Principles of management in neonates with acute pulmonary hypertension

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Note: This document applies to mechanically ventilated neonates with persistent hypoxemic respiratory failure (HRF) in association with suspected/proven acute pulmonary hypertension (PH). This document is not applicable for infants with congenital diaphragmatic hernia.
The document has been subdivided into broad monitoring and management topics and each topic is subdivided into 3 sections, domain, recommendation, and strength of recommendation following the EPIQ bundle format.

A. Monitoring of clinical variables

Domain	Recommendation	Strength of recommendation & certainty of evidence
What clinical variables should be monitored?	**Recommended:** ***Non-invasive:*** Blood pressure (systolic, mean, diastolic) Heart rate Capillary refill time Urine output Continuous pre and post ductal oxygen saturation monitoring ***Invasive:*** Arterial line should be used for monitoring of BP in neonates with PPHN (when possible) Serial assessments of oxygen index (OI) is recommended [OI = MAP × Fio_2 × 100 / Pao_2] OI 15-25: Moderate HRF 25-40: Severe HRF >40: Very severe HRF **Suggested:** If OI is not available, may consider OSI (oxygen saturation index) - OSI = MAP × FiO_2 × 100 / SpO_2 [OI=0.0745 + (1.783xOSI)] (not validated for OI >25 or SpO2 <85 or >95) CVP monitoring may be helpful	Strong recommendation [based on group consensus; low to very low certainty of evidence] Weak recommendation [based on group consensus; low to very low certainty of evidence]

	[Low values (<5 cm H_2O) suggest hypovolemia; trending may be helpful]	
What BP thresholds should be used to define hypotension?	Target Blood Pressure systolic / diastolic and mean BP above the 3rd centile for gestational age (Zubrows)- or mean BP > CGA as per standard local protocol. May use patient specific BP threshold where tissue oxygen delivery is deemed compromised based on clinical judgement	Weak recommendation [low certainty of evidence]
What should be the frequency of non-invasive BP monitoring?	BP should be measured q 15 min until patient is hemodynamically stable following which q 1 hour pre-ductal BP should be preferred in non-invasive BP measurement	Weak recommendation [based on group consensus; very low certainty of evidence]
How should urine output be monitored?	Routine UOP monitoring q 4-8 h based on local practice. A urine output of <0.5 ml/kg/hr or greater than 50% drop from baseline urine output with optimized intravenous fluids may suggest hemodynamic compromise – may consider more frequent monitoring. Monitoring using in dwelling urinary catheter may be used in anuria or suspected retention [eg. from opioids or muscle relaxant]	Weak recommendation [based on group consensus; very low certainty of evidence]
Should NIRS be routinely used?	Clinicians may use NIRS as an adjunct in centres where NIRS monitoring is available and local practice guidelines have been developed. Insufficient evidence to suggest thresholds for intervention	Weak recommendation [low certainty of evidence]

B. Fluids

What type of fluid?	Normal Saline (NS)	Strong recommendation [based on group consensus; low certainty of evidence]

Volume of each bolus	10ml/kg over 20-30min	Strong recommendation [based on group consensus; low certainty of evidence]
Maximum volume of initial resuscitation	In patients with suspected hypovolemia consider giving 1-2 NS boluses. In neonates with PPHN avoid multiple fluid boluses due to potential concomitant cardiac dysfunction.	Weak recommendation [based on group consensus; low to very low certainty of evidence]

C. Ventilation

What mode of ventilation should be used?	Both conventional and high frequency modes can be used as per local clinical practice.	Strong recommendation [moderate certainty of evidence]
What should be the SpO2, pH, pCO2 and paO2 targets in patients with PPHN?	Suggested clinical targets: pH: 7.25-7.35 pCO2: 45-55 mm Hg [avoid hypocarbia] PaO2: 60-80 mm Hg [avoid hyper and hypoxia] Preductal SpO2 targets: 91-95% (in refractory cases may consider 92-97%; avoid hyperoxia)	Weak recommendation [based on group consensus; low to very low certainty of evidence]

D. Sedation / Muscle relaxants

Is there indication for routine use of muscle relaxants?	Should not be used routinely in preterm infants Maybe attempted in selected cases with refractory hypoxemia in spontaneously breathing infants	Strong recommendation [based on group consensus; low certainty of evidence] Weak recommendation [based on group consensus; low certainty of evidence]
Is there indication for routine use of sedation?	Should not be used routinely in preterm infants.	Strong recommendation [based on group

		consensus; low certainty of evidence] Weak recommendation [based on group consensus; low certainty of evidence]
	Maybe considered in selected cases to ensure patient comfort.	

E. Vasopressor / Inotropes

In acute PH neonates with potential hemodynamic compromise, early use of echocardiography (TNE where available) is recommended to confirm diagnosis, establish severity and guide hemodynamic management. Critical cyanotic CHD should be ruled out by a pediatric cardiologist in patients with persistent HRF. In the absence of echocardiography (or when not feasible), the first choice of cardiotropic agent should be informed by clinical suspicion of cardiac dysfunction or peripheral vasodilatation. Hypotension driven by low diastolic BP may indicate low systemic vascular resistance (SVR) while low systolic BP may indicate cardiac dysfunction/low cardiac output. Vasopressor may be considered as primary agent for former while an inotrope may be considered for the latter. Careful assessment for treatment response is warranted.		Strong recommendation [based on group consensus; low to very low certainty of evidence]
What is the first line vasopressor?	Norepinephrine or vasopressin are suggested as first line agents [due to their relatively low potential to adversely affect PVR/SVR ratio] Dopamine should be used with caution and is not recommended as first line vasopressor in PPHN as it may worsen PVR/SVR ratio	Weak recommendation [based on group consensus; low to very low certainty of evidence]
What is the starting dose of vasopressors and the rate of titration?	*[All dosages mentioned below are suggested starting dosages; for maximum dose and drug interactions consult local formulary]* Vasopressin: 0.0003 u/kg/min, increased by 0.0001-0.0003 u/kg/min q 30 min Norepinephrine: 0.05mcg/kg/min, increase by 0.05mcg/kg/min q30 minutes	Weak recommendation [based on group consensus; low to very low certainty of evidence]
What is the first line inotrope?	Dobutamine or Epinephrine	Weak recommendation [low to very low

	Milrinone is the agent of choice in patients with low cardiac output (CO) in the presence of normal or high BP. May induce hypotension in neonates with HIE undergoing therapeutic cooling.	certainty of evidence] Strong recommendation [moderate certainty of evidence]
What is the starting dose and titration dose of first line inotrope and the rate of titration?	Dobutamine: 5mcg/kg/min, increase by 5mcg/kg/min q30 minutes Epinephrine: starting dose 0.01 mcg/ kg/min. Increase by 0.01-0.02 q 30-60 minutes Milrinone: starting dose 0.33mcg/kg min, may be increased up to 0.66 mcg/kg/min, no loading dose	Weak recommendation [based on group consensus; low to very low certainty of evidence]
What clinical and biochemical monitoring should be used?	Specific additional Biochemical parameters: Blood gas, serum lactate, glucose (epinephrine), Na (if vasopressin)	Strong recommendation [based on group consensus; low to very low certainty of evidence]

F. Pulmonary vasodilator therapy

What is the first line pulmonary vasodilator therapy?	Inhaled nitric oxide (iNO) Dose: 20 ppm	For term and near-term infants: Strong recommendation [moderate certainty of evidence] For preterm infants: Weak recommendation [low certainty of evidence]
Are there any additional pulmonary vasodilator therapy?	No clear evidence for 2nd line therapy. When additional pulmonary vasodilatory effect is desired, and BP is not a concern: Milrinone Slidenafil Prostacyclin MgSO4	Weak recommendation [very low certainty of evidence]

	Bosentan When opening the ductus to protect systemic circulation and cardiac function is required: PGE1	

G. Adjunct therapies

Is there any indication for the routine use of sodium bicarbonate infusions?	Use of sodium bicarbonate in the context of PPHN is not routinely recommended However, to optimize the pH milieu for a minimal critical threshold to prevent inactivation of vasopressor/inotropes bicarbonate may be used in selected cases	Strong recommendation [based on group consensus; low certainty of evidence] Weak recommendation [based on group consensus; very low certainty of evidence]
Is there any indication for the use of corticosteroids?	No available evidence to support use of steroids in the context of PPHN. For inotrope-refractory hypotension its use may be considered. Choice of corticosteroid: Hydrocortisone 0.5-1.0 mg/kg – as per local protocol	Weak recommendation [based on group consensus; very low certainty of evidence]

Suggested role of TNE guided care in neonates with acute PH

A complete echocardiography reported by pediatric cardiologist is recommended in patients with refractory PH/HRF, to rule out congenital heart disease [Strong recommendation; based on group consensus]	
For sites with TNE capabilities, when should a TNE be requested?	Early TNE is suggested to delineate underlying circulatory physiology in patients with worsening oxygenation, where PH is suspected or in patients with PH-associated hemodynamic compromise

How some TNE findings may influence management decisions in presence of elevated pulmonary pressures?	
Good biventricular systolic function or only RV dysfunction, normal range biventricular outputs, and normal blood pressure.	May consider addition of pulmonary vasodilators. If a systemic agent is being used and results in significant reduction in blood pressure, consider using vasopressin or norepinephrine to treat resultant systemic vasodilation.
Good biventricular systolic function or only RV dysfunction, normal range biventricular outputs, and low blood pressure.	Consider using vasopressin or norepinephrine to treat systemic hypotension.
Good biventricular systolic function or only RV dysfunction, normal RV output, low volume left ventricle (LV) with low LVO, bidirectional or right to left shunting PDA.	Suggest low pulmonary blood flow from right to left ductal shunt. May consider therapies which will reduce ratio of pulmonary to systemic vascular resistance – selective pulmonary vasodilators (iNO), selective rise in systemic vascular resistance (vasopressin) or relatively more rise in systemic vascular resistance than pulmonary (norepinephrine).
RV dysfunction and low RV output, good LV function.	May select therapies aimed to improve RV function/output and reduce RV afterload – selective pulmonary vasodilator (iNO), Milrinone for combined affect of pulmonary vasodilation and positive inotropy (if patient normotensive), Other systemic pulmonary vasodilators (if patient normotensive) Dobutamine or beta dose epinephrine to improve RV inotropy and output (especially if systemic hypotension). Assess ductus, if restrictive or closed, consider using prostaglandin in order to offload the RV and support systemic circulation (especially if RV dysfunction persists despite above).
Biventricular dysfunction and low cardiac outputs	Therapies to improve cardiac function and outputs should be considered early (dobutamine, beta dose epinephrine) along with selective pulmonary vasodilator (iNO).

	Caution is advised in the use of systemic pulmonary vasodilators unless blood pressure are robust.
Exclusive LV dysfunction and low LVO	The adequacy of systemic circulation may be duct dependant. May consider dobutamine or beta dose epinephrine to improve LV function and output before initiating treatments that may drop pulmonary vascular resistance. Caution is advised in the use of therapies which may increase LV afterload, such as vasopressin. Assess ductus, if restrictive or closed, consider using prostaglandin in order to support systemic circulation.

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