Evidence Supports

Ventilation and Permissive Hypercapnia

- Permissive hypercapnia and gentle ventilation can decrease lung injury by preserving spontaneous respirations, avoiding high ventilator pressures, avoiding muscle relaxants and oversedation, and acceptance of lower preductal saturations >80% and allow patients to accommodate and stabilize [1]. The primary treatment goal in atraumatic reversal of persistent pulmonary hypertension (PPHN) is avoiding over ventilation and barotrauma with gentle ventilation. A ventilation strategy aiming for preductal saturation between 80 and 95%, postductal saturation above 70% and arterial CO2 levels between 50 and 70 mm Hg (6.9–9.3 kPa, permissive hypercapnia) is well accepted [17].
- The mode of ventilation does not appear to be related to outcome. Snoek et al., found no significant difference in combined outcome and development of Brochopulmonary Dysplasia in the use of Conventional versus High Frequency Oscillatory Ventilation in management of CDH when taking into account the lung to head ratio (LHR), side and size of the defect, and position of the liver [18]. The infants managed with conventional ventilation were found to have a shorter duration of ventilation and inotrope support. Additionally, they were less likely to receive vasoactive medications, phosphodiesterase inhibitors or be placed on ECMO.

Other

- **Serial oxygenation index (OI)** has been shown to predict the survival of infants with CDH on day of life 1 (DOL 1) [14, 18]. The main determining factor in the survival of these infants is the severity of pulmonary hypoplasia and persistent pulmonary hypertension. Utilization of serial OI in management decisions for patients with CDH can assist with postnatal counseling regarding prognosis, guide escalation of therapy such as ECMO, and potentially guide timing of surgery. OI can be calculated according to the formula, OI =(MAPx FiO2x100)/PaO2. Consecutive **post-ductal** blood gases with an OI of greater than 40 is generally considered an indication for ECMO [15]. **Pre-ductal** blood gases are ideal to guide management as post-ductal OI's can be falsely elevated in the setting of right to left shunting at the PDA, however are often not available with arterial access via the UAC.
- **B-type natriuretic peptide (BNP)** has been shown to be significantly increased in patients with pulmonary hypertension. Partridge et. al., describe serial BNP levels on DOL 1, post operative day 1, and weekly aids in guiding management decisions [11].
- **Surfactant therapy** is recommended in neonates < 34 weeks gestation with findings of atelectasis on chest x-ray suggestive of respiratory distress syndrome (RDS) [4]. Furthermore, surfactant is recommended in infants who underwent fetal tracheal occlusion (FETO) when the occlusion is released <48h prior to delivery. In addition, it does not appear to be effective therapy when PPHN is the primary diagnosis, but should be considered in the presence of associated parenchymal lung disease when there is a suspected surfactant deficiency or impairment as in RDS or meconium aspiration syndrome [19].
- **Echocardiogram** Echocardiography should be performed on admission for all infants. Perform echo emergently if there is any clinical instability as well as prior to the initiation of iNO [6].
- **Vasopressin** usage in CDH patients with catecholamine resistant hypotension has been shown to prevent ECMO in 6 of 11 cases while norepinephrine has also been shown to improve pulmonary artery to systemic blood pressure ratios [21, 32].

- **Sildenafil** is recommended as an adjunctive therapy for infants with PPHN refractory to iNO especially when OI exceeds 25. Further, It may augment the pulmonary vasodilator effects of iNO. Intravenous Sildenafil should be considered in infants with severe pulmonary hypertension not responsive to iNO, and has been shown to improve oxygenation and cardiac output [17]. PH has been shown to resolve with prolonged Sildenafil therapy in patients with CDH with recommended dosing of 1mg/kg QID PO. Sildenafil administration should be delayed in extremely preterm infants until retinal vascularization is established. Kelly et. al, found that in a systematic review meta-analysis of three studies including 77 patients showed enteral sildenafil therapy had a reduction of mortality and improved oxygen levels, however, the studies were done in settings where iNO and HFOV were not available resources. Therefore, Stark et. al., does not recommend enteral Sildenafil as initial therapy if iNO is available and should only be considered in a resource limited setting since the data of its efficacy and safety are insufficient.
- **iNO**: In one retrospective review, evidence showed that iNO may improve PaO2, AA gradient, and PaO2/FiO2 ratio in patients with preserved ventricular function. In addition, iNO may lower the rate of patients requiring ECMO in the same group [8].
- **PGE**: In one small retrospective study where the average age of the participants was 11 days, researchers noted improved O2 in patients that received PGE. In that same study, researchers concluded that flow velocity in the ductus arteriosus was decreased with PGE. Using PGE prophylactically may decrease the duration of non-invasive ventilation, ventilatory support, and decrease the O2 requirement in these patients as compared to administering it reactively [9].
- Ventricular dysfunction and performance has been associated with disease severity, need for ECMO, and mortality in patients with CDH.

Evidence Against

- Surfactant therapy showed no benefit in the treatment of term infants > 37 weeks prenatally diagnosed with isolated CDH. The CDH study group identified 522 infants with similar demographic characteristics with the exception of race, and found that the use of ECMO and incidence of chronic lung disease were higher, and survival lower in the surfactant treatment arm than those not treated with surfactant [19].
- **iNO** use may be associated with increased mortality. A prospective review of seventy centers in 13 countries with a total of 3367 infants in the Congenital Diaphragmatic Hernia Study Group registry revealed that iNO use is common but highly variable among the centers. 97.1% of all centers participating used iNO to treat patients with CDH both with and without the presence of pHTN. Furthermore, the use of iNO fails to reduce the risk of death and ECMO use [13].
- Kumar, et. al. suggest the poor response to iNO in CDH pulmonary hypertension may be secondary to preexisting pulmonary venous hypertension [6]. Ventricular dysfunction in CDH can lead to post capillary or pulmonary venous hypertension that does not respond to and may worsen with inhaled vasodilators [29].
- Systemic antibiotics are generally not indicated until timing of surgical repair, at which time perioperative antibiotics are administered. A postoperative course of one to 5 days is dependent on whether or not a patch was used [15].
- **Dopamine** administration can ensure end organ perfusion and improve left ventricular function and right ventricular failure when hypotension is present. After hypovolemia is corrected and ensures adequate intravascular volume, Dopamine may be needed to manage initial systemic hypotension [20, 22]. Dopamine, however, is not ideal in patients with reactive pulmonary blood vasculature.[23]

Evidence Lacking/Inconclusive

- There does not exist sufficient evidence in the literature reviewed regarding the use of steroids, vasopressors, and prostaglandin.
- **Hydrocortisone** has been shown to decrease the need for inotropes in infants with refractory hypotension and may benefit infants with CDH and catecholamine-resistant hypotension following ECMO. However, there is no data to support that empiric treatment with hydrocortisone improves outcomes [20].

- **Prostacyclin**, inhaled or IV is a potential intervention in infants who fail to respond to iNO but is not recommended for routine use due to lack of data on the safety and efficacy of its use [20].
- **Epinephrine** can be used for PPHN, to increase systemic blood pressure and left ventricular output. However, increased left ventricular afterload due to increased pulmonary vascular resistance in these infants may exacerbate right ventricular afterload [20].

Practice Recommendations

Delivery Room Management:

The resuscitation goal is to establish an airway and hemodynamic stability, and if unable to do so, to place the infant on ECMO as quickly as possible. Initial stabilization will occur in the L&D/stabilization nursery, with further management occurring in the NICU. Please notify the on call pediatric surgeon upon the infant's arrival to the NICU.

1. Preparation
   a. Notification of surgical team of impending delivery if not already notified during surgical huddle
   b. Team huddle with discussion of plan of care and clearly defined team member roles.
   c. Advanced preparation of supplies including intubation equipment, 10 French replogle, ECG leads, pulse oximeter, potential normal saline fluid boluses, and resuscitative medications and supplies (see equipment checklist). Infant Code Blue cart should be immediately available.
   d. T-piece resuscitator should be set with PEEP of 5 and PIP of 20 initially. May be increased to 25 cm H20 as needed.
   e. Drager ventilator or other volume controlled ventilator.
2. Intubation, Ventilation, and Oxygenation
   a. Immediate intubation without performing bag mask ventilation. Use **Microcuff** cuffed ETT.
   b. If ventilation is required for resuscitation prior to placing on ventilator, use T-piece resuscitator with initial pressures of PIP 20, PEEP 5.
   c. Place infant on volume-controlled ventilation as soon as feasible. Pressure controlled ventilation may be needed for transport from the resuscitation room to the NICU.
      i. PEEP 4-5 cm H20
      ii. TV : 4-5 ml/kg
      iii. MAX PIP 25
      iv. Rate : 40 breaths per minute
      v. IT : 0.35 seconds
   d. Initiate FiO2 at 40% and titrate as needed.
   e. Target preductal saturations > 70% for the first ten minutes of life and then 80-95% in delivery room
   f. Adjust ventilator settings (TV and PEEP) as indicated for respiratory distress or preductal saturations less than target goal.
   g. May use T-piece resuscitator with minimal PIP and PEEP (20/5) as needed if unable to maintain appropriate saturations and arrange for HFOV use upon NICU admission
   h. No routine surfactant administration. May consider if infant is premature < 37 weeks or has undergone Fetal Endoluminal Tracheal Occlusion (FETO)
3. Access/Monitoring
   a. Place preductal pulse oximeter on right arm and ECG leads
   b. Place temperature probe, ensure radiant heater is changed from manual to servo/baby
   c. Place a hat to reduce heat loss
   d. Place peripheral IV. If unable to obtain after two attempts, transfer to NICU.

4. Gastric Decompression
    a. Insert 10 french replogle (8 french if < 1500 grams) and place to low continuous suction (40-60 mmHg)
5. Medications
    a. Start D10W at 60 ml/kg/day for term infants. May be adjusted based on gestational age.
    b. If poor perfusion or mean arterial pressure < gestational age, consider 10 ml/kg normal saline bolus
    c. Give normal newborn medications: Vitamin K, erythromycin ointment.

NICU Management

Monitoring and Vascular Access

1. Pre- and post-ductal pulse oximetry
2. Routine NICU intensive care monitoring
3. Place umbilical arterial catheter and umbilical venous catheter. Consider triple lumen UVC.
    a. If appropriately placed UVC cannot be obtained, low-lying UVC may be left in place until alternative access is obtained
    b. If unable to obtain appropriately placed UAC, place a peripheral arterial line. For infants at risk for ECMO, consider placing right upper extremity peripheral arterial line for monitoring of preductal PaO2. Consider muscle relaxation prior to PAL placement.
4. Chest X-ray should be performed as soon as possible to confirm the diagnosis, assess severity and confirm position of ETT, umbilical lines, and replogle.
5. Consider PICC line placement prior to surgical repair.

Ventilation

1. Tidal volume and PEEP should be adjusted to meet optimal physiological parameters of
    a. Pre-ductal saturations > 85% after two hours of life. May tolerate > 70% in the first two hours of life if other parameters are met and saturations are improving. Post-ductal saturation goal above 70% .
    b. pH > 7.25
    c. pCO2 between 50-70
    d. PaO2 between 40-90
2. Titrate FiO2 for preductal saturation 85-95% with minimal pre-post ductal splitting of < 10% as well as postductal PaO2 40-90. Once targets are met, do not wean FiO2 for the first 6 hours unless postductal PaO2 supraphysiologic. Once FiO2 weaning is initiated, wean slowly by ~3% per hour to maintain pre-ductal saturations > 85% and PaO2 > 40 (pre or post ductal).
3. If unable to maintain above physiologic parameters with PIP Max of 25, infant should be transitioned to High Frequency Oscillatory Ventilation
    a. Initial MAP 13-17 cmH20
    b. Initial Hz 10
    c. Initial amplitude 30-50 cmH20
    d. Regular chest x-rays should be performed to avoid over-inflation
4. Oxygenation index and PEP scores should be monitored Q1-4 hours with ABGs to determine potential eligibility for ECMO
5. Consider ECMO based on *DCMC Guidelines for ECMO Initiation of CDH*.

Hemodynamic Management

1. Goal is to achieve appropriate end-organ perfusion determined by heart rate, urine output, and lactate levels.
2. If heart rate is normal, urine output is > 1 ml/kg/hr and lactate is < 3, and there are no other symptoms of poor tissue perfusion, vasopressor support is not required.
3. Echocardiography should be performed on admission for all infants. Perform echo emergently if there is any clinical instability as well as prior to the initiation of iNO. Echocardiogram will also help to determine significance of pulmonary hypertension and pathophysiological phenotype based on assessment of atrial and ductal shunting. Serial echocardiograms should be performed with clinical changes as phenotypes evolve and may change rapidly.
   a. Phenotypic types include
      i. Phenotype 1: Mild or no pulmonary hypertension with a compliant RV: Left to right shunting at both the PDA and atrial level with normal function and septal geometry consistent with mild pulmonary hypertension. If echo demonstrates phenotype 1, hypoxia may be related to poor alveolar gas exchange requiring adjustments in ventilator strategy.
      ii. Phenotype 2: Pre-capillary pulmonary hypertension and no cardiac dysfunction or primary RV dysfunction: predominant right to left shunting at both PDA and atrial levels
      iii. Phenotype 3: Post-capillary pulmonary hypertension with primary LV dysfunction, elevated left ventricular end diastolic pressure and left atrial pressure with right to left shunting at the PDA and left to right atrial shunts.

Fig. 1 - PH Phenotype Descriptions [25]

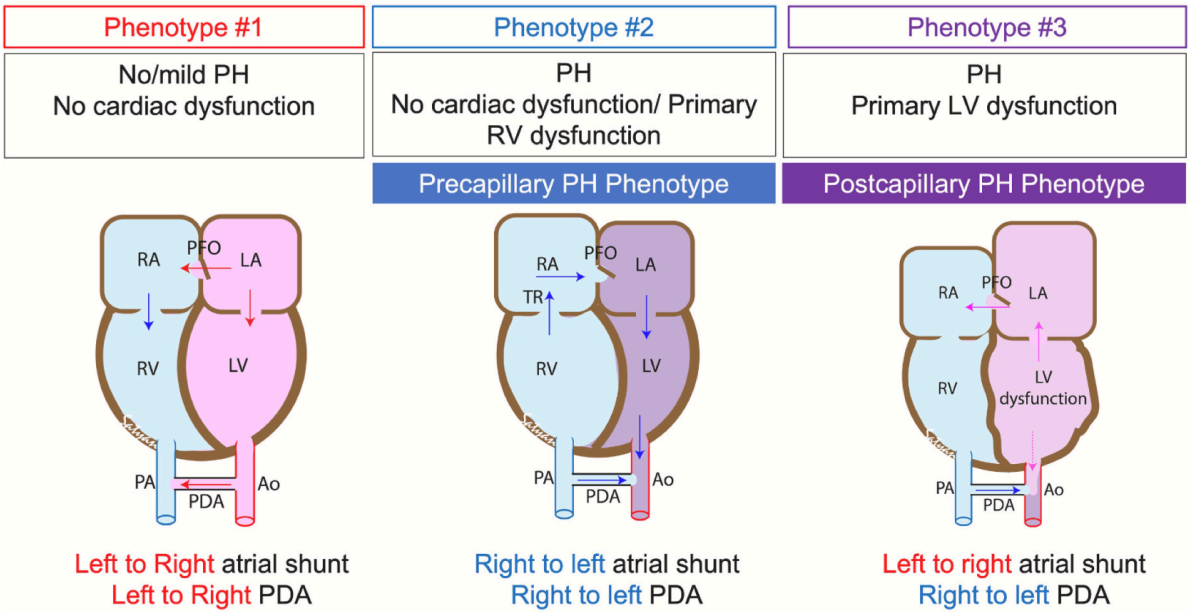

Fig. 2. Three hemodynamic phenotypes indicating relative contributions of pulmonary hypoplasia and ventricular compromise in PH in CDH; image copyright Satyan Lakshminrusimha.

4. For infants with evidence of precapillary hypertension with or without RV dysfunction (phenotype 2), management should focus on reducing pre-capillary PVR and pulmonary vasodilator strategies
   a. iNO can be initiated in a time limited trial if there is evidence of an extra-pulmonary right to left shunt, and the OI is > 20 and/or a pre- and postductal saturation difference of 10% or more.
   b. Potential contraindications to iNO initiation: Left ventricular dysfunction, left atrial enlargement, and small left sided structures, post-capillary phenotype as described below.
      i. Trial of iNO may be for at least one hour
      ii. If no effect after initiation, and administered for less than 4 hours, iNO should be discontinued without weaning. If administered for >4 hours, initiate Ascension Seton Neonatal iNO protocol. One study demonstrated that more infants treated with iNO required ECMO.
      iii. iNO responders are defined by
         1. Decline of 10-20% in pre- postductal saturation difference
         2. PaO2 increase of 10-20%
         3. Improvement in hemodynamics including a decrease in lactate levels or a 10% increase in mean blood pressure.
   c. In the setting of suprasystemic pulmonary hypertension and right to left shunting through the PDA/PFO, alprostadil should be considered to maintain ductal patency and decrease afterload helping to protect the right ventricle in the setting of a small or closing PDA.
   d. Consideration of initiation of epinephrine and/or vasopressin for systolic and diastolic RV support
      i. Start epinephrine at 0.02 mcg/kg/min for beta effect and to help with contractility. Goal <0.05. If hypotension persists, start vasopressin.
      ii. Start Vasopressin at 0.0002 units/kg/min and titrate as needed to 0.002 units/kg/min.
   e. Intravenous sildenafil 0.5 mg/kg IV q6hr should be considered in infants with severe pulmonary hypertension (administer over AT LEAST an hour to avoid hypotension)
5. If echo demonstrates a post-capillary phenotype, consider the following modifications for primary LV dysfunction
   a. iNO is contraindicated[8]
   b. Milrinone should be considered to improve LV performance if not hypotensive. Initiate at dose 0.3 mcg/kg/min and may be titrated to 0.7 mcg/kg/min
   c. Low dose epinephrine should be initiated as first line vasopressor at 0.02 mcg/kg/min and titrate to a dose of 0.1 mcg/kg/min generally. In more extreme situations may titrate to max of 0.3 mcg/kg/min.
   d. Dobutamine may be considered as second line vasopressor. Initiate at 5 mcg/kg/min and titrate to maximum dose of 20 mcg/kg/min
   e. PGE may be considered to maintain ductal patency in the setting of a restrictive or closing PDA to augment systemic blood flow via right to left shunting through the PDA
   f. Left ventricular dysfunction predicts risk of ECMO and mortality.
6. Pulmonary Hypertension and Cardiology should be consulted within 24 hours for all infants with evidence of ventricular dysfunction or infants requiring vasopressor support to help guide management.
7. Decision making on optimal use of nitric oxide, inotropes and pressors is challenging, and is probably best achieved by multidisciplinary discussions with the pulmonary hypertension, cardiology and ICU teams, with decision making based on multiple metrics of cardiorespiratory status including saturations, PO2 levels, echo findings, lactate levels, etc. Given the unpredictable nature of the pulmonary circulation in infants with CDH, response to all interventions should be carefully monitored, with the clinical team being prepared to rapidly discontinue interventions which appeared ineffective or deleterious.

Sedation and Paralysis

1. Initiate Dexmedetomidine (Precedex) as first line agent. Dosing and titration vary based on gestational age.
2. Fentanyl infusion at 1 mcg/kg/hr and titrate to desired sedation level as needed for additional sedation or pain control
3. Paralysis may be required in cases of severe pulmonary hypertension or difficulty maintaining appropriate oxygenation or ventilation in an infant who is otherwise adequately sedated. If paralysis is required, vecuronium should be initiated.

Fluids/Electrolytes/Nutrition

1. D10 at 60 ml/kg/day should be initiated for term infants. Volume may be adjusted based on gestational age and birthweight.
2. Infants < 1500 grams, should be initiated on starter TPN
3. Infants are maintained NPO with replogle to low continuous suction.
4. Parenteral nutrition should be advanced per NICU feeding guidelines.
5. Post-operatively and after return of bowel function and hemodynamic stability, enteral nutrition should be initiated and advanced as tolerated per NICU feeding guidelines.

Laboratory/Radiographic Analysis

1. Admission: ABG, lactate, CBC with differential, Type and Screen, and blood culture if concern for sepsis
2. ABG, lactate q1-4 hr after NICU admission depending on clinical status
3. Methemoglobin daily if applicable for monitoring of iNO
4. 24 hours of life: BNP, BMP, total bilirubin, and chromosomal microarray
5. Chest x-ray with KUB on admission and daily prior to repair.
6. Newborn screening per protocol
7. BNP should be obtained weekly, before surgery, post-operative day 1, and as needed.
8. Routine cranial and renal US do not need to be performed until risk of ECMO is deemed high and should be performed prior to cannulation.
9. Routine US of the neck vessels is not indicated unless requested by pediatric surgery.

Antimicrobial Therapy

1. Not routinely indicated
2. Thirty-six hours of empiric antibiotics as dictated by maternal risk factors for infection and concern for sepsis

Transport to Dell Children's

1. A plan should be made for transfer to Dell Children's Medical Center NICU once stabilized and umbilical lines are placed.
2. If infant meets ECMO criteria (see DCMC Guidelines for ECMO Initiation of CDH) and does not have congenital heart disease, infant should be transported to the DCMC Pediatric ICU
   a. Neonatology should be consulted after arrival
3. If infant meets ECMO criteria and does have congenital heart disease, infant should be transported to the Cardiac Care Unit
   a. Neonatology should be consulted after arrival

Consultations and Discharge Planning

1. Pediatric surgery should be notified prior to delivery, updated after delivery, notified of the plan for transport, and notified upon arrival to DCMC.
2. Pediatric Pulmonology should be consulted prior to discharge on all patients with CDH with plan for follow-up for at least the first three years of life
3. Pediatric Pulmonary Hypertension service should be consulted on admission and follow-up arranged as an outpatient for all patients.

4. Pediatric cardiology should be consulted on all patients and follow-up as an outpatient if the patient has cardiac disease.
5. Pediatric gastroenterology as needed for symptoms of GER, dysmotility, etc.
6. Neurodevelopmental follow-up should be in place for all patients at the time of discharge.
   a. MRI should be performed prior to discharge in all patients with abnormal head ultrasound findings, abnormal neurologic exam, history of seizures, need for ECMO or who required a patch repair
7. See recommended schedule of follow-ups.

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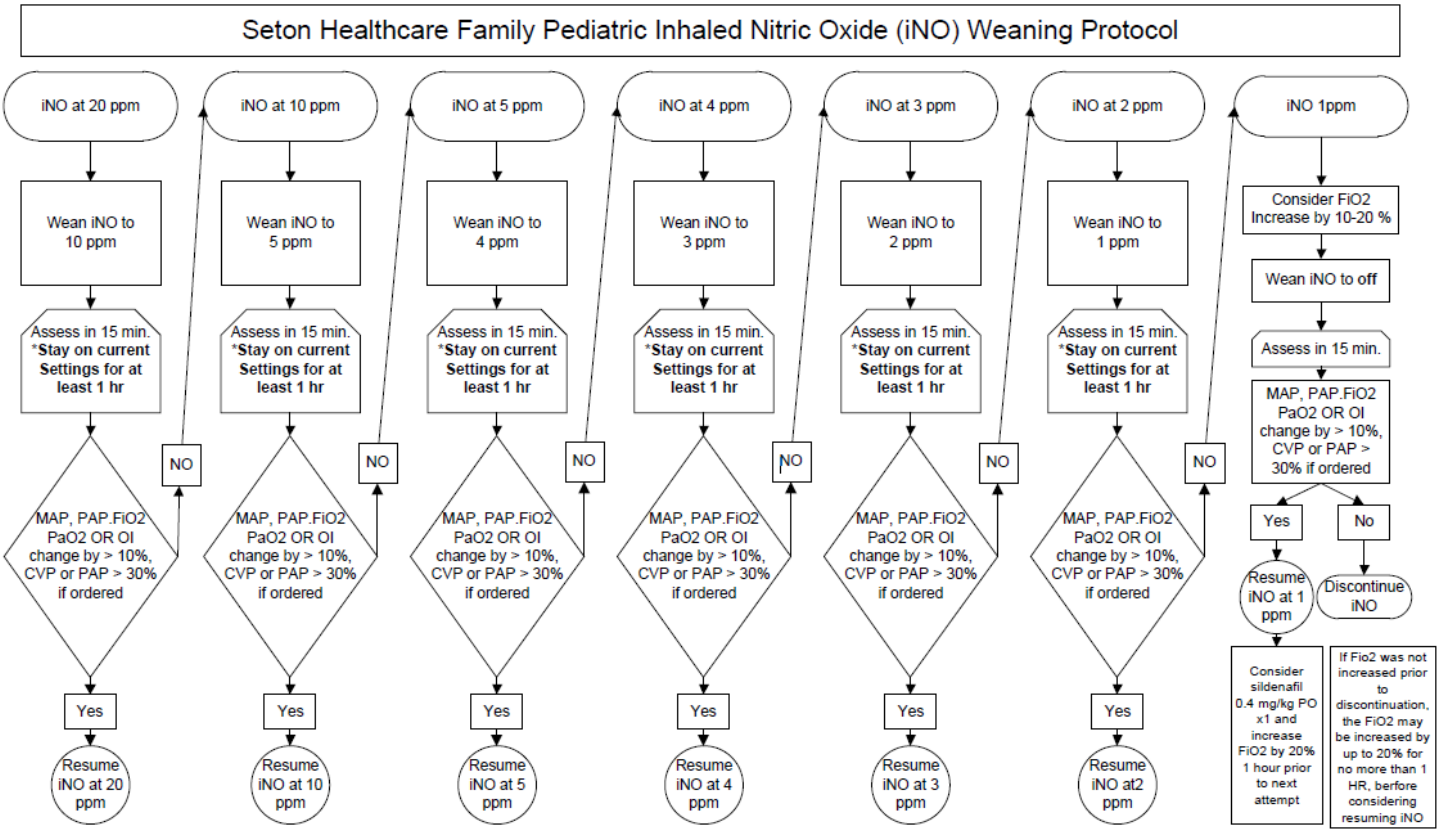
Appendix 1 – Neonatal Inhaled Nitric Oxide Protocol



- **PHYSICIAN MUST BE CALLED BEFOFE INITIATION AND REINITIATION AFTER FAILED ATTEMPT**
- Call physician to initiate weaning protocol when patient stable with following:
- PaO2 > 80%
- FiO2 of less than or equal to 60%
- If patient fails weaning, return to lowest effective dose of iNO, call the physician and attempt weaning in 24 hours
- If methemoglobin of greater than 5 % is detected, call physician to wean iNO
- Consider increasing FiO2 10 – 20% prior to discontinuing iNO
- Patient should have an ordered SpO2 parameter ordered before placement on the weaning protocol

OI = (Paw xFiO2)/PaO2
Paw = Mean Airway Pressure
Pa02 = Partial Arterial Oxygen Pressure
MAP = Mean Arterial Pressure
PAP = Pulmonary Artery Pressure
*Used only if measured available

Appendix 2 – Recommended Schedule of Follow-up for Patients with CDH

TABLE 1 Recommended Schedule of Follow-up for Infants With CDH

	Before Discharge	1–3 mo After Birth	4–6 mo After Birth	9–12 mo After Birth	15–18 mo After Birth	Annual Through 16 y
Weight, length, occipital-frontal circumference	X	X	X	X	X	X
Chest radiograph	X	If patched	If patched	If patched	If patched	If patched
Pulmonary function testing			If indicated		If indicated	If indicated
Childhood immunizations	As indicated throughout childhood	X	X	X	X	X
RSV prophylaxis	RSV season during first 2 years after birth (if evidence of chronic lung disease)	X	X	X	X	X
Echocardiogram and cardiology follow-up	X	If previously abnormal or if on supplemental oxygen	If previously abnormal or if on supplemental oxygen	If previously abnormal or if on supplemental oxygen	If previously abnormal or if on supplemental oxygen	If previously abnormal or if on supplemental oxygen
Head computed tomography or MRI	If (1) abnormal finding on head ultrasound; (2) seizures/abnormal neurologic findings[a]; or (3) ECMO or patch repair	As indicated	As indicated	As indicated	As indicated	As indicated
Hearing evaluation[44]	Auditory brainstem evoked response or otoacoustic emissions screen	X	X	X	X	Every 6 mo to age 3 y, then annually to age 5 y
Developmental screening evaluation	X	X	X	X		Annually to age 5 y
Neurodevelopmental evaluation	X			X		Annually to age 5 y
Assessment for oral feeding problems	X	X	If oral feeding problems	If oral feeding problems	If oral feeding problems	If oral feeding problems
Upper gastrointestinal study, pH probe, and/or gastric scintiscan	Consider for all patients	If symptoms	If symptoms	Consider for all patients	If symptoms	If symptoms
Esophagoscopy		If symptoms	If symptoms	If symptoms or if abnormal gastrointestinal evaluations	If symptoms	If symptoms
Scoliosis and chest wall deformity screening (physical examination, chest radiograph, and/or computed tomography of the chest)				X		X

The neurosensory tests performed and frequency of surveillance may differ among infants with CDH because of variability in neurologic, developmental, and physiologic impairments. Follow-up should be tailored to each infant. RSV indicates respiratory syncytial virus.
[a] Muscle weakness, hypotonia, hypertonia, or other abnormal neurologic sign or symptom.