National Guideline for the Management of Persistent Pulmonary Hypertension in Newborn (PPHN)

Ministry of Health
Male', Republic of Maldives

RELEASE RECORD

Version No	Version Date	Description of change
1	30 January 2024	Initial release

DOCUMENT NUMBER: MOH-QA/G/24/160-0

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Published by Quality Assurance and Regulations Division

Ministry of Health, Male, Republic of Maldives

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1. INTRODUCTION

Persistent PPHN is defined as imbalance between vasoconstrictor and vasodilator mechanisms resulting in elevated pulmonary vascular resistance (PVR) to the point that systemic venous blood is diverted to some degree through intra- and extra-cardiac (e.g. ductus arteriosus and foramen ovale) channels into the systemic circulation by passing the lungs and leading to systemic arterial hypoxemia.

2. SCOPE OF THE GUIDELINE

The goal of this policy is to identify babies with persistent pulmonary hypertension and to commence therapy immediately and appropriately. The therapeutic goal should be to avoid hypoxia, decrease pulmonary resistance, decrease shunting and improve oxygenation with optimal hemodynamic stability

3. PRINCIPLES/ GUIDELINES

3.1 Definition:

Persistent pulmonary hypertension of the newborn (PPHN), previously referred to as persistent fetal circulation, is a syndrome of impaired circulatory adaptation at birth. The hallmark of PPHN physiology is sustained elevation of pulmonary vascular resistance (PVR) and persistent hypoxemia after birth.

3.2 Incidence

PPHN is an uncommon condition, its prevalence is at 1 - 7 per 1000 live births. The vast majority of infants with PPHN are born at term or near term, although around 2% cases are born prematurely. Mortality is at 10 to 15% and PPHN remains as one of the leading causes of critical illness in the neonatal intensive care unit. For survivors, significant long-term morbidities including neurodevelopmental, cognitive, and hearing abnormalities are observed.

3.3 Aetiology

PPHN is usually secondary to an identifiable insult however it can be primary or idiopathic. Leading causes of PPHN - infection (30%), MAS (24%), idiopathic (20%) RDS (7%) and CDH (6%)

Primary PPHN, accounting to 10 to 20% cases, refers to the absence of parenchymal lung disease to explain elevated pulmonary arterial pressure and implies intrauterine pulmonary vascular remodelling. Primary PPHN presents in the early postnatal period as cyanosis where the level of hypoxia is disproportionate to the degree of respiratory distress.

Primary PPHN is usually idiopathic in origin. It is often associated with a variety of complications of pregnancy including: –

1. Maternal diabetes,
2. Maternal hypertension
3. Advanced maternal age
4. Obesity and post maturity
5. Polycythaemia
6. Fetal anaemia
7. Premature ductal closure
8. Premature of rupture of membranes (PROM)

Secondary PPHN is PPHN which is secondary to a disease in the parenchyma of the lungs. It arises due to abnormally constricted pulmonary vasculature, mainly comprising of acute respiratory disease processes such as MAS.

Secondary PPHN primarily present as respiratory distress, often with respiratory failure and the need for high ventilator pressures and increasing oxygen requirements.

The CXR is mostly abnormal, keeping in line with the underlying respiratory condition

Common Respiratory causes include:

1. Meconium Aspiration Syndrome (MAS)
2. Respiratory distress Syndrome
3. Congenital Pneumonia
4. Bronchopulmonary dysplasia (BPD)
5. -Congenital Diaphragmatic Hernia (CDH)
6. Pulmonary Hypoplasia e.g.: from CDH or renal abnormalities/oligohydramnios

Non- Respiratory causes of PAH

1. -Sepsis,
2. -Hypoxic Ischaemic Encephalopathy (HIE/Perinatal asphyxia)
3. -Drugs (Selective Serotonin Reuptake Inhibitors (SSRIs),

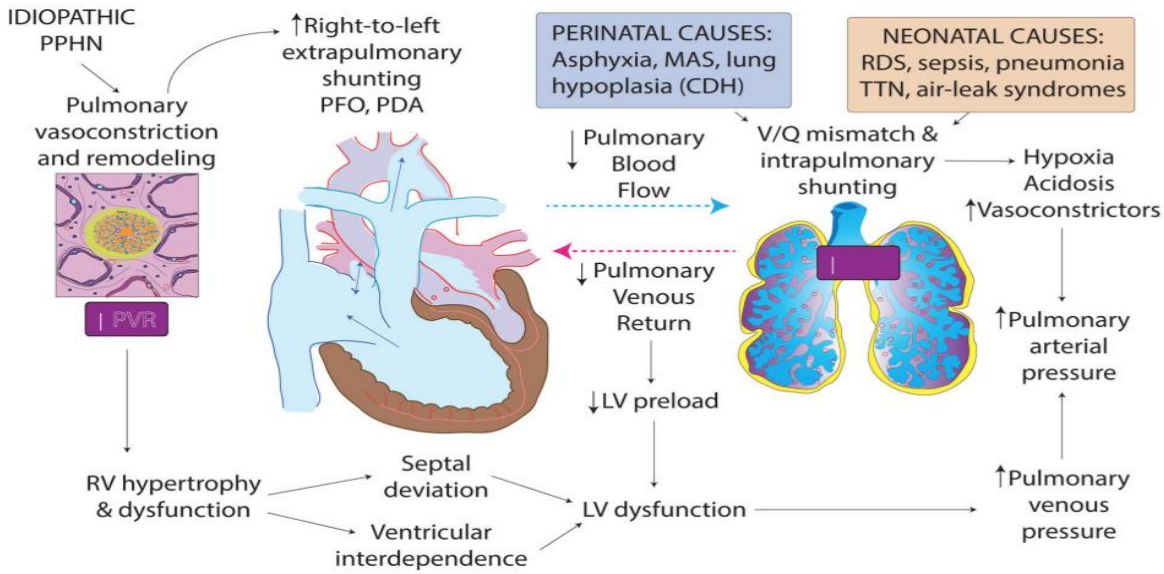
3.4 Pathophysiology

During fetal life, the placenta serves as the organ of gas exchange. Blood flow in the pulmonary circulation remains highly restricted by pulmonary vasoconstriction of the small pulmonary arteries.

This is reversed at birth due to the sudden increase in lung oxygenation when the newborn takes their first breath. The first few breaths induce a rapid decrease in pulmonary vascular resistance and an increase in pulmonary vascular flow with lung expansion.

The pathophysiology of PPHN is complex, multifactorial and dynamic – it evolves with time and is significantly affected by the intervention and disease process. See figure 1 for pathophysiology of PPHN.

Figure 1: Pathophysiology of PPHN



Pathophysiology of extrapulmonary shunts, ventricular dysfunction and interventricular function interdependence in PPHN (10). RV – right ventricle, LV – left ventricle, MAS – meconium aspiration syndrome, CDH – congenital diaphragmatic hernia, TTN – transient tachypnea of newborn, PVR – pulmonary vascular resistance. Courtesy of Satyan Lakshminrusimha and Yogen Singh.

The **hallmark** of the PPHN pathophysiology **is increased pulmonary vascular resistance (PVR)** resulting in decreased pulmonary blood flow (PBF) and hence, decreased amount of oxygenated blood returning to left side of the heart leading to hypoxia, decreased end-organ perfusion, acidosis and cyanosis.

Hypoxemia and acidosis are potent vasoconstrictors leading to increase in PVR and worsening of PPHN. Hypoxemia is the clinical hallmark of PPHN, and it occurs due to intrapulmonary shunting secondary to ventilation/ perfusion (V/Q) mismatch and/or extrapulmonary right-to-left shunting of blood.

In some newborns, a single mechanism predominates (e.g. extrapulmonary right to left shunting in idiopathic PPHN). However, in clinical practice several of these mechanisms often contribute to hypoxemia. E.g. in MAS, pneumonia and sepsis, hypoxemia from VQ mismatch increases intrapulmonary right-to-left shunt while extrapulmonary right-to-left shunting at the ductus arteriosus and foramen ovale results in further exacerbation of hypoxemia. Refer to Table 1 for mechanism of hypoxemia in different disease condition

Table 1: Mechanism of hypoxia in different disease condition

Disease process	Mechanism of hypoxemia
MAS, Pneumonia, Sepsis	Alveolar hypoxia, inflammatory mediators, metabolic acidosis, abnormal pulmonary vascular muscularization
HIE/perinatal asphyxia	- Altered or delayed transition leading to persistent high PVR - Myocardial ischemia leads to poor cardiac function, acidosis and low cardiac output
PPROM/Congenital diaphragmatic hernia	Lung hypoplasia
Exposure NSAID/SSRI	Constriction of the fetal ductus arteriosus

Persistently elevated PVR results in hypertrophy of right ventricle (RV) from pumping of blood against high vascular resistance, which may lead to impaired RV function and RV dilatation, and in severe cases it can lead to in RV failure – which may further decrease PBF and worsen hypoxemia.

In severe cases of PPHN this becomes a vicious cycle. PVR is often higher than the systemic vascular resistance (SVR) in infants with moderate to severe PPHN. Elevated PVR to SVR ratio leads to right-to-left shunting of blood across the ductus arteriosus and foramen ovale resulting in severe hypoxemia

RV dysfunction may impair left ventricle. Poor LV function may decrease LV cardiac output and systemic blood flow leading to poor end-organ perfusion and acidosis, and hence worsening of PPHN. Severe LV dysfunction may also impair left ventricle filling due to poor compliance.

When to suspect PPHN

1. Respiratory distress with cyanosis and hypoxaemia which is refractory to oxygen therapy, in the absence of congenital heart disease
2. Severe hypoxemia with respiratory distress, disproportionate to the level of respiratory distress.
3. Radiography may reveal features associated with secondary PPHN (such as a CDH or pneumonia), but in primary PPHN, lung fields can be clear with severe hypoxaemia.
4. Difference in pre & post-ductal oxygen saturations: Post ductal maybe 5% lower than pre-ductal, consistent with Right to Left shunting (NB: PPHN not excluded if ≤5% difference).
5. Anticipate PPHN in the presence of any of the secondary causes. E.g. MAS

3.5 Clinical Diagnosis:

Hypoxic respiratory failure is a hallmark feature of PPHN.

The initial evaluation should include

1. Thorough history of risk factors for PPHN
2. Meticulous physical examination including close monitoring of vitals (BP, PR, RR, pulse volume, CRT, spo2 (pre and post ductal) hourly.
3. Watch for signs of respiratory distress, tachypnoea, recessions, nasal flaring
4. Watch for signs of shock (Tachycardia, poor perfusion, prolonged CRT, weak pulse, falling MAP)
5. Clinically, these neonates may have a prominent precordial impulse, loud second heart sound, a systolic parasternal murmur due to tricuspid incompetence.

6. Simultaneous measurement of pre-ductal (right upper limb) and post-ductal (lower limb) oxygen saturation to check the difference between them
7. Saturation differences of greater than 5%–10% or PaO2 differences of 10–20 mm Hg between right upper limb and lower limbs, with pre-ductal levels being higher than post-ductal levels, are considered significant
8. The hyperoxia test may be useful in differentiating the cardiac causes from respiratory causes in cyanotic newborns.
9. On confirmation of central cyanosis, response of PaO2 to 100% oxygen inhalation is tested (hyperoxia test).
10. Absence of a pre- and post-ductal gradient in oxygenation does **not** exclude the diagnosis of PPHN
11. A hyperoxia test should be interpreted in the context of the clinical picture and the degree of pulmonary pathology seen on X-ray
12. The clinical presentation closely mimics that of cyanotic congenital heart disease. However, Hypoxemia is often labile in PPHN, unlike fixed hypoxemia seen in cyanotic congenital heart disease. Refer to Table 2 for differential diagnosis of hypoxemia in newborn infants

Table 2: Differential diagnosis of hypoxemia in newborn infants

	Lung disease without PPHN	Cyanotic Congenital Heart Disease	PPHN
History	Fetal distress, PROM, chorioamnionitis	Ante-natal diagnosis	Often negative other than in secondary PPHN
Respiratory distress	Present	Usually absent	Often present
Oxygen saturation on pulse oximetry	Improves with supplemental oxygen	Fixed low saturations minimal response to supplemental oxygen	Labile saturations. Differential cyanosis
Hyperoxia test*	PaO_2 often > 150 mmHg	PaO_2 often <100 mmHg	PaO_2 often >100 mmHg
$PaCO_2$	Elevated	Normal/ low	Often elevated (except in idiopathic PPHN)
Hyperoxia-Hyperventilation*	PaO2 > 150 mmHg	PaO_2 often <100 mmHg	PaO_2 improves with hyperventilation
Chest X-ray	Abnormal	Abnormalities of cardiac silhouette and pulmonary vascularity	Decreased vascularity in idiopathic PPHN
Echocardiogram	Normal	Structural cardiac abnormalities	Structurally normal heart (see text for characteristic echo findings of PPHN)

3.6 Echocardiographic diagnosis

This allows accurate diagnosis of PPHN and should be done as soon as practical in the clinical course. The benefits of echocardiography include:

- Echocardiography is the gold standard to confirm the diagnosis of PPHN. Refer to table 3 for echocardiographic parameters in PPHN
- The ability to exclude congenital heart disease and to monitor the response to therapeutic interventions
- The ability to define the pulmonary artery pressure using tricuspid incompetence or ductal shunt velocities and to define severity of PPHN
- Define the presence, degree and direction of shunt through the ductus arteriosus and foramen ovale.
- Define the ventricular outputs. These are commonly very low in the early course of the disease
- Serial echocardiographic assessment can help in understanding evolving pathophysiology, guide ionotropic support and response to the therapeutic intervention.

On ECHO, the following are indicative of pulmonary hypertension

- Pulmonary pressures equivalent or greater than systemic pressures measured on the TR jet using continuous wave doppler
- Pulmonary Artery Time to peak velocity to Rav ejection time ratio < 0.2
- Reduced LPA velocity – low velocities are predictive of good response to in
- The direction and velocity of the ductal shunt – a right to left shunt for more than 30% of the cardiac cycle indicates that pulmonary artery pressure is higher than systemic pressure.

Table 3: Echocardiographic parameters in assessment of PPHN

Echocardiographic parameters	Comments
Disproportionately large right side of the heart with right ventricle (RV) hypertrophy and or RV dilatation on visual inspection	In multiple views on visual inspection "eyeballing" shows cardiac asymmetry with right side of the heart bigger than left side
Estimation of pulmonary artery systolic pressure (PASP)	By using tricuspid gradient (when present) or ductal shunt – Doppler assessment
Direction of blood flow across patent ductus arteriosus (PDA)	Right to left shunt: supra-systemic pulmonary artery pressure (PAP) Left to right shunt: sub-systemic PAP Bidirectional shunt: PAP equal to systemic blood pressure
Direction of blood flow across Patent Foramen Ovale (PFO)	Often, it's bidirectional and seldom purely right to left
Flattening of interventricular septum (due to sustained high pressure in the right ventricle and flattening proportional to severity of PPHN	Helps in estimating severity of PPHN in absence of TR or PDA, can be categorized as mild, moderate and severe flattening
Assessment of right ventricular functioning	On visual inspection Tricuspid annular pan systolic excursion (TAPSE) Tei index using Tissue Doppler Imaging (TDI)
Assessment of left ventricular function	On visual inspection Tei index using Tissue Doppler Imaging (TDI) (note fraction shortening may be unreliable in presence of RV hypertrophy and dysfunction)
Assessment of cardiac filling (preload)	IVC size and collapsibility
Advanced echocardiography and haemodynamic evaluation	RV fractional area change PAAT and PAAT/RVET ratio Speckle tracking and strain rate Estimation of left and right cardiac output and serial assessment to see the response to therapy

3.7 Management principles

- Keep a high Index of suspicion for PPHN
- The severity of PPHN can range from mild hypoxemia with minimal respiratory distress to severe hypoxemic respiratory failure and cardiopulmonary instability.
- Early aggressive management to prevent spiralling deterioration

3.7.1 Equipment and Monitoring

3.7.1.1 Vascular Access

Both UAC and UVC should be done by an experienced person

- Obtain central access: umbilical venous catheter or peripherally inserted central venous catheter. Double lumen catheters may be more helpful
- Place one peripheral IV line for blood products, fluids, and medication boluses.
- Obtain arterial access: umbilical arterial catheter/Rt radial arterial line is indicated for all ventilated PPHN patients

3.7.1.2 Monitoring

1. Continuous monitoring of pre- and post-ductal saturations
   - Pre-ductal saturation – to titrate supplemental oxygen based on goals.
   - Target post-ductal saturations - to trend shunting that approximates pH severity.
2. Utilise transcutaneous Carbon dioxide monitoring devices
3. Serial oxygenation index (OI) calculation following each arterial blood gas measurement. Oxygenation index (OI) = FiO2 × mean airway pressure × 100/PaO2
   - Severity of hypoxic respiratory failure based on OI:
     - Mild ≤15
     - Moderate 15 to ≤25
     - Severe 25 to ≤40
     - Very severe >40
   - Low OI values reflect healthy lung mechanics while a rising OI indicates progressively compromised oxygenation consistent with sicker lungs

- Severity assessment based on P/F ratio: = PaO2/ FiO2

  -Mild >200 to ≤300

  -Moderate >100 to ≤200

  -Severe ≤100 mm Hg.

4. Perform continuous blood pressure (BP) monitoring via arterial line.
5. Consider placement of a urinary catheter. Because urine output represents an important marker of end-organ perfusion, close monitoring is critical.

3.7.2 General management principles for the newborn

1. Minimal handling -- PVR in these infants is so labile that small changes in oxygenation or pH caused by handling and stress can result in rapid changes in PVR and instability. To prevent, keep eyes and ears covered, maintaining a low-noise environment
2. Sedate adequately with infusions of Fentanyl/ midazolam. In rare cases, consider paralysis with a continuous infusion of vecuronium if difficult to sedate
3. Maintain normal temperature, blood glucose, calcium, magnesium and haematocrit (40-55%).
4. Optimise ventilation aiming for good oxygenation until the primary condition improves
5. Monitor blood pressure continuously, ideally invasively and avoid systemic arterial hypotension.
6. Promote pulmonary vasodilatation by specific use of oxygen and consider inhaled NO and other intravenous drugs
7. Improve cardiac contractility and systemic blood pressure by judicious use of volume and inotropes thus reducing the right-to-left shunting. Syringes containing inotropes should be placed above patient heart level and inotropes should be refilled before it finishes. **Do NOT** Discontinue inotropes
8. Send initial septic screen and start on first line antibiotics

3.8 Interventions

The aim of treatment is to maintain normal arterial oxygen levels and normal oxygen delivery to the organs of the body. The two most potent natural pulmonary vasodilators are oxygen and lung inflation.

3.8.1. Oxygen

- Oxygen is a potent pulmonary vasodilator. Aim for saturations in the normal range (95-100%), aiming to maintain paO2 between 60-100 mmHg in term infants.
- Target preductal saturations at 95 +/- 2. In PPHN, equally important is avoidance of hypoxemia and hyperoxia, both of which can increase PVR

3.8.2. Pulmonary Optimization

3.8.2.1 Conventional ventilation

1. Babies often require intubation & ventilation, particularly when oxygen requirement is ≥ 70%.
2. Optimise Endotracheal tube position and size. Suction only if needed so as to allow minimal handling
3. Oxygenation is often very sensitive to small reductions in minute volume such as can occur with retained secretions or handling
4. Adjust Peak Inspiratory pressure and PEEP to achieve lung inflation equivalent to 8 – 9th posterior ribs on the chest x-ray whilst avoiding hyperinflation and atelectasis. Hyperinflation not only compress the alveolar vascular supply but also causes systemic hypotension thus aggravating the right-to-left shunt.
5. Aim for a pO2 > 60 mmHg as oxygen is the strongest pulmonary vasodilator (compared to CO2 and pH).
6. Aim for a pH within the normal range (7.35 - 7.45) and pCO2 between 35 – 45mmHg (avoid hypocarbia < 35 mmHg as it affects cerebral perfusion) and correct any concomitant metabolic acidosis.
7. To maintain normal blood gases, it is sometimes necessary to achieve higher than usual tidal volumes (up to 6mls/kg).
8. Muscle relaxants should be reserved for newborns where there is difficulty establishing adequate ventilation despite good sedation.

Gentle Ventilation

- Utilize a “gentle ventilation” strategy focusing on optimized PEEP, low PIP, and high rate to minimize volutrauma.

Based on expert consensus

- Conventional ventilator settings: PEEP 5 to 8 mm Hg, PIP 18 to 25 mm Hg, rate 30 to 40 breaths/min.
- Maximum conventional ventilator settings: PIP 25 to 28 mm Hg, PEEP 10, rate 45 to 50 breaths/min

3.8.2.2 High Frequency Oscillatory Ventilation (HFOV):

- In severe lung disease, high-frequency (jet or oscillator) ventilation is frequently used in RDS, congenital pneumonia or MAS
- -In these disease processes, HFOV ventilation decreases need for ECMO and augments iNO response more effectively than does conventional ventilation.
- Indication to commence HFOV include inadequate lung inflation despite unacceptably high or potentially injurious conventional ventilator settings. (PIP exceeds 30)
- While HFOV in use, do CXR imaging at 1 to 2 hours, and again at 6 hours following HFOV transition
- Initial HFOV settings: MAP 13 to 18 mm Hg, amplitude 30 to 40, frequency 10 Hz

The combination of HFOV and INO has been shown to be better than conventional ventilation and INO in randomised controlled trials of term babies with significant parenchymal lung disease and PPHN.

In comparing HFOV with conventional ventilation in babies with severe hypoxic respiratory failure has shown no differences in mortality, chronic lung disease or air leak.

Advantage is HFOV allowed for better oxygenation by allowing better lung inflation.

In babies with secondary PPHN and underlying lung parenchymal disease HFOV improves oxygenation and reduces right to left extrapulmonary shunting due to aggressive lung recruitment.

3.8.2.3 Surfactant Replacement Therapy

Surfactant inactivation occurs with MAS, pneumonia and sepsis

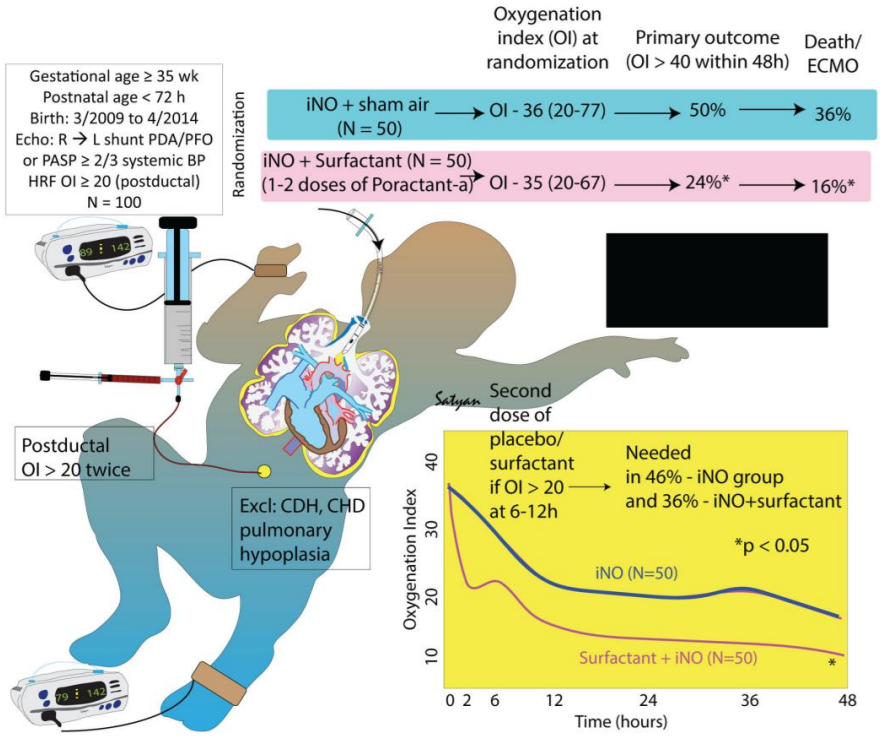
Surfactant therapy leads to improvement in oxygenation by improving V/Q matching and decreases intrapulmonary shunting

A multicentre trial demonstrated that this benefit was greatest for infants with relatively mild disease, and with an oxygenation index (OI) of 15-25

In newborn infants with parenchymal lung disease, surfactant replacement prior to initiation of iNO improves outcome and reduces the need for extracorporeal membrane oxygenation. Figure 3 compares effect of surfactant combined with iNO versus iNO alone.

Use surfactant in standard dose for RDS and meconium aspiration syndrome. Repeat dose maybe needed in meconium aspiration syndrome. Early administration resulted in better outcome

Figure 3: Effect of Surfactant combined with INO vs iNO alone



Graphic abstract of randomized controlled trial of surfactant + iNO vs. iNO only in infants with PPHN by Gonzalez et al (80). Addition of surfactant to iNO resulted in reduced progression of hypoxemic respiratory failure (HRF), decreased incidence of ECMO/death and more rapid reduction in oxygenation index (OI). Courtesy of Satyan Lakshminrusimha.

3.8.3 Cardiovascular Optimization

3.8.3.1 Blood Pressure

- Goal is adequate perfusion with appropriate oxygen delivery to meet the metabolic needs.

- Optimal BP goals for PPHN management depend on gestational age. Suggested MAP for term babies is usually 45 to 55 mmHg

- Consider a slow 10 mL/kg normal saline bolus. If BP response is observed, consider a second bolus while initiating vasopressor and/or inotropic support. Table 4 highlights commonly used vasoactive medications and pulmonary vasodilators in PPHN

- Correlate tissue perfusion by correlating UOP and Serum lactate level.
- In the presence of systemic hypotension without cardiac dysfunction, the agents of choice are dopamine, norepinephrine and vasopressin
- If systemic hypotension is associated with cardiac dysfunction, epinephrine or a combination of dopamine/vasopressin and milrinone are the agents of choice.
- In the presence of stable systemic blood pressure and cardiac dysfunction, milrinone is the agent of choice
- Escalating vasopressor therapy may reverse right-to-left PPHN-associated ductal shunting but it negatively impacts cardiac function, cardiac output, impairs tissue perfusion, and contributes to lactic acidosis

3.8.3.2 Hydrocortisone

- Consider early hydrocortisone therapy for BP support.
- Hydrocortisone improves responsiveness to inotropes through upregulation of catecholamine receptors and calcium availability
- Hydrocortisone initial dose: 1 to 2 mg/kg, followed by 1 mg/kg every 6 hours throughout the acute stabilization phase.
- Experts have suggested doses as low as 0.5 mg/kg may be adequate to support BP
- Anticipate a delayed time to effect, with anecdotal BP response typically achieved around the time of the second dose

Table 4: Commonly used vasoactive medications and pulmonary vasodilators in PPHN

Name of the drug	Dose	Site of action	Haemodynamic effects
Epinephrine	0.02-0.3 micrograms/kg/min	β1 and β2 receptors	Inotropic effects; decrease SVR
	0.3-1 microgram/kg/min	α1 receptors	Vasopressor effects; increase SVR
Norepinephrine	0.1-1 microgram/kg/min	α1 and α2 receptors	Vasopressor effect; increase SVR
Milrinone	0.25-0.75micrograms/kg/min	Phosphodiesterase III inhibitor and effects at β1 and β2 receptors	Inodilator effects; Lusitropic effects; contractility; decrease SVR
Dobutamine	5-20micrograms/kg/min	β1 and β2 receptors, some effect on α receptors	Inotropic effects: decrease SVR: increase cardiac output
Dopamine	1-4 micrograms/kg/min	Dopaminergic receptors 1 & 2	Renal and mesenteric dilatation
	4-10 micrograms/kg/min	α receptors	Inotropic effects
	11-20 micrograms/kg/min	β receptors	Vasopressor, increase SVR and increase PVR
Hydrocortisone	1-2.5 mg/kg: 4-6 hourly		Uncertain- enhance sensitivity to catecholamines
Vasopressin	0.018-0.12 units/kg/hour	Vasopressin 1 receptors	Increase SVR: No inotropic effect
Pulmonary vasodilators			
Inhaled nitric oxide	1-20ppm	Selective pulmonary vasodilator	Decrease PVR
Sildenafil	IV: load of 0.42mg/kg for 3 hours followed by 1.6mg/kg per day as a maintenance infusion	Phosphodiesterase (PDE) 5 inhibitor	Pulmonary and systemic vasodilator, decrease PVR, decrease SVR
	Oral: 1-2 mg/kg every 6 hours		
Synthetic prostacyclin (Iloprost)	Aerosolized: 1-2.5mg/kg every 2-4 hours	Pulmonary vasodilator acting locally	Decrease PVR
	IV 0.5 to 3ng/kg per minute and titrated to 1-10ng/kg per minute	Pulmonary and systemic vasodilator	Decrease SVR and hypotension
Prostacyclin 1_2 ($PG1_2$)	Inhaled prostaglandin 12 at a dose of 50ng/kg per minute	Pulmonary vasodilator acting locally	Decrease SVR

SV- systemic vascular resistance: PVR- pulmonary vascular resistance: α- alpha and β- beta receptors, IV- intravenous

3.9 Vasodilators

3.9.1 Inhaled Nitric Oxide (iNO)

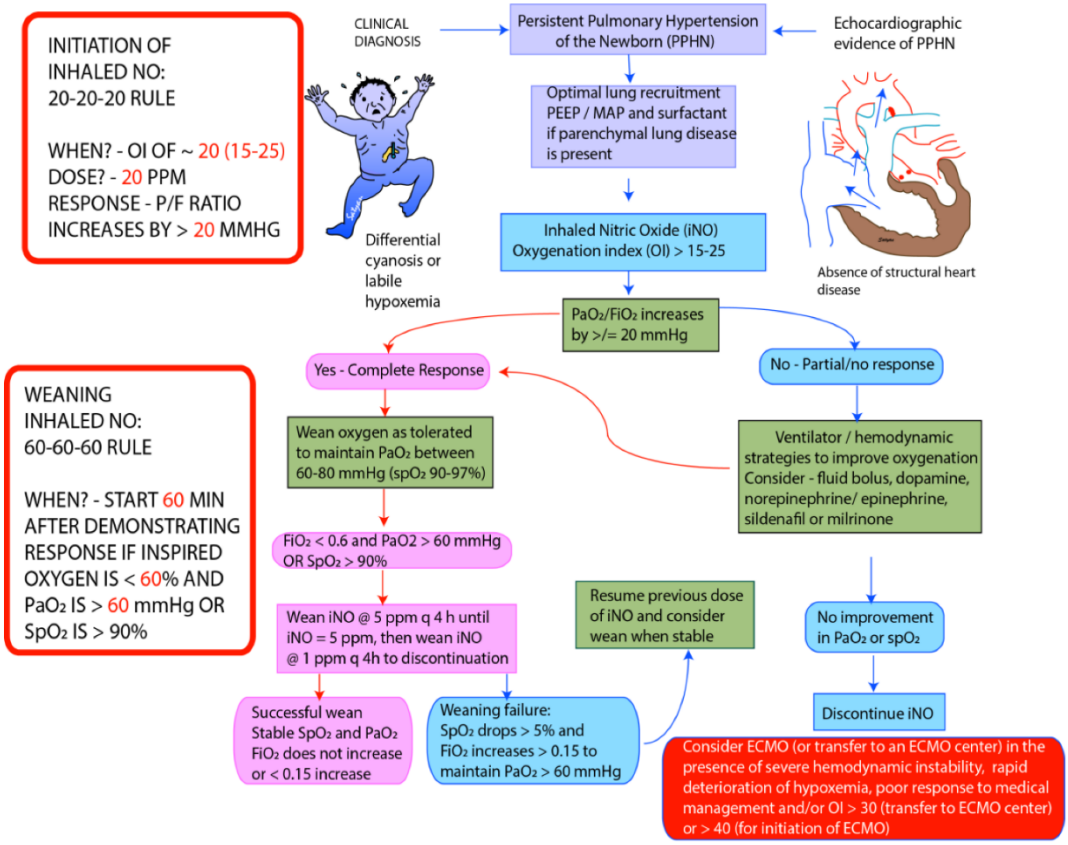
START Inhaled NITRIC OXIDE (iNO) EARLY

- iNO is a potent and selective pulmonary vasodilator
- Increases pulmonary blood flow
- Significantly improves oxygenation
- Improve ventilation perfusion mismatch with having less effect on the systemic vasculature
- Reduces the need for rescue with ECMO

Criteria to commence iNO
Difference in pre & post-ductal sats ≥ 5%;
Oxygen index (OI) >15 with evidence of PPHN in ECHO or OI > 20
Evidence of significant Tricuspid regurgitation on Echocardiography.
Hypoxic respiratory failure with paO2 < 60mmHg or sats < 90% despite maximal respiratory support and FiO2 > 80
A ventilated baby with FiO2>50% with echocardiographic evidence of pulmonary hypertension +/- low cardiac output

- Start iNO at 20 ppm expect response in 2/3 of babies within 30 to 60 minutes.
- Repeat ABG after 30 minutes of starting INO.
- A positive response to INO is defined as a rise in pO2 > 22mmHg.
- Others include reduction in the pre post ductal saturation difference and a reduction in FiO2 > 10
- Also, an increase in PaO2/FiO2 ratio of 20 mm Hg
- (20-20-20 rule for initiation of iNO). (start at OI 20, NO at 20ppm and response by inc in PF ratio by 20). Refer to figure 4 for a summary regarding starting and weaning iNO
- iNO can be adjusted in the range between 5-20ppm

Figure 4: Commencing iNO and weaning iNO



Cardiac pathophysiology in PPHN. (A) In severe PPHN, the PFO and PDA shunt right-to-left with IVS bulging to the left decreasing left ventricular (LV) preload. Extremely high right ventricular (RV) afterload leads to uncoupling of RV function leading to RV dilation. An open PDA might benefit the RV by providing a pop-off mechanism to reduce RV afterload. (B) Inhaled nitric oxide reduces PVR and reduces RV afterload and milrinone can improve RV function leading to synergy with ductal patency maintained by IV prostaglandin E1 (PGE1) Modified from Lakshminrusimha and Keszler – Diagnosis and management of PPHN in Assisted Ventilation of the Neonate, Elsevier.

Monitor methaemoglobin

- Methaemoglobin levels should be checked at 1 hour after starting INO and then every 6 - 12 hours.
- Monitor Methaemoglobin while on iNO (< 2.5% normal; reduce NO if ≥4%; give Methylene blue if >7%) Meth levels to be seen in VBG.
- Before starting iNO – R/O CHD with duct dependant lesions with right > left shunt such as Hypoplastic Left Heart Syndrome (HLHS), interrupted Aortic Arch, Pulmonary Veins Stenosis, TAPVD,
- Cranial USS should be performed prior to starting therapy and at least 24 - 48 hours after starting therapy

Weaning iNO

- Gradual process to minimize the risk of rebound vasoconstriction and resultant pulmonary hypertension
- Wean Oxygen 1st maintaining sats >95%
- If good response to iNO, weaning should start 30 minutes to 1 hr after initiation, if inspired oxygen concentration is below 60%,
- iNO is weaned only if PaO2 can be maintained at 60 mm Hg or higher (or preductal oxygen saturation as measured by pulse oximetry >90%) (30-60-90 rule of weaning iNO)
- wean iNO by 5 ppm every 4 hours, and once iNO dose is 5 ppm, gradual weaning by 1 ppm every 2 to 4 hours
- Reduce the INO dose to the minimum effective dose by 2ppm every 1 – 2 hours until the pre-ductal oxygen saturation drops > 5% or the pO2 drops below 60mmHg.
- -At this point, increase the INO dose back to the previous effective dose.
- -This dose should be maintained and formal weaning process undertaken when OI reaches 10.
- Continue weaning INO once the OI is around 10.
- At each step, success of weaning should be recorded by arterial blood gases and saturation monitoring.
- If at any step there is deterioration, INO dose should be increased to the previous successful step and weaning reconsidered after 8 - 12 hours.
- A smaller step in weaning can be considered at this stage.
- **Stop INO** in responders and non-responders at a dose of 1 ppm to avoid rebound hypoxaemia.
- -Before stopping INO increase the FiO2 by 0.2 - 0.4. The nitric oxide circuit should remain connected to the ventilator for 24 hours after stopping INO.
- **Non-responders to INO** should be weaned off as soon as possible so as to avoid dependence.
- **iNO is contraindicated**
- In the presence of LV dysfunction and evidence pulmonary venous hypertension
- Major Cardiac anomalies
- Lethal congenital anomalies

3.9.2 Sildenafil:

- Start early once a positive response to Nitric Oxide is demonstrated or when iNO is unavailable
- Sildenafil is a PDE5 inhibitor and causes pulmonary vascular dilatation by increasing cGMP levels
- IV administration may be beneficial as gastro-intestinal absorption may be impaired in critically ill patients.
- Dose 0.5mg to 3mg/kg/dose 6 H orally.

Weaning Sildenafil

Wean Sildenafil once NO has been successfully weaned and stopped.

-Reduce by 0.5mg/kg every 12-24hrs

3.9.3 Milrinone

- Milrinone is a PDE3A inhibitor and increases cAMP levels, resulting in pulmonary vascular vasodilatation
- Decreases rebound pulmonary hypertension when iNO is ceased.
- It has inotropic effects and is also effective in reducing the afterload by improving right sided cardiac output.
- Leads to better oxygenation and improvement in pulmonary and systemic haemodynamic in patients with suboptimal response to iNO2
- Can be used when iNO contraindicated
- In neonates use intravenous infusion without loading dose to avoid hypotension
- -Milrinone is administered at 0.33 µg/kg/min as a continuous infusion. The dose may be titrated up to 1 µg/kg/min with close monitoring of systemic blood pressure.

Role of prostaglandin E1 in management of PPHN

Critically unwell infants with failing right ventricle may benefit from a patent ductus arteriosus (PDA), which can work as a “pop off” valve in cases with severely elated PVR.

In infants with a constricting PDA, prostaglandin E1 will open the ductus arteriosus and keep in patent

This will decrease the RV afterload by allowing right to left shunt

Use should be guided by the echocardiography, and it would be specifically useful in infants with failing RV and a constricting ductus arteriosus.

Extracorporeal membrane oxygenation (ECMO)

Since the introduction of iNO and HFOV, together with surfactant, the need for ECMO in PPHN has declined considerably. In babies with an OI >40 despite iNO and HFOV, transfer to a paediatric intensive care for ECMO should be considered. Table 5 highlights criteria for starting and table 6 for exclusion criteria for ECMO.

Table 5: Criteria for ECMO

Selection Criteria for ECMO
1. Respiratory or cardio-respiratory failure, including severe barotraumas
2. OI > 40 for 4 hours or over 20 for 24 hours despite medical optimization
3. No lethal congenital anomalies
4. Disease is thought to be reversible
5. Gestation > 34 weeks and weight >1.9 kg
6. Less than10 days of high-pressure ventilation

Table 6: Exclusion criteria for ECMO

Exclusion Criteria (Absolute)
1. < 2.5kg for V-V ECMO and < 1.8kg for V-A ECMO
2. Major intracranial haemorrhage (Grade 3 or 4)

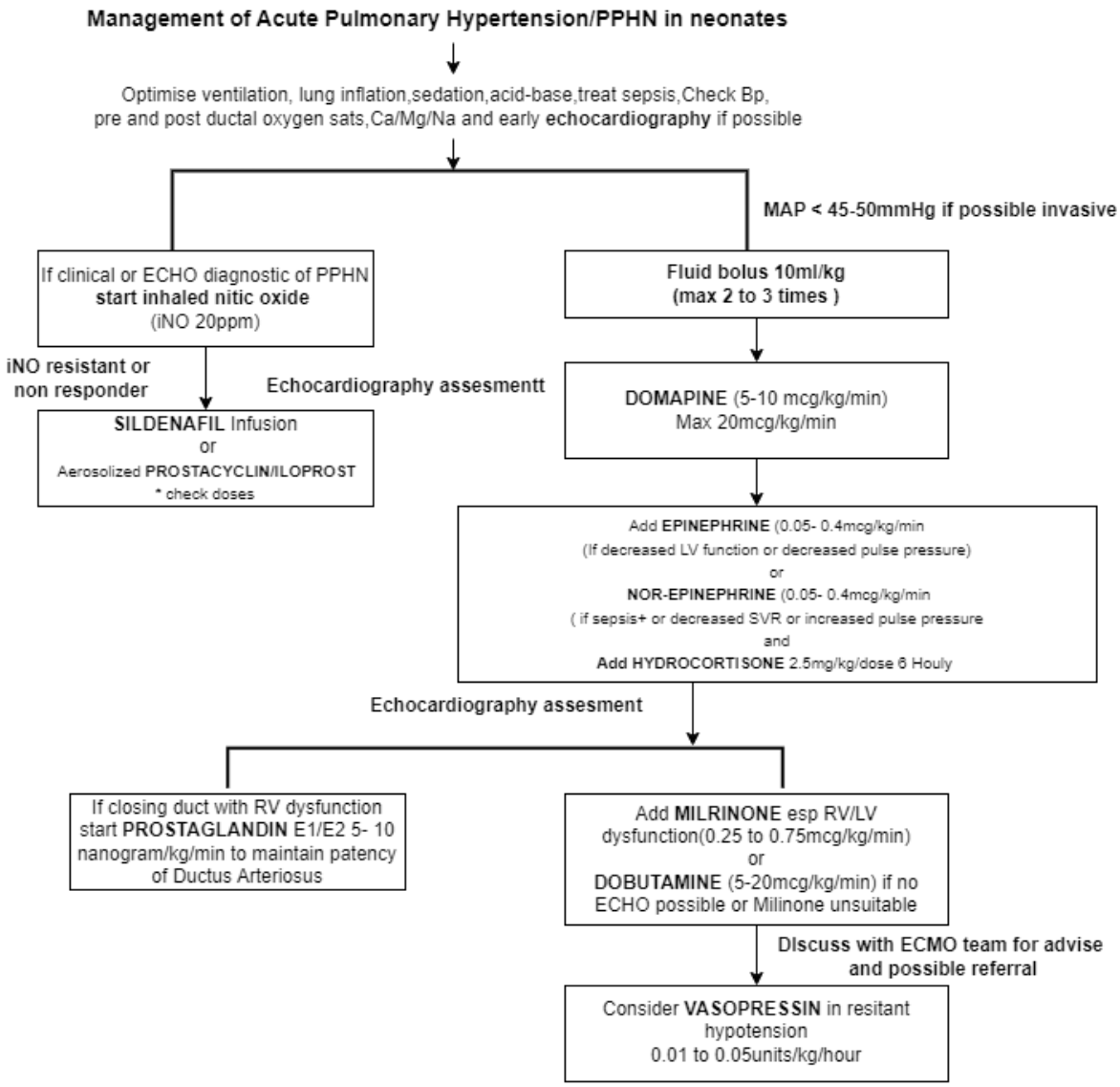
4.0 Laboratory Evaluation

4.1 Admission investigations:

- Complete blood count and differential, blood type and cross match, coagulation profile
- consider chemistries (Ca, Mg, K) consider cultures
- Arterial blood gas (ABG) every hour until pH >7.2, then ABG every 2 to 4 hours in ventilated patients for the initial 24 hours of life
- Serum lactate levels every 1 to 4 hours for the initial 24 hours, then trend if elevated or as indicated with level of metabolic acidosis, impaired organ perfusion, or with clinical change.

• Trend renal function laboratories based on age, clinical scenario, and urine output.

Figure 5: Approach to management of PPHN in term or near- term infants



1. Hyperoxia test: In this test, Oxygen should be administered through a plastic hood for at least 10 minutes. In cyanotic CHD case, the rise in PaO2 is usually no more than 10–30 mmHg and hardly ever exceeds 100 mmHg. With pulmonary diseases, PaO2 often rises greater than 100 mmHg.

   In infants with massive intra-pulmonary shunt from a respiratory disease may not show a rise in PaO2 to 100 mmHg. Conversely, some infants with cyanotic defects with a large pulmonary blood flow, such as TAPVC, may demonstrate a rise in PaO2 of 100 mmHg or higher
2. Normalization of the “cardiac electrolytes” calcium, potassium and magnesium are particularly important for optimal heart function, we recommend monitoring ionized calcium levels every 6 hours for the initial 24 hours, with de-escalation as indicated, based on replacement needs and clinical stability. Additionally, monitor chemistries at least every 12 hours in the acute period, with more frequent monitoring indicated when electrolyte replacement is required and for changes in urine output
3. When interpreting serum lactate levels, it is helpful to reassess potential causes for persistent lactic acidosis, such as hypovolemia, hypoperfusion, cardiac dysfunction, seizures, fevers, and/or increased metabolic demands. Additionally, high dose vasopressors may cause lactic acidosis through excessive vasoconstriction leading to impaired tissue perfusion or accelerated aerobic metabolism

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