Neonatal Pulmonary Hypertension

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Objectives:

1) Cardiovascular physiology: fetal, transitional, post-natal

2) Pulmonary hypertension pathogenesis: acute, chronic, arterial, venous

3) Pulmonary hypertension: presentation, diagnosis, treatment, and outcomes

ABSTRACT:

Neonatal pulmonary hypertension, also known as persistent pulmonary hypertension in the newborn (PPHN), is characterized by elevated pulmonary vascular resistance resulting in hypoxemia. Labile hypoxemia and differential cyanosis are clinical signs of pulmonary hypertension. An echocardiogram is the best study to confirm the diagnosis of PPHN. Management is mainly supportive with goals to recruit optimal lung volume, stabilize blood pressure, optimize oxygenation, reduce shunting, sedate when indicated, and correct acidosis. There are multiple available pulmonary vasodilators. Despite maximal intervention, some patients require extracorporeal membrane oxygenation (ECMO). The purpose of this paper is to review (1) fetal, transitional and postnatal cardiovascular physiology; (2) pulmonary hypertension pathogenesis; (3) clinical presentation, diagnosis, treatment and outcomes in patients with pulmonary hypertension. (1,2)

INTRODUCTION:

Neonatal pulmonary hypertension occurs in about 2 cases per 1000 births with mortality ranging from 4% to 33%. (3) Neonatal pulmonary hypertension occurs when pulmonary vascular resistance remains elevated after birth. While many instances of PPHN are idiopathic, common known causes of PPHN include meconium aspiration (MAS), pneumonia, respiratory distress syndrome, asphyxia, congenital diaphragmatic hernia (CDH) and Down syndrome. (14)

FETAL AND TRANSITIONAL CIRCULATION:

In fetal circulation, there is physiologic pulmonary hypertension because the lungs are fluid-filled. Similarly, the fetal systemic pressure is low because the placenta has low vascular resistance. At the time of birth, following the first breaths, the lungs are filled with air, and pulmonary vascular resistance decreases rapidly. Increase in oxygen tension associated with the extrauterine environment further vasodilates the pulmonary vasculature. At the same time, when the umbilical cord is clamped, and placental circulation is disconnected from the newborn, systemic arterial pressure rapidly rises to allow more blood to fill the lungs. (10)

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PATHOPHYSIOLOGY:

Risk factors:

Prenatally, risk factors for PPHN include being of African or Asian heritage, male gender, and certain maternal conditions including obesity, diabetes or asthma. Maternal substance exposures that increase the risk of PPHN to the neonate include nicotine, SSRI use after 20 weeks of gestation, late non-steroidal anti-inflammatory drugs (NSAID) or illicit substance abuse. (14)

Antenatal risk factors include being born post-term or early term/ late preterm birth, large for gestational age (LGA), delivery via Cesarean section, prolonged premature rupture of membrane,

(PPROM), chorioamnionitis, group B streptococcal infection, meconium passage before birth, perinatal acidosis, asphyxia, hypothermia, hypocalcemia, polycythemia, and other lung parenchymal diseases. (10,14)

PPHN presents in three patterns: (12)

1) Maladaptation: abnormally constricted pulmonary vasculature due to lung parenchymal disease.

2) Mal-development: abnormally constricted pulmonary vasculature in the absence of parenchymal disease.

3) Under-development: lungs and pulmonary vessels are underdeveloped due to decreased lung fluid or external mass effect.

Maladaptation: occurs in parenchymal diseases such as MAS, respiratory distress syndrome (RDS), and pneumonia. The underlying parenchymal disease causes hypoxia and acidosis which further leads to pulmonary vasospasm and vasoconstriction. Inflammatory cytokines (TNF, IL, PAF, ET-1) may play a role.

These cases of PPHN are often more reversible as the parenchymal disease is treated. Although the incidence has decreased likely due to a reduction in post-term births, a common case of maladaptation is meconium aspiration syndrome. Meconium aspiration causes obstruction in the airways, inactivates surfactant

and initiates the inflammatory cascade, all of which participate in the worsening of PPHN. (10,13)

Mal-development (excessive muscularization): occurs when there is normal lung parenchyma, but there are remodeled or muscularized pulmonary arteries. Most cases are idiopathic. Chronic exposure to hypoxemia (e.g., placental insufficiency, maternal diabetes) may be factors. Over-circulation of the pulmonary vasculature from intrauterine ductal closure, total anomalous pulmonary venous return (TAPVR), and chronic patent ductus arteriosus(PDA) are some other etiologies. Intrauterine exposure to selective serotonin reuptake inhibitors (SSRI), non-steroid anti-inflammatory drugs (NSAIDs), and nicotine have also been shown to be associated with mal-development PPHN. (10)

Underdevelopment (hypoplastic vasculature): occurs when prenatal conditions affect both alveolar and pulmonary arterial development. Oligohydramnios, PPROM, posterior urethral valves, renal agenesis, congenital diaphragmatic hernia (CDH) are examples of this type of process. In CDH, abdominal viscera herniate into the chest through the diaphragm defect. Although defects can be on either side or both, left-sided defects are more common. Lung development on both sides is disturbed, with the ipsilateral side more severely affected. Parenchymal lung reduction is usually present. Vascular development is altered and underdeveloped as well. There is also secondary surfactant deficiency and irregular alveolarization. Left ventricular hypoplasia has also been shown to be a contributing factor to pulmonary hypertension in CDH. (8)

Trisomy 21 is associated with pulmonary hypertension, as is alveolar capillary dysplasia, omphalocele and other disorders of physiological development. (6,12)

CHRONIC PULMONARY HYPERTENSION:

While most neonatal pulmonary hypertension cases are acute in onset and experienced soon after birth, some can progress into chronic pulmonary hypertension. Pulmonary hypertension associated with CDH or omphalocele, (1,6) for example, can continue for years, requiring chronic therapy.

Neonates may acquire pulmonary hypertension from underlying diseases, including bronchopulmonary disease (BPD) or congenital heart diseases. (1,2,5)

Pulmonary hypertension in bronchopulmonary disease (BPD) has been reported in 20-25% of patients with BPD and up to 50% in those with severe BPD3, (13)

Pulmonary hypertension in BPD is multifactorial. Poor alveolar septation, lung fibrosis, inflammation, altered microvascular development are observed in BPD. As a result, pulmonary vasculature remodels and subsequently leads to increased pulmonary vascular resistance and elevated pulmonary arterial pressures. (13)

Pulmonary venous hypertension (PVH) due to pulmonary venous stenosis (PVS) in neonates is due to the neo-intimal proliferation of myofibroblasts, progressing luminal stenosis or obliteration. (4) PVH can be congenital or acquired, isolated or associated with congenital heart disease. It is also often associated with BPD, specifically in the extremely premature infants with intrauterine growth retardation (IUGR). (15) Little is known about PVS in neonates. Diagnosis is via echocardiogram and confirmed by catheterization. Patients develop chronic pulmonary edema, pulmonary hypertension, and heart failure. Treatments are limited and overall prognosis is very poor. Some suggested therapies include balloon angioplasty, stenting, anti-VEGF, or surgical repair. (3,4,7,11)

CLINICAL PRESENTATION OF EARLY PPHN:

Generally, patients present with low Apgar scores, in respiratory distress and labile hypoxemia. They are often cyanotic with low PaO_2 and differential saturations where the postductal saturation is >5-10% lower than the pre-ductal saturation (this will not be observed if the PDA is closed).

The severity of hypoxemia is often communicated by the oxygenation index (OI):

OI = FiO_2 x Mean airway pressure X 100 / post-ductal PaO_2

An OI above 15 is concerning and is an indication for inhaled nitric oxide (iNO) therapy.

DIAGNOSIS:

Diagnosis of pulmonary hypertension is primarily by clinical presentation, typically respiratory distress, hypoxemia and differential cyanosis. Diagnosis should be confirmed by echocardiogram.

Echocardiographic evidence of pulmonary hypertension includes right to left shunting at the level of the PDA, right ventricular (RV) dilation and hypertrophy, ventricular septal flattening, poor RV function, and possible left ventricular (LV) dysfunction.

In patients with chronic pulmonary hypertension, pulmonary artery pressure is estimated by echocardiogram and confirmed by cardiac catheterization.

Pulmonary arterial pressure is considered elevated if:

- Mean pulmonary artery pressure > 25 mmHg
- Pulmonary artery wedge < 15 mmHg
- PVR > 3 $WU.m^2$

MANAGEMENT: (2,9,10,12)

Treatment for PPHN is mainly supportive care while treating the underlying disease (e.g., antibiotics for pneumonia) or allowing time for the injured lung to recover.

Mechanical ventilation:

Gentle ventilator management is vital to prevent further lung injury, but atelectasis is to be avoided. Both under-inflation and over-inflation of the lungs increase pulmonary vascular resistance. The goal is to have lung expansion to 8-9 ribs, $PaCO_2$ 45-60, and pH 7.25-7.40. High-frequency ventilation may help optimize lung recruitment and prevent volutrauma or barotrauma associated with high peak inflation pressure or tidal volume on conventional ventilation.

Surfactant:

Surfactant inactivation and deficiency are frequently seen in neonates with aspiration, RDS, pneumonia, and meconium aspiration syndrome. In patients with parenchymal lung disease, surfactant replacement therapy has been proven to decrease needs for ECMO or death by at least three fold. Surfactant does not improve outcomes in patients with CDH. Discretion should be used in situations where CDH is complicated by other risk factors.

Oxygen:

Oxygen is a potent vasodilator. However, clinicians should be aware of oxygen toxicity. Pre-ductal saturations 90-95% may be adequate. If serum lactate levels are normal (<3 mM/L) and urine output is sufficient (>1 ml/kg/hour), a post-ductal oxygen saturation in the 70%-80% range is acceptable. Oxygen carrying capacity (OC) is equally important. 16-22 is considered the normal range. Adequate hemoglobin to maintain OC plays an important role in the management of PPHN.

High oxygen delivery above 60% and even only brief exposure to 100% have been shown to increase vasoconstriction and reduce response to iNO as well as increase rebound PPHN when weaned off iNO. (9)

Sodium bicarbonate:

Sodium bicarbonate should be used with caution. It may help correct metabolic acidosis but also produce respiratory acidosis. Carbon dioxide crosses the blood-brain freely and may decrease cerebral pH. Further, alkalosis must be avoided as it causes cerebral vasoconstriction hence reduces cerebral blood flow. Alkaline infusions are reported to be associated with increased use of ECMO.

Sedation/Analgesia/Paralysis:

During supportive care for PPHN, sedation and analgesia are often needed. Paralysis should not be used routinely. Paralysis may be required on occasion if sedation and analgesia alone are inadequate. However, paralysis can precipitate atelectasis and worsen V-Q mismatch. It has been shown that routine paralysis is associated with increased mortality. Prolonged chemical paralysis is also associated with sensorineural hearing loss in survivors of CDH.

Blood pressure stabilization: blood pressure should be targeted within the normal range for age with boluses and inotropes if necessary. The provided algorithm has specific suggestions for management of cardiac dysfunction and blood pressure support.

Pulmonary vasodilators

As mentioned earlier, oxygen is a potent vasodilator. Many patients, however, even after the above management and oxygen, remain hypoxemic. Other pulmonary vasodilators are often needed. ECMO should be considered if the patient fails medical management or deteriorates rapidly.

1. Inhaled nitric oxide: should be initiated if OI >15 and lungs well recruited. A dose of 20 ppm is considered most optimal in improving pulmonary to systemic arterial pressure ratio. Higher doses are not recommended as they do not provide better results, yet there is an increased association with methemoglobinemia.

Weaning iNO should be gradual to minimize the risk of rebound vasoconstriction. It is generally recommended that once there is improved and stable oxygenation, the first effort should be to wean inspired oxygen concentration to below 60%. Inhaled nitric oxide then can be weaned stepwise if pre-ductal saturations remain stable and within range, possibly by 5 ppm every 1-4 hours until the dose is 5 ppm, then by 1 ppm.

Contraindications:

- Congenital heart defects that depend on right to left shunting across the ductus arteriosus such as critical aortic stenosis interrupted aortic arch, hypoplastic left heart syndrome, etc. iNO may worsen cyanosis.
- iNO can worsen pulmonary edema in conditions with pulmonary overflow such as total anomalous pulmonary venous return.

2. Phosphodiesterase (PDE) 3A inhibitor: works by increasing cAMP availability and thus vasodilation. Milrinone is preferred when blood pressure is normal, but there is evidence of ventricular dysfunction. A loading dose of 50 µg/kg over 30-60 minutes followed by a maintenance dose of 0.33 µg /kg/min and titrating to 0.66 µg/kg/min and up to 1 µg /kg/min based on the response. Since milrinone has systemic vasodilation effect, it may cause hypotension. A bolus 10 mg/kg of fluid given prior to the loading dose might prevent hypotension.

3. Phosphodiesterase (PDE) 5 inhibitor: works by preventing cGMP breakdown and may work in conjunction with iNO to improve oxygenation. Sildenafil can be administered orally or intravenously although the intravenous route is preferred during acute illness due to uncertain absorption if given via the oral route. Hypotension is a common side effect. Sildenafil is given as a loading dose 0.42 mg/kg over 3 hours (0.14 mg/kg/hour), then continuous infusion at 0.07 mg/kg/hour. If intravenous preparation is not feasible, sildenafil can be given orally as a dose of 1-2 mg/kg q 6 hours.

4. Prostaglandins: A continuous drip of alprostadil (prostin) may help with vasodilation and also maintains patency of the ductus arteriosus thus reducing afterload on the RV. Little is known about the efficacy and side effects of aerosolized prostaglandin E1 and inhaled prostaglandin I2 on neonates.

In neonates with chronic pulmonary hypertension, other medications might offer benefits:

1. Endothelin receptor blocker: (Bosentan) works by decreasing vascular tone. Side effects are hepatic toxicity and anemia.

2. Prostacyclins: works by increasing cAMP and resulting in direct vasodilatation.

3. Treprostinil (Remodulin): starting dose is 2 ng/kg/min and increase gradually to a goal of 50-80 ng/kg/min over days or weeks. It can be given via IV or SQ routes. Side Effects include hypotension, pain, nausea, vomiting, diarrhea, and abdominal pain.

4. Inhaled prostacyclins (Iloprost): little is known about efficacy on neonates. The need for frequent administration (6-9 times/day) and bronchoconstriction side effects limit its use on this patient population.

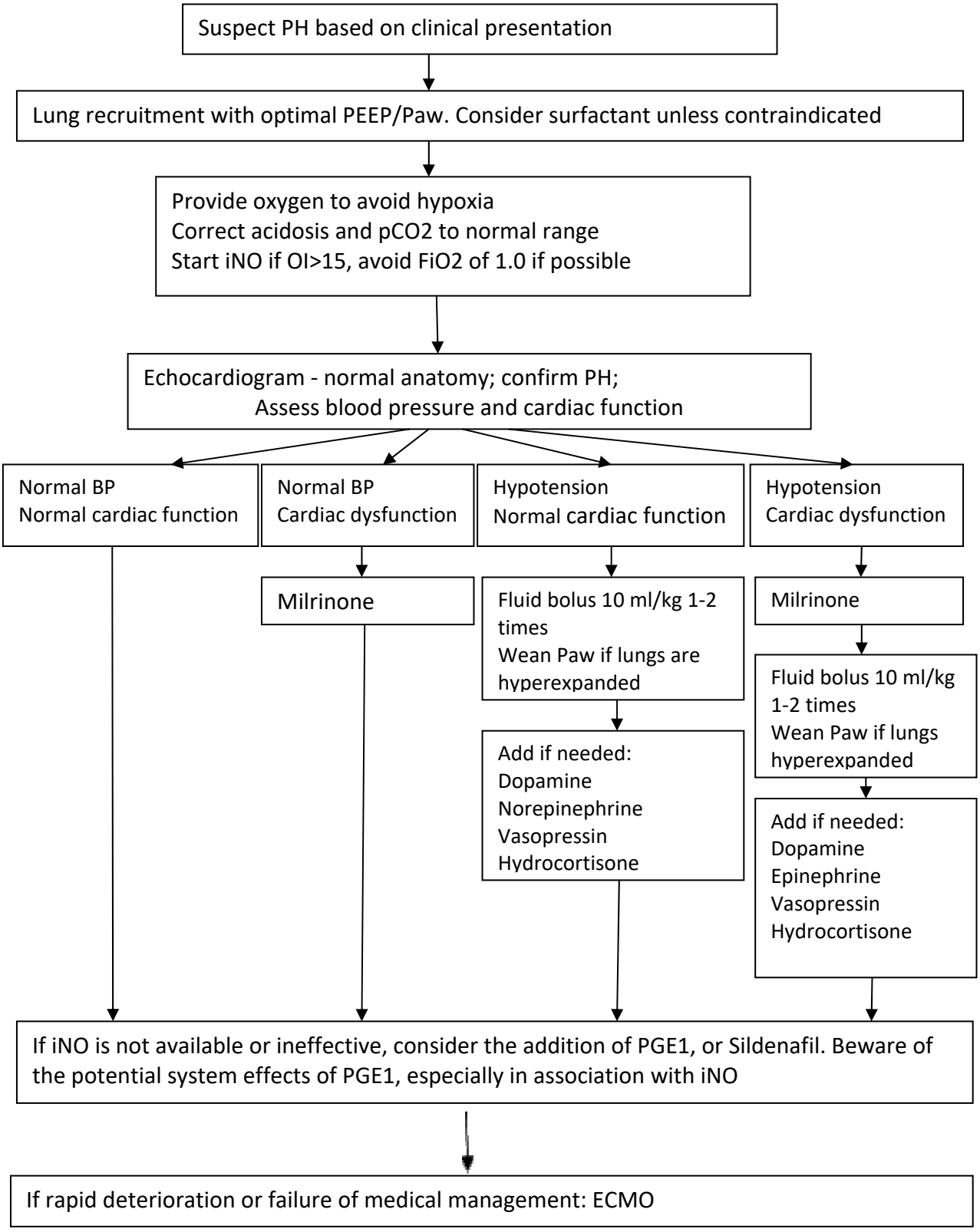

Figure: a Suggested algorithm for the management of acute pulmonary hypertension

References:

1. *Abman, SH. Differences between the fetal, newborn, and adult pulmonary circulations: relevance for age-specific therapies. Pul-Circ 2014;4(3):424-40.*
2. *Abman, SH. Pediatric Pulmonary Hypertension. Guidelines from the American Heart Association and American Thoracic Society. Circulation 2015;132:2037-99.*
3. *Ambalavanan, N. Pulmonary hypertension in bronchopulmonary dysplasia. Birth Defects Research 2014;100:240-6.*
4. *Backes, CH. Pulmonary Vein Stenosis in Infants: A Systemic Review, Meta-Analysis, and Meta-Regression. J. Pediatr 2018.*
5. *Durmowicz, AG. Mechanisms of Structural Remodeling in / Chronic Pulmonary Hypertension.NeoReviews. 1999.*
6. *Hutson, S. et al. High Prevalence of Pulmonary Hypertension Complicates the Care of Infants with Omphalocele. Neonatology.2017; 112(3).*
7. *Leopold, JA. Pulmonary Venous Remodeling in Pulmonary Hypertension. Circulation 2018;137:1811-13.*
8. *Kinsella, JP. The Left Ventricle in Congenital Diaphragmatic Hernia: Implications for the Management of Pulmonary Hypertension. J Pediatr 2018.*
9. *Lakshminrusimha S. Considerations in the management of hypoxemic respiratory failure and persistent pulmonary hypertension in term and late preterm neonates. J Perinatol 2016;36.*
10. *Nair J, Lakshminrusimha S. Update on PPHN: mechanisms and treatment. Seminars in perinatology. 2014;38(2):78-91.*
11. *Quinonez, LG. Outcomes of surgery for young children with multivessel pulmonary vein stenosis.Cardiovasc Surg 2015;150:911-7.*
12. *Steinhorn, RH. Diagnosis and treatment of pulmonary hypertension in infancy. Early Hum Dev. 2013;89(11):865-874.*
13. *Steinhorn, RH. Pulmonary hypertension in bronchopulmonary dysplasia. Seminars in Perinatol 2013;37:124-31.*
14. *Steurer, MA. Persistent Pulmonary Hypertension of the Newborn in Late Preterm and Term Infants in California. Pediatrics 2017;139.*
15. *Swier, NL. Pulmonary Vein Stenosis in Neonates with Severe Bronchopulmonary Dysplasia. Am J Perinatol;33:671-7.*

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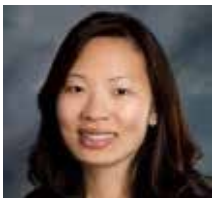

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