchymal diseases such as meconium aspiration syndrome (MAS), respiratory distress syndrome (RDS), or pneumonia;
b. ***Maldevelopment***: Lung with normal parenchyma and remodeled pulmonary vasculature, also known as idiopathic PPHN or black-lung PPHN.
c. ***Underdevelopment***: Hypoplastic vasculature as seen in CDH and other causes of pulmonary hypoplasia (oligohydramnios secondary to Potter's Syndrome, renal disease or chronic leakage of amniotic fluid).
d. ***Intrinsic obstruction***: high viscosity due to polycythemia resulting in intravascular obstruction and elevated PVR.

F) **Etiology of PPHN:**

a. *Meconium aspiration syndrome (*MAS) in newborns leads to acute respiratory failure with a mortality of up to 10%[2]. Meconium stained amniotic fluid (MSAF) complicates 3-14% of pregnancies. Approximately 5-10% of neonates born through MSAF develop MAS. Meconium causes chemical pneumonitis and surfactant inactivation that leads to ventilation-perfusion mismatch. Resulting hypoxemia and hypercarbia cause pulmonary vasoconstriction and PPHN. The incidence of MAS has decreased in developed countries but continues to be prevalent in resource-limited settings often associated with asphyxia[3]. Management of a neonate born through meconium stained amniotic fluid has changed dramatically over the last decade. Amnioinfusion, suctioning at the perineum and tracheal suctioning in vigorous infants did not alter the incidence of MAS in multicenter randomized trials [4-6]. The current guidelines recommend tracheal suctioning only if the infant born through meconium stained amniotic fluid is not vigorous at birth[7]. Recent data from a randomized trial[8,9] and a translational study have pushed further to question the benefit of tracheal suctioning of meconium at birth even if the newborn is not vigorous[10,11]. Additional studies are required to evaluate the effect of tracheal suctioning in MAS and the incidence and severity of PPHN.

b. *Pneumonia and sepsis* often present with elevated PVR associated with systemic hypotension and decreased SVR. In addition, some infants with sepsis have myocardial dysfunction resulting in pulmonary venous hypertension due to elevated left atrial pressures[12].

c. *Pulmonary hypertension in premature infants:* Although PPHN is traditionally considered a disease of term and late preterm infants, it is increasingly being diagnosed in extremely preterm infants.[13] Pulmonary hypertension in preterm infants has a bimodal postnatal age distribution. Some preterm infants with RDS present with PPHN in the first few days of life[14] while preterm infants with bronchopulmonary dysplasia (BPD) may be diagnosed with pulmonary hypertension later in the hospital course or after discharge from the Neonatal Intensive Care Unit (NICU). Preterm infants

with fetal growth restriction and born after prolonged rupture of membranes are at higher risk for developing pulmonary hypertension.[15] Pulmonary vascular disease significantly increases morbidity and mortality in BPD[16].

d. *Maldevelopment / Idiopathic PPHN ("Black-lung PPHN):* Some cases of PPHN are not secondary to parenchymal lung disease and are referred to as idiopathic or "black-lung" (referring to paucity of pulmonary vascularity and absence of lung disease) PPHN. Idiopathic pulmonary hypertension is secondary to remodeled pulmonary arteries, characterized by smooth muscle hyperplasia and extension of smooth muscle in intra-acinar arteries. The abnormal structural remodeling of the pulmonary circulation as seen in PPHN affects the responsivity to vasodilator stimuli, and may prevent the access of NO to the vascular smooth muscle cells[17]. Maternal use of NSAIDs during third trimester of pregnancy can lead to premature closure of ductus arteriosus [18] and "black-lung" PPHN although this association has recently been questioned.

e. *Congenital diaphragmatic hernia (CDH)* is a muscle defect between the abdomen and the thoracic cavity and is the most important cause of pulmonary hypoplasia resulting in PPHN. The muscle defect leads to a herniation of the abdominal viscera into the thoracic cavity. CDH occurs in 1/2,500 to 5,000 live births. CDH has a mortality rate of 20-30% and the degree of associated pulmonary hypoplasia and the severity of pulmonary hypertension remain the major determinants of survival[19]. Pulmonary hypoplasia secondary to renal dysfunction and oligohydramnios or thoracic dystrophy can be associated with pulmonary hypertension [20-22]. Prolonged rupture of membranes is also a risk factor for pulmonary hypertension in preterm infants [23].

f. *Alveolar capillary dysplasia (ACD):* Alveolar capillary dysplasia is generally associated with malalignment of the pulmonary veins (ACD/MPV) and produces respiratory failure early in life and carries a mortality rate that approaches 100%[24]. Recent reports of infants presenting with fulminant

symptoms of ACD/MPV well beyond the neonatal period, even as late as 7 months of age, have begun to emerge, challenging the established phenotype and offering the possibility that long-term survivors with milder forms of the disease may exist[25]. A lung biopsy to rule out ACD should be considered for neonates who do not respond to conventional medical management or fail attempts at ECMO decannulation.

G) **CLINICAL FEATURES:**

a. Index of suspicion – A neonate with *labile hypoxemia* (SpO_2 fluctuating without any significant changes in ventilation settings and with minimal stimulation) out of proportion to lung disease should be suspected to have PPHN. These infants readily drop their SpO_2 with routine handling such as suctioning, diaper change, stimulation by parents etc., Other factors consistent with the diagnosis of PPHN include:

i. Oxygen requirement disproportional to lung disease and pressure settings on the ventilator

ii. History of a disease such as asphyxia, MAS or CDH commonly associated with PPHN.

iii. Differential cyanosis – SpO_2 in the right arm is higher than values obtained from the legs.

iv. Onset of symptoms within the first few hours of life (late onset is common in preterm infants and infants with CDH).

v. Cardiac examination demonstrates right ventricular heave, a loud second heart sound and a harsh systolic murmur heard best at the left lower sternal border secondary to tricuspid regurgitation.

b. Diagnosis: In a term or near-term infant with respiratory distress, the initial evaluation should include a chest X-ray and an arterial blood gas. Hypoxemia disproportionate to the severity of

parenchymal disease on a chest radiograph should suggest idiopathic PPHN (or cyanotic heart disease). Evidence of the underlying parenchymal disease such as RDS, MAS, or pneumonia may be seen on chest X-ray in secondary PPHN. A complete blood count with differential is often obtained on admission to evaluate for high hematocrit level (polycythemia and increased viscosity contributing to intrinsic vascular obstruction) and to evaluate the risk of underlying infection.

c. **Differential cyanosis and hyperoxia-hyperventilation test:** Differentiating PPHN from cyanotic CHD soon after admission is of paramount importance. Preductal and postductal oxygen saturation/PaO_2 measurements are used to differentiate PPHN from structural heart disease. Saturation differences of > 5-10% or PaO_2 differences of 10-20 mmHg between right upper limb and lower limbs are considered significant. In neonates with PPHN and atrial-level right-to-left shunting without a significant ductal shunt, both the right arm and the right leg saturations will be low. Conversely, babies with PDA and coarctation of the aorta might have differential cyanosis. In PPHN, hypoxemia is often labile unlike fixed hypoxemia seen in cyanotic CHD.

    i. **Hyperoxia test** (obtaining an arterial gas after 10-15 minutes of exposure to 100% oxygen) may help in differentiating pulmonary parenchymal or respiratory depression (where PaO_2 typically increases > 150 mmHg) from cyanotic heart disease or PPHN (PaO_2 does not exceed 150 mmHg). False positive conclusion may result from severe parenchymal disease, especially if oxygen is delivered through a hood without any pressure. False negative conclusion may be derived in some cases of PPHN and total anomalous pulmonary venous return (TAPVR) due to oxygen-induced pulmonary vasodilation and alteration of shunts.

    ii. **Hyperoxia-hyperventilation** (hyperoxia and alkalosis to induce pulmonary vasodilation and improve PaO_2) may be helpful in some cases of PPHN. Infants with reactive pulmonary vasculature and PPHN may improve oxygenation in response to alkalosis. Infants with severe

PPHN with remodeled pulmonary vasculature and cyanotic CHD patients do not respond to hyperoxia and hyperventilation. It is important to remember that hyperventilation induced hypocapnia can cause cerebral vasoconstriction. These tests can be avoided by confirming elevated pulmonary pressures by an early echocardiogram.

d. **Chest X-ray** is useful in diagnosing the primary lung condition. Classic description of radiologic appearance of various neonatal respiratory disorders is given below:

   i. Grainy – often with low expansion: RDS (may be pneumonia)

   ii. Patchy – Pneumonia

   iii. Fluffy – often with hyperexpansion: MAS

   iv. Streaky – often with hyperexpansion: Retained lung liquid or TTN

   v. Black – dark lung fields: primary or idiopathic PPHN or pulmonic stenosis (including tetralogy of Fallot); similar picture is also seen in pneumothorax

   vi. White-out – collapse/ atelectasis; severe RDS or pneumonia; also infradiaphragmatic TAPVR with obstruction

   vii. Bubbly – pulmonary interstitial emphysema (PIE)

e. **Echocardiography** is gold standard to confirm the diagnosis, and to monitor the efficacy of specific therapeutic interventions[26]. Measurement of the direction of ductal and foramen ovale shunt, flattening or left-deviation of the interventricular septum and tricuspid regurgitation velocity with simultaneous systemic blood pressure measurement provides an indication of right-sided pressures and hemodynamic physiology. Echocardiographic features suggestive of PPHN include:

i. Absence of structural heart disease

ii. Dilated right ventricle (hypertrophy in long-standing PPHN)

iii. Dilated right atrium

iv. Septal bulge to left

v. Tricuspid regurgitation (TR) and pulmonary insufficiency

vi. Pulmonary pressures 30 to 60 mm Hg. Pulmonary systolic pressure is similar to the right ventricular systolic pressure (RVSP) and is detected by the modified Bernoulli equation: RVSP= $4v^2$ TR+ RAP; where v is the velocity of tricuspid regurgitation in m/sec and RAP is the right atrial pressure in mmHg.

f. **B-type natriuretic peptide (BNP)** concentrations in plasma correspond well with echocardiographic findings of ventricular strain[27]. Reynolds et al suggested BNP as an early indicator of PPHN in the presence of respiratory illness in neonates without CHD[28]. BNP has been proposed as a biomarker in PPHN, especially to assess efficacy of treatment and to predict rebound PPHN[28,29]. However, its value in the practical management of PPHN is presently unclear. Some centers obtain serial (monthly) echocardiograms with BNP levels to screen for pulmonary hypertension associated with BPD in preterm infants.

H) **Severity of PPHN** is commonly assessed by oxygenation index (OI) and Alveolar-arterial oxygen difference ($AaDO_2$).

a. **Oxygenation index** (OI, figure 5) is more commonly used during medical management of PPHN since it takes ventilator support into the consideration and is calculated as OI = MAP × FiO_2 × 100/ PaO_2 where MAP is the mean airway pressure in cmH_2O, FiO_2 is the fraction of inspired oxygen, and PaO_2

is partial pressure of oxygen in arterial blood (in mmHg).

i. Based on OI, hypoxemic respiratory failure can be classified into

1. Mild (OI ≤ 15),
2. Moderate (OI > 15 to 25),
3. Severe (OI 25 to 40) and
4. Very severe (OI > 40) [30].

ii. Disadvantages of OI include:(a) it can be manipulated by changing FiO_2 or MAP or based on the type of ventilator; (b) it requires arterial access; (c) the value may vary based on the site of arterial access – right radial (preductal) vs. umbilical or posterior tibial (postductal).

iii. Oxygen saturation index (OSI): More recently, oxygen saturation index (OSI = MAP × FiO_2 × 100 / Preductal SpO_2) has been used in patients without arterial access[31]. If preductal SpO_2 is in the 70-99% range, OSI corresponds to approximately half of OI (OSI of 8 = OI of 16) [32]. More research evaluating the clinical role for this non-invasive index is needed prior to its widespread use (figure 5) .

b. **Alveolar-arterial oxygen gradient ($AaDO_2$)** is the difference between Alveolar partial pressure of oxygen and arterial partial pressure of oxygen and is calculated using the following formula. $AaDO_2 = (ATM - P_{H_2O}) \times FiO_2 - PaO_2 - PaCO_2 / RQ$ where ATM is the atmospheric pressure, which is usually equal to 760 mmHg at sea level but needs to be adjusted in high altitude. P_{H_2O} is the pressure of water vapor in one ATM, which is usually considered to be 47 mmHg. RQ is the respiratory quotient and equal to 1 if the energy source is purely carbohydrate or equal to 0.8 when

the nutritional source is a combination of carbohydrate, protein, and lipid. The disadvantage of $AaDO_2$ is that it does not take ventilator pressure into account.

l) **Management:**

a. Management of PPHN centers around three key issues (figure 6):

   i. **Optimizing oxygenation and ventilation (lung function)**

   ii. **Optimizing hemodynamics – systemic blood pressure (cardiac function)**

   iii. **Pulmonary vasodilator therapy**

b. The severity of PPHN can range from mild hypoxemia with minimal respiratory distress to severe hypoxemia and cardio-pulmonary instability that requires intensive care support. Infants with PPHN require supportive care tailored to the degree of hypoxemia and physiologic instability. PPHN is often associated with underlying parenchymal lung disease or systemic illness; therapy should target the underlying disease (such as antibiotics for sepsis).

c. Mild cases of PPHN with minimal or no respiratory distress can be detected in the newborn nursery either following a desaturation episode or by low postductal oxygen saturation detected on routine oximetry. These infants can be managed with supportive care and oxygen supplementation. Close monitoring is important as some of these infants may rapidly deteriorate and require non-invasive ventilation or intubation and mechanical ventilation. Infection should be considered as elevated pulmonary pressures (often associated with systemic hypotension) can be the presenting clinical feature of pneumonia or sepsis.

d. S*upportive care:* It is important to maintain normothermia and correct metabolic and hematologic abnormalities such as hypoglycemia, hypocalcaemia, acidosis and polycythemia.

i. Sedation may be necessary to provide comfort and decrease oxygen consumption from agitation in hypoxemic or ventilated patients. A combination of fentanyl (1-2 mcg/kg/dose or morphine 0.05 to 0.1 mg/kg/dose and/or midazolam 0.1 mg/kg/dose q 2-4 h PRN are commonly used. Close attention to systemic blood pressure is necessary while using narcotic medications.

ii. Paralysis should be avoided if possible, as it has been associated with increased mortality[1]. The goal of medical management is to selectively reduce pulmonary arterial pressure and to maintain systemic blood pressure.

e. *Correction of metabolic acidosis*: Hyperventilation and alkali infusions to maintain an alkaline pH were strategies previously in use but are now under question as concerns of impaired cerebral perfusion and sensorineural deafness with respiratory alkalosis have been raised[33,34]. Similar or improved outcomes with less chronic lung disease were also observed in infants with PPHN maintaining normal P_{CO_2} (45–60 mmHg)[35,36]. Alkali infusion was associated with increased use of ECMO and need for oxygen at 28 days[1]. Thus, lack of convincing data to support hyperventilation/alkali infusion therapy along with better therapeutic options including inhaled vasodilators have led to decreased use of alkalosis. Most centers avoid acidosis based on animal studies demonstrating exaggerated hypoxic pulmonary vasoconstriction with pH < 7.25[37]. We recommend maintaining pH > 7.25, preferably 7.30 to 7.40 during the acute phase of PPHN. If severe metabolic acidosis is present and $PaCO_2$ is within normal limits, 1-2 mEq/kg of sodium bicarbonate may be administered by slow intravenous infusion.

f. **Mechanical ventilation:** Given the important contribution of parenchymal lung disease in many cases of PPHN, pharmacologic pulmonary vasodilation alone without lung recruitment would not be expected to cause sustained clinical improvement[38,39].

i. *Non-invasive ventilation*: Mild cases of PPHN can be managed with CPAP, low-flow nasal cannula (usually defined as ≤ 2 LPM of humidified gas), high flow intensely humidified nasal cannula (usually defined as ≥ 2 LPM of warm, intensely humidified gas) or non-invasive ventilation. During CPAP and non-invasive ventilation, settings are chosen based on severity of lung disease – a PEEP/CPAP of 4 cmH_2O is adequate for black-lung PPHN without parenchymal lung disease, 4-7 cmH_2O is usually adequate for parenchymal lung disease although higher pressures may be required if the lungs are poorly compliant as in RDS or pneumonia. The goal is to achieve 8-9 rib expansion (along the highest margin of the diaphragm on an AP chest film).

ii. *Intubation:* Indications for intubation and mechanical ventilation include:

    1. Moderate to severe respiratory distress with poor air entry, intercostal and subcostal retractions.

    2. Inspired oxygen concentration > 60% to maintain preductal $SpO_2 \geq 90\%$

    3. $PaCO_2 > 60$ mmHg or pH < 7.25

    4. Severe parenchymal lung disease requiring surfactant administration

iii. *Surfactant* - Exogenous surfactant therapy improved oxygenation and reduced the need for extracorporeal membrane oxygenation (ECMO) in neonates with PPHN secondary to parenchymal lung disease such as RDS, pneumonia/sepsis or MAS[40]. A multicenter trial demonstrated that this benefit was greatest for infants with mild to moderate disease, and with an OI of 15-25[41]. A *post-hoc* analysis of the randomized trial of early nitric oxide use showed that early use of surfactant prior to randomization decreased the risk of death/ECMO especially in infants with parenchymal lung disease[42]. Over the past decade,

the use of surfactant in treating secondary PPHN and respiratory failure has increased and might have contributed to improved effectiveness of iNO with reduced need for ECMO. Surfactant inactivation and deficiency are observed in many neonatal respiratory disorders such as pneumonia, RDS and MAS. We recommend that infants with PPHN secondary to parenchymal lung disease receive a dose of surfactant rich in surfactant protein-B (SP-B, such as calfactant - Infasurf® [ONY Inc, Amherst NY] or poractant-α - Curosurf® [Chiesi Farmaceutici, S.p.A, Parma, Italy]) especially if OI ≥ 15.

iv. *"Gentle" ventilation strategies* with optimal PEEP, relatively low PIP or tidal volume and a degree of permissive hypercapnia are recommended to ensure adequate lung expansion while limiting barotrauma and volutrauma[36,43]. Low PEEP increases alveolar collapse and increases PVR by kinking alveolar pulmonary vasculature. Extremely high PEEP decreases venous return and causes over-distension and compresses extra-alveolar vessels and increases PVR. Optimal PEEP maintains the lungs at functional residual capacity (FRC) during expiration and results in lowest PVR. A tidal volume of 4-5 ml/kg is targeted.

v. *High frequency ventilation:* In newborns with severe lung disease, high frequency ventilation is frequently used to optimize lung inflation and minimize lung injury[44]. If a PIP of > 28 cmH_2O or tidal volumes > 6 ml/kg are required to maintain $PaCO_2$ < 60 mmHg on conventional ventilation, we recommend switching to high frequency (jet or oscillator) ventilation. In clinical studies using iNO, the combination of high frequency ventilation and iNO resulted in the greatest improvement in oxygenation in PPHN associated with diffuse parenchymal lung disease such as RDS and pneumonia[45,46].

vi. **Oxygen** is a specific and potent pulmonary vasodilator and increased oxygen tension is an important mediator of reduction in PVR at birth. Avoiding hypoxemia by mechanical

ventilation with high concentrations of oxygen used to be a mainstay of PPHN management. Fetal lamb studies demonstrate that increased fetal oxygen tension augments endogenous NO release[47] and increased pulmonary blood flow induced by rhythmic distention of the lung and oxygen are mediated in part by endogenous NO[48]. However, it has also been shown that brief exposure to 100% oxygen in newborn lambs results in increased contractility of pulmonary arteries[49], reduces response to iNO[50,51] and increases the potential for oxidative stress[52]. In addition to direct inactivation of NO, ROS can decrease eNOS activity, sGC activity and increase PDE5 activity, resulting in decreased cGMP levels and potentiation of pulmonary vasoconstriction. In the ovine ductal ligation model of PPHN, maintaining oxygen saturations in the 90-97% range results in low PVR[51]. We recommend maintaining preductal oxygen saturations in low to mid-90s with PaO_2 levels between 55 and 80 mmHg during management of infants with PPHN.

J) **Inhaled Nitric Oxide (iNO)** is a potent vasodilator that has also been shown to be an important regulator of vascular tone, growth and remodeling[53]. In the endothelium, NO is produced from the terminal guanidino nitrogen of L-arginine on its conversion to L-citrulline by the enzyme eNOS in a reaction that requires molecular oxygen[53]. As an inhaled vasodilator, iNO selectively dilates the pulmonary circulation without a significant decrease in systemic blood pressure (*selective effect of iNO,* figure 7*).* Inhaled NO is also preferentially distributed to the ventilated segments of the lung, resulting in increased perfusion of the ventilated segments, optimizing VQ match (*micro-selective effect of iNO)*. Studies have shown that iNO therapy causes marked improvement in oxygenation in term newborns with PPHN[54]. Multicenter randomized clinical studies subsequently confirmed that iNO therapy reduces the need for ECMO in late-preterm and term neonates (>34 weeks gestation) with hypoxemic respiratory failure[55-57].

a. *Initiation of iNO*: There has been a debate regarding the timing of initiation and optimum starting dose of iNO in PPHN. Konduri et al initially demonstrated that earlier initiation of iNO with an OI of

15-25 did not reduce the need for ECMO but may have a tendency to reduce the risk of progression to severe hypoxemic respiratory failure[58]. *Post-hoc* analysis of the same study suggested that the use of surfactant prior to randomization and enrollment (and use of iNO) at an OI of ≤ 20 was associated with reduced incidence of ECMO/death[42]. We recommend initiation of iNO at OI ≥ 20 if there is clinical or echocardiographic evidence of PPHN.

b. *Dosing of iNO:* Previous clinical trials suggested that the ideal starting dose for iNO is 20 parts per million (ppm) with the effective doses between 5 and 20 ppm[59]. Doses > 20 ppm did not increase the efficacy and were associated with more adverse effects in these infants[56] such as elevated methemoglobin (>7%) and nitrogen dioxide (NO_2) (>3 ppm)[54]. A dose of 5 ppm results in improved oxygenation in PPHN. A dose of 20 ppm results in improved oxygenation *and* results in the most optimal decrease in pulmonary to systemic arterial pressure ratio [60]. To summarize, we recommend initiation of iNO if OI is ~ **20** at a dose of **20** ppm. A complete response to iNO is defined as an increase in PaO_2/ FiO_2 ratio of ≥ **20**mmHg. (**20-20-20 rule** for initiation of iNO, figure 8).

c. Methemoglobin levels are monitored at 2h, 8h after initiation of iNO and then once a day for the duration of iNO therapy. High inspired oxygen and high mean iNO dose are risk factors for elevated methemoglobin in term infants[61]. Levels should be maintained < 5%.

d. *Weaning iNO*: Due to rebound vasoconstriction and resultant pulmonary hypertension on abrupt withdrawal, iNO needs to be weaned gradually[62]. Weaning in steps from 20 ppm gradually over a period of time before its discontinuation has been shown to prevent the rebound effect[63]. If there is oxygenation response, inspired oxygen concentration is first weaned below **60**% and then iNO is weaned only if PaO_2 can be maintained ≥ **60**mmHg (or preductal SpO_2 ≥ 90%) for **60** min (**60-60-60** rule of weaning iNO). At our center, we wean iNO at a rate of 5 ppm every 4 hours. Once iNO dose is 5 ppm, gradual weaning by 1 ppm q 4 hours is performed (figure 8).

e. *Failure of iNO*: In approximately a third of term and near-term infants with PPHN, iNO does not result in sustained improvement in oxygenation[56]. The following steps are recommended in the management of iNO-resistant PPHN (figure 9).

   i. Adequate lung recruitment (with surfactant and/or optimal PEEP/MAP preferably with high frequency ventilation) is crucial to deliver iNO to its target site – the pulmonary vasculature[64].

   ii. A repeat echocardiogram to evaluate ventricular function and severity of PPHN (and to rule out cyanotic CHD such as total anomalous pulmonary venous return (TAPVR) that may have been missed on the first echocardiogram[65]) is the next step.

   iii. Management of systemic hypotension in PPHN is discussed below. Optimal systemic blood pressure is necessary to avoid persistent right-to-left shunting in PPHN.

   iv. If lung recruitment and hemodynamic stability are achieved and iNO is still not effective, patient should be managed in a tertiary center with access to ECMO. Other pulmonary vasodilators such as prostaglandin E1, sildenafil, milrinone, bosentan and hydrocortisone should be considered. Other causes of PPHN and HRF such as ACD and genetic surfactant abnormalities should be considered.

f. *Contraindications to iNO:*

   i. Inhaled NO is contraindicated in the presence of left ventricular dysfunction and pulmonary venous hypertension due to increased risk of pulmonary edema and worsening of oxygenation. Such left ventricular dysfunction is common in diaphragmatic hernia, sepsis and asphyxia.

ii. Congenital heart disease where systemic circulation is dependent on the ductus (such as hypoplastic left heart syndrome, critical aortic stenosis, severe coarctation or interrupted aortic arch survive on high PVR driving blood across a PDA to maintain systemic blood flow. If PVR is decreased by iNO in these conditions decreases left-to-right shunt and decreases systemic blood flow resulting in metabolic acidosis, anuria and shock.

g. **Management of iNO-resistant PPHN (figure 9):** hile approximately two-thirds of patients with PPHN respond well to iNO, some do not achieve or sustain an improvement in oxygenation [56]. Adequate lung recruitment (with surfactant and/or optimal PEEP/MAP preferably with high frequency ventilation) is crucial to deliver iNO to its target site – the pulmonary vasculature [64]. A repeat echocardiogram to evaluate ventricular function and severity of PPHN (and to rule out cyanotic heart disease such as total anomalous pulmonary venous return (TAPVR) that may have been missed on the first echocardiogram [65]) is the next step. Management of systemic hypotension in PPHN is discussed previously. If lung recruitment and hemodynamic stability are achieved and iNO is still not effective, patient should be managed in a tertiary center with access to ECMO. Our recommendations for management of iNO-resistant PPHN not responding to iNO in spite of lung recruitment with increased MAP and surfactant are outlined in figure 9 and summarized here.

i. Hemodynamic evaluation: A repeat echocardiogram should be performed to evaluate structural heart disease, left ventricular dysfunction, right ventricular dysfunction, and ventricular output For example, if left ventricular dysfunction is associated high left atrial pressures and a left-to-right shunt at the level of the oval foramen in the presence of a right-to-left shunt at the ductus arteriosus, iNO is contraindicated and an inodilator such as milrinone should be initiated.

ii. Rapid deterioration with hemodynamic instability should necessitate cannulation for ECMO (or immediate transfer to an ECMO center).

iii. In the presence of systemic hypotension, a fluid bolus (10 ml/kg of Lactated Ringers or isotonic saline) followed by dopamine is recommended. Some centers prefer the use of norepinephrine or vasopressin. A cortisol level is drawn in these patients. If the levels are low relative to the infant's stress level and there is no evidence of infection (viral or bacterial), the authors recommend a stress dose of hydrocortisone.

iv. If blood pressure is relatively stable but hypoxemia persists, consider the use of PDE inhibitors. Sildenafil is preferred if normal liver and ventricular function are present and may have added benefit in the context of prolonged hyperoxia. Ventricular dysfunction or hepatic compromise are indications for Milrinone rather than sildenafil as long as normal renal function is present. Chronic therapy (especially in the presence of CDH or BPD) involves PDE 5 inhibitors followed by endothelin receptor antagonists and non-invasive iNO (figure 9).

K) OTHER PULMONARY VASODILATORS:

a. **Prostaglandin E1 (PGE1):** Aerosolized prostaglandin E1 (Alprostadil) has been used to treat pulmonary hypertension in adults and has been shown to be safe in neonate in small pilot phase I-II studies[66] [67] . Published case reports also suggest beneficial effects of Inhaled PGE1 in patients with iNO refractory PPHN[68].

i. **Dose:** PGE1 solution for aerosolization is prepared from Alprostadil® (Prostin VR 500, Pfizer, New York NY) and administered as a continuous nebulization through a MiniHeart low flow jet nebulizer (WestMed Inc, Tuczon, AZ) at 150-300 ng/kg/min diluted in saline to provide 4 ml/hr[67].

ii. Intravenous PGE1 has also been used in patients with CDH in combination with iNO to promote pulmonary vasodilation and to maintain ductal patency and reduce right

ventricular afterload[69].

iii. Advantage – easy availability in many pediatric institutions to maintain ductal patency for critical CHD.

b. **Inhaled Prostacyclin (PGI_2):** Prostacyclin administered intravenously is a common therapy in adults with pulmonary arterial hypertension.

i. **Dose:** Inhaled PGI_2 has been used in PPHN resistant to iNO at a dose of 50 ng/kg/min[68]. The intravenous formulation Flolan° (Glaxo-Wellcome, Middlesex, UK) is dissolved in 20 ml of manufacturer's diluent (a glycine buffer, pH -10). Fresh solution is added to the nebulization chamber every 4 hours[68].

ii. The effect of such alkaline pH on neonatal respiratory tract is not known.

iii. Iloprost is an analog of prostacyclin and has anecdotally shown to be effective in neonates and children with pulmonary hypertension[70-73].

c. **Phosphodiesterase Inhibitors:**

i. *Sildenafil* (phosphodiesterase 5, PDE 5 Inhibitor): Sildenafil acts by inhibiting cGMP-specific phosphodiesterase type 5 (PDE 5), an enzyme that promotes degradation of cGMP.

1. Studies have shown that oral sildenafil (dose range 1-2 mg/kg every 6 h) improves oxygenation and reduces mortality, in centers limited by non-availability of iNO and ECMO[74,75].

2. Intravenous sildenafil was shown to be effective in improving oxygenation in patients with PPHN with and without prior exposure to iNO[76]. The use of

intravenous sildenafil should be restricted to refractory cases at a center with ECMO back-up, due the potential risk of systemic hypotension[77] and pulmonary hemorrhage, presumably due to sudden reversal of ductal shunt[78]. Based on pharmacokinetic data in neonates with PPHN, intravenous sildenafil is administered as a load of 0.42 mg/kg over 3 hours (0.14 mg/kg/h) followed by 1.6 mg/kg/day as a continuous maintenance infusion (0.07mg/kg/h).

3. Systemic hypotension is a major side effect of sildenafil and can increase morbidity in PPHN by worsening right-to-left shunt. Long-term therapy with sildenafil in children (1-17 years) has been associated with increased mortality.

ii. *Milrinone* (PDE 3 Inhibitor): Milrinone inhibits PDE3 and increases concentration of cAMP in pulmonary and systemic arterial smooth muscle and in cardiac muscle. Infants with PPHN refractory to iNO therapy have responded to IV milrinone in 3 case series [79-81]. An optional loading dose (50 mcg/kg over 30-60 min) followed by a maintenance dose (0.33 mcg/kg/min and escalated to 0.66 and then to 1 mcg/kg/min based on response) is commonly used.

1. As with any systemic vasodilator, hypotension is a clinical concern and blood pressure needs to be closely monitored. A fluid bolus (10ml/kg of lactated Ringer's solution) prior to loading dose may decrease the risk of hypotension.

2. In addition, one case series described an increased incidence of intracranial hemorrhage with the use of milrinone in PPHN[80]. Milrinone may be the pulmonary vasodilator of choice in the presence of PPHN with left ventricular dysfunction (figure 9).

d. Bosentan (Endothelin-1 receptor blocker): Endothelin receptor antagonists are beneficial and well

tolerated in adult patients with pulmonary arterial hypertension[82]. Initial reports suggested that bosentan was an effective drug in the management of PPHN [83]. The results of a multi-center, randomized, double-blind, placebo-controlled exploratory trial of bosentan in PPHN was recently reported. Bosentan (2mg/kg/dose BID) did not show any additive effect on the top of iNO in term neonates with PPHN[84]. However, endothelin receptor antagonists may have a role in the management of chronic pulmonary hypertension associated with BPD or CDH.

e. **Steroids:** Antenatal betamethasone attenuated oxidative stress and improved in vitro response to vasodilators in a fetal lamb model of pulmonary hypertension[85]. Glucocorticoids have been found to improve oxygenation and attenuate the pulmonary hypertensive response in animal models of meconium aspiration syndrome, which is a common cause of PPHN[86]. Steroids have been reported to decrease hospital stay and duration of oxygen use in infants with meconium aspiration[87,88]. It is proposed that hydrocortisone attenuates ROS production by induction of superoxide dismutase and normalization of PDE5 activity [89]. Looking at the evidence this far, we do not recommend routine use of steroids in patients with PPHN especially if there is suspicion of viral (especially, enterovirus, herpes or CMV) or bacterial sepsis. Anecdotal use of stress dose hydrocortisone in iNO resistant PPHN associated with systemic hypotension in our unit has resulted in stabilization of systemic blood pressure and improved oxygenation possibly secondary to hemodynamic stability and PDE-5 inhibitory effects[90,91]

L) **Extracorporeal membrane oxygenation (ECMO)** is a technique of modified cardiopulmonary bypass used over a prolonged period to support heart and lung function. In newborns with PPHN, mechanical ventilation with oxygen and iNO is the initial treatment, but prolongation of iNO with high oxygen levels may induce chronic lung disease and extend the length of stay in the NICU[92] . On the other hand, initiating ECMO too early may expose newborns to major vessel cannulation and systemic anticoagulation[93]. General accepted

criteria to start ECMO are as follows:

a. Persistent hypoxemia (with an OI of >40 or $AaDO_2$ >600 in spite of aggressive medical management of PPHN with mechanical ventilation and iNO) and

b. Presence of hemodynamic instability

M) Management of systemic hypotension in PPHN: Systemic hypotension is common in infants with PPHN. Decreased systemic blood pressure exacerbates right-to-left shunt and worsens hypoxemia in PPHN. The cause of systemic hypotension should be addressed first – administration of volume bolus in hypovolemia, decrease in MAP in the presence of hyperinflation and antibiotics for sepsis. The use of dopamine to increase systemic blood pressure to reduce right-to-left shunt is a common practice. However, dopamine (especially at > 10 mcg/kg/min) is not selective to systemic vasculature and can increase pulmonary arterial pressure in PPHN[64]. Norepinephrine infusion is also effective in stabilizing systemic blood pressure and improving oxygenation in neonates with PPHN[94]. As mentioned in the previous paragraph, hydrocortisone may also stabilize blood pressure in PPHN.

N) Asphyxia, hypothermia and management of PPHN: Asphyxia is associated with hypoxemia and acidosis. Infants with asphyxia also have evidence of surfactant deficiency and/or meconium aspiration syndrome[95]. The use of moderate hypothermia (33.5°C for 72 hours) does not result in a significant increase in the incidence of PPHN (25% vs. 22% with conventional management without hypothermia)[96]. However, as compared to moderated hypothermia (33.5°C), deeper whole-body cooling to 32°C is associated with a tendency to increased PPHN (34 vs 25%, p-0.06), increased need for inhaled NO (34 vs 24%, p-0.03) and ECMO (9 vs 4%, p-0.005)[97]. Case reports indicate that patients with hypoxemic respiratory disorders prior to the onset of cooling (especially those that need > 50% inspired oxygen and/or iNO)[98], may experience exacerbation of PPHN with hypothermia and/or rewarming [99]. Mild therapeutic hypothermia by itself is not

a cause for PPHN. However, infants predisposed to elevated PVR due to the presence of asphyxia and respiratory disease may not tolerate hypothermia induced pulmonary vasoconstriction[100]. These findings emphasize the need for close monitoring of core temperature, systemic/pulmonary hemodynamics and oxygenation during hypothermia and rewarming for asphyxia. In many centers, confusion exists regarding optimal reporting of $PaCO_2$ during whole-body hypothermia. The laboratory may report $PaCO_2$ levels either at baby's temperature (known as the pH-stat method) or corrected for 37°C (alpha-stat method). Decreasing temperature increases the solubility of CO_2 in the blood and decreases $PaCO_2$ and may have implications for PPHN management with potential of overventilation or underventilation. We recommend the pH-stat method and reporting of $PaCO_2$ at actual (and not corrected) body temperature.

O) **LONG TERM OUTCOME OF PPHN:** PPHN is a disease with significant long-term morbidity, irrespective of the treatment modality. These infants suffer from long-term consequences such as neurodevelopmental, cognitive and hearing abnormalities[101-103]. Thus, it is essential to provide long-term multidisciplinary follow-up after discharge. Konduri et al in their long-term follow-up of infants randomized to early iNO in PPHN, noted neurodevelopmental impairment in about 25% of infants and hearing impairment in approximately 23%[101]. Long-term neurodevelopmental outcome at school age for neonates with PPHN critical enough to receive inhaled NO or ECMO is generally encouraging. Rosenberg et al reported that among 109 school age survivors of PPHN (77 of whom received inhaled NO and 12 that required ECMO), medical, neurodevelopmental and behavioral outcomes did not differ between those treated with or without inhaled NO or ECMO,. However, 24% had persistent respiratory problems, 60% had abnormal chest X-rays and 6.4% had some degree of sensorineural hearing loss. Overall, 9.2% of the cohort had a full scale IQ less than 70 and 7.4% had an IQ from 70 to 84[104]. The UK collaborative trial randomized critically ill neonates into transfer to a regional center for ECMO or continued conventional care at the local NICU. At 7 year follow-up, mortality was significantly lower in the ECMO group with no increase in disability[105]. The presence of neurodevelopmental and medical disabilities may reflect the severity of the underlying illnesses experienced

by these infants rather than complications of interventions received.

P) **CONCLUSIONS:** Over the last two decades, use of improved ventilation strategies to optimize lung recruitment, provide "gentle" ventilation and minimize oxygen toxicity paired with the therapeutic use of surfactant and iNO has led to a substantial decrease in the number of neonatal PPHN patients requiring ECMO for respiratory disorders. Animal models have contributed to our understanding of fetal circulation, pulmonary vascular transition at birth and hemodynamic and biochemical abnormalities associate with PPHN. Further clinical research into pulmonary vasodilator therapy, reversal of remodeling of the pulmonary vasculature and right ventricle are crucial. Two challenges which remain in the field of PPHN include management of pulmonary hypoplasia and pulmonary hypertension in CDH and BPD-associated pulmonary hypertension in the premature infant[106]. In addition, asphyxia (with or without MAS and/or therapeutic hypothermia) remains an important cause for PPHN worldwide. Further research to evaluate and develop appropriate strategies to ameliorate pulmonary vascular disease in these conditions are warranted.

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FIGURE LEGENDS

Figure-1. Various etiological factors causing PPHN and hemodynamic changes in PPHN/HRF: PA–pulmonary artery; RV–right ventricle; LV–left ventricle; TR–tricuspid regurgitation; RA–right atrium; LA–left atrium; PDA–patent ductus arteriosus; PFO–patent foramen ovale; MAS–meconium aspiration syndrome; RDS–respiratory distress syndrome; CDH–congenital diaphragmatic hernia; TTN–transient tachypnea of the newborn. *(Copyright-Lakshminrusimha).*

Figure 2. Etiology of secondary PPHN: Common conditions associated with secondary PPHN are shown in this figure. Some controversy exists regarding maternal intake of non-steroidal anti- inflammatory medications (NSAIDs) and selective serotonin reuptake inhibitors (SSRI) and PPHN. *(Copyright-Lakshminrusimha).*

Figure 3. Labile oxygenation in PPHN: The relationship between systemic vascular resistance (SVR) and pulmonary vascular resistance (PVR) determines oxygenation in PPHN. During postnatal life, normally, SVR is higher than PVR. However, in PPHN, PVR is higher or equal to SVR resulting in right-to-left or bidirectional shunt at PDA and PFO. Correcting systemic hypotension with fluids and inotropes will reduce right-to-left shunt and improve oxygenation. However, maintaining systemic blood pressure at supraphysiological levels adds to ventricular strain and is not recommended. *(Copyright-Lakshminrusimha).*

Figure 4. Mechanisms of PPHN – Elevated pulmonary vascular resistance (PVR) is typically secondary to four mechanisms. Parenchymal lung disease (such as hyaline membrane disease – HMD, resulting in acute alveolar hypoxia leads to pulmonary vasoconstriction. Intravascular obstruction secondary to hyperviscosity often due to polycythemia can lead to PPHN. Remodeled vasculature (*maladaptation* of pulmonary circulation) due to congenital diaphragmatic hernia, intrauterine closure of ductus arteriosus and chronic intrauterine hypoxia leads to PPHN. Pulmonary hypoplasia secondary intrathoracic space occupying lesions such as congenital pulmonary malformations, diaphragmatic hernia and oligohydramnios due to renal disease or chronic leakage leads to

PPHN. Finally, infants born with malformations of alveolar and vascular development such as alveolar capillary dysplasia (ACD) with malalignment of pulmonary veins (MPV) have intractable and often lethal PPHN. *(Copyright Satyan Lakshminrusimha).*

Figure 5. Clinical features and assessment of severity of PPHN with oxygenation index (OI) and oxygen saturation index (OSI). Infants with PPHN present with labile hypoxemia with differential cyanosis (preductal oxygenation higher than postductal oxygenation, in the presence of a right-to-left shunt at the PDA level) and may have a loud second heart sound and a precordial right ventricular heave. Severity of PPHN can be assessed by calculating OI. Factors that influence oxygenation are in the numerator (mean airway pressure – MAP and inspired oxygen) and oxygen level is in the denominator. OSI is similar to OI but substitutes PaO_2 by SpO_2 as a measurement of oxygenation. OSI values are approximately half of OI (OI of 16 is approximately equal to OSI of 8). *Copyright Satyan Lakshminrusimha*

Figure 6. Management of PPHN. See text for details. *Copyright Satyan Lakshminrusimha*

Figure 7. Selective and microselective action of inhaled nitric oxide (NO). Inhaled NO is a selective dilator of the pulmonary circulation without any significant systemic vasodilation as it combines with hemoglobin to form methemoglobin (MHb). As it is an inhaled vasodilator, it selectively goes to the well ventilated alveoli and improves blood flow to these alveoli and reduces V/Q mismatch (microselective effect). *(Copyright-Lakshminrusimha).*

Figure 8. Weaning protocol for inhaled nitric oxide in use at Women and Children's Hospital of Buffalo *(Copyright-Lakshminrusimha).*

Figure 9. Flow chart showing the author's suggested guidelines for management of iNO resistant PPHN. *(copyright Satyan Lakshminrusimha)*.