Acute Stabilization & Management of PPHN

STABILIZING: FROM INITIAL EVALUATION TO OPTIMIZATION

INITIAL EVALUATION

- Chest radiograph should be used on admission and over time to detect the underlying etiology of PPHN and evaluate lung inflation as a result of therapy
- Echocardiograms assess pulmonary vascular resistance, vascular anatomy, and cardiac structure and function. Check for:

  * Patent Foramen Ovale or Patent Ductus Arteriosus: right-to-left or bidirectional shunt * Ventricular septal position: "flattening" or "leftward bowing"
  *Ventricular dysfunction (right and/or left ventricle) * Pulmonary artery/right ventricle systolic pressure from <1/2 systemic, to systemic, to supersystemic

PULMONARY OPTIMIZATION

- Optimal lung inflation and mean arterial pressure are the goals of therapy. Consider the particular applications of different ventilator modalities, such as use of high-frequency oscillatory ventilation for children with congenital pneumonia, inadequate lung inflation despite potentially dangerous conventional ventilator settings, etc.
- Use surfactant therapy unless contraindicated to reduce need for ECMO.
- Pre-ductal saturation targets should be 92-97%. Actively wean FiO_2 supplementation when that range is exceeded.
- Manage with normal carbon dioxide levels when feasible, via "gentle" ventilation.
- Avoid alkalosis and acidosis by maintaining a minimal arterial pH of 7.25 to 7.3 (higher when the child is critically ill).

CARDIOVASCULAR OPTIMIZATION

Blood pressure goals target adequate perfusion and mean arterial blood pressure based on gestational age, with enough oxygen to meet local tissue bed metabolic needs.

- DO NOT create systemic pressure greater than pulmonary pressure to reverse right-to-left ductal shunting and improve saturations.
- Target BP: normal for age; 45-55 mmHg (with urine output)
- For hypoperfusion or hypotension, consider slow normal saline bolus of 10 mL/kg
- Consider dosing with hydrocortisone every 6 hours through the acute stabilization phase to help with blood pressure and oxygenation (~1 mg/kg, with a delayed time to effect)
- If needed, administer cardiotonic drugs, such as low-dose epinephrine and vasopressin, based on the underlying cause of PPHN

MONITORING: CRITICAL TO BOTH STABILIZING AND CONTINUED MANAGEMENT

VASCULAR ACCESS

Vascular access should be central (umbilical venous catheter or peripherally inserted central venous catheter) when possible, with at least one peripheral IV for medication, fluids and blood products

MONITORING AND LAB VALUES

- Electrocardiogram (ECG) should be done after initial cardiopulmonary stability is achieved to provide a baseline indication of the nature of the PPHN.
- Monitor continually for pre- and post-ductal saturations, transcutaneous carbon dioxide, oxygenation index, blood pressure and urine-based indicators
  - Target preductal saturation of SpO_2 92-97%
  - OI = (MAP × FiO_2)/PaO_2 [Oxygenation index = (mean airway pressure × fraction of inspired O_2)/partial pressure of O_2]
- Laboratory evaluation should include complete blood count and differential, blood type and cross, with chemistries and cultures as appropriate
  - Monitor arterial blood gas hourly until pH >7.2
  - Check serum lactate levels every 1-4 hours for first 24 hours
  - Monitor blood glucose, anemia, ionized calcium, serum magnesium and potassium
  - Cardiac electrolytes and renal function labs offer information on stability

MANAGING: CONTINUING CARE THROUGH ESCALATION OR WEANING

GENERAL MEDICAL OPTIMIZATION

- Evaluate children for sepsis, congenital pneumonia and other infections. consider empric antibiotics.
- Minimize stimulation of any kind (touch, noise, bright lights, suctioning, repositioning, etc.) to help avoid unrecoverable hypertension crisis.
- Sedation can help improve cardiopulmonary stability and decrease pain and discomfort. Pharmacologic paralysis is NOT recommended.
- Optimize tissue oxygen delivery, which depends on cardiac output and blood oxygen content.
  - Tissue oxygenation depends more on hemoglobin concentration than arterial oxygen content; transfusion is only recommended to help achieve hemoglobin concentrations of 10-14 g/dL, or as indicated for hypovolemia or anemia.
- Consider one or more PPHN-specific therapies: milrinone, nitric oxide, prostacyclin analogues, prostaglandin and sildenafil.

HYPOXEMIA

- Use FiO_2 to target preductal saturations 92-97%; actively wean at higher saturations to avoid excessive O_2
- Use inhaled NO (iNO) for OI>20, starting at 20 ppm
  - Wean FiO_2 for responders to ~60% as saturation allows
  - Discontinue/wean nonresponders
- Consider Sildenafil (IV, 0.4 mg/kg over 3 hours to start, 1.6 mg/kg/day to maintain) or Iloprost (IH, 2.5 mcg every 2 hours to start, range of 1.25-5 mcg every 2-6 hours) IF:
  - OI reaches 25 or higher or
  - Preductal SaO_2 is below 90% when on >80% FiO_2 or
  - Preductal PaO_2 falls below 60 mmHg or
  - On echocardiogram, right ventricular pressures is >3/4 systemic AND there is normal left ventricular function (with left ventricular dysfunction, use milrinone or epinephrine)

HYPOTENSION OR HYPOPERFUSION

- Consider use of epinephrine, particularly in cases of cardiac dysfunction.
  - Doses range from 0.02-0.3 mcg/kg/min
  - Consider adding a second agent when dose exceeds 0.1 mcg/kg/min
  - NOT with tachycardia (heart rate >160 bpm)
- Consider adding hydrocortisone, but take caution as use can mask infection or sepsis symptoms. Note it takes several hours for the first dose to take effect.
  - Starting dose of 2 mg/kg
  - Maintenance dose of 1 mg/kg every 6 hours
- For patients with hypotension with normal heart function, consider use of vasopressin. It increases SVR but not PVR, and has no effect on contractility or cardiac function.
  - Doses range from 0.1-1.2 milli-units/kg/min, which can be doubled to effect/max
  - Monitor closely for hyponatremia and urinary retention

CARDIAC DYSFUNCTION

After blood pressure is stabilized:

- Start milrinone, with lower doses for patients with kidney injury; lower doses result in less systemic hypotension
  - Doses range from 0.125-0.5 mcg/kg/min
  - Increase in 0.05 mcg/kg/min increments as needed (common dose is 0.25-0.35 mcg/kg/min)
- Use prostaglandin for moderate-to-severe right ventricle dysfunction and possible ductal-dependent CCHD
  - PGE1 maintains ductal patency and offloads failing right ventricle (shunts from right to left; expect postductal saturations to fall), and may reduce PVR
  - Start dose at 0.015-0.025 mcg/kg/min

ESCALATION TO ECMO SUPPORT

- Consider combination therapies or clinical trials for children failing PPHN-specific treatments
- ECMO indications include:
  - OI > 40 for 4-6 hours
  - OI > 25-30 for 12-24 hours despite optimal management, including addition of second PVR agent
  - Severe PPHN or hypoxemia refractory to iNO and optimal cardiorespiratory conditions
  - Pressor-resistant hypotension or lactic acidosis

WEANING THERAPY

- Re-evaluate frequently with labs, and use a post-stabilization echocardiogram or chest radiograph to guide ongoing management
- Avoid rapid weans as they can result in rapid decompensation

Adapted from Ball MK, Seabrook RB, Bonachea EM, Chen B, Fathi O, Nankervis CA, Osman A, Schlegel AB, Magers J, Kulpa T, Sharpin P, Snyder ML, Gajarski RJ, Nandi D, Backes CH. Evidence-based guidelines for acute stabilization and management of neonates with persistent pulmonary hypertension of the newborn. *American Journal of Perinatology*. 2021 Dec 1. Epub ahead of print.

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