MANAGEMENT OF INFANTS WITH CONGENITAL DIAPHRAGMATIC HERNIA FROM BIRTH TO SURGERY

Scope of Topic
This guideline will address the pre-operative management of infants with congenital diaphragmatic hernia (CDH). This guideline does not address prenatal management, prognostication, and/or post-operative management of infants with CDH.

Target Population
Infants with CDH.

Literature Search
Relevant studies were identified from the search of PubMed for "congenital diaphragmatic hernia". The search was limited to English language. Reference lists of relevant articles, including review articles, were examined and the search was supplemented by a review of personal files. Review articles and textbook chapters were used for the background section. The search was conducted on August 29th, 2011 and June 30th, 2016.

Appraisal Criteria
References identified in the conducted searches were screened for relevance and methodological quality. The search and screening was focused on systematic reviews and randomized controlled trials initially. When these were not available, the search for specific questions was expanded to include high-quality cohort studies (including randomized trials of related questions). Studies were appraised using the Critical Appraisal Skills Program (CASP) criteria. When high-quality primary data were unavailable, expert opinion was considered in developing these guidelines.

Stakeholders
Representatives from pediatric surgery and neonatology services were involved in the development of these guidelines.

Background
Congenital diaphragmatic hernia affects 1 in every 3000 deliveries.[1] The defect is present on the left in ~84% of infants and only 2 % of infants have bilateral defects.[2] The severity of the disease is affected by the degree of pulmonary hypoplasia and pulmonary hypertension (CDH-PH) and reported mortality for CDH ranges between 10 and 35%.[1] Survival rates have reportedly increased over time and are purported to be due to changing management styles from emergent surgery to surgery after clinical stabilization along with the use of pressure-limited, goal-directed ventilation strategies and ECMO. Even though the survival rate has increased, long term morbidity associated with CDH including pulmonary disease, neurodevelopmental challenges, gastrointestinal complications, and CDH-PH are being increasingly recognized.[3] Evidence based management of infants with CDH is complicated by the fact that there are few true high quality randomized control trials (and those that exist lack sufficient power for definitive conclusions). Most studies are retrospective, single center studies which are further complicated by lack of sufficient cases at any single center. However, databases such as the CDH registry, Canadian pediatric surgery registry, and Euro consortium group are addressing low patient numbers by combining data from various centers. Further, a randomized control trial completed and published in 2016 attempted to identify the optimal initial mode of ventilation (conventional versus HFOV). Despite being underpowered, some meaningful results were obtained and are included in this version. Data suggesting that standardizing pre-, peri-, and post-operative management of patients with CDH results in better outcomes continue to mount. In this regard, Anotonoff *et al* showed improved survival among patient managed with a protocol versus infants who were managed without a protocol in a single center.[4] Additionally, Grushka *et al* showed significantly higher survival rates among centers that took care of larger numbers of patients with CDH as compared to centers that took care of fewer patients with CDH.[5] In an effort to develop a management protocol, we examined the management

protocol developed as a part of an international multicenter randomized controlled trial of high frequency oscillation versus conventional mechanical ventilation in infants with congenital diaphragmatic hernia: the VICI-trial. Researchers associated with this trial developed a management protocol based on best available evidence.[6] This protocol is based on key principles which have been reported to affect morbidity and mortality associated with CDH. First, surgery to close the defect should be performed after clinical stabilization and stabilization of CDH-PH.[7] Second, use lower peak pressures to avoid barotrauma and volutrauma.[8] We used the VICI protocol as a template and developed a management protocol specific for our patients at CMHH.

MANAGEMENT IN THE DELIVERY ROOM

- If the diagnosis of CDH is known or suspected, patients should NOT be resuscitated with bag mask ventilation to reduce gastrointestinal/abdominal distention. Most infants with CDH will have significant respiratory distress at birth and they should be intubated immediately after birth. [E] Infants with good respiratory effort may be managed with may be managed according to NRP recommendations.
- If the infant is intubated, the infant should be ventilated using a Neo puff with PIP no higher than 22-24 and PEEP of 5. [E]
- A Replogle tube should be placed in the delivery room to decompress the stomach and after admission to the NICU it should put on suction. [E]
- The infant should be transported to the NICU as efficiently as possible to avoid delay in management.
- If the infant is intubated in the delivery room, the infant should be placed on the transport ventilator for transport to the NICU. The ventilator should be set for: PIP of 22-24, PEEP of 5, IMV of 40 and I-time of 0.35. [E]
- The infant should be monitored in the delivery room and during transport according to NRP recommendations and current NICU practice except, oxygenation should be assessed ONLY via preductal SaO_2. Acceptable preductal SaO_2 is 80-95% during the initial stabilization. Saturations 70-80% will be tolerated for 2-6 hours (allowing for the transitional circulation to stabilize) and should be trending toward the target range of 80-95%. [E]

MANAGEMENT IN THE NICU

- ***Monitoring***
  - Similar to all other infants admitted to the NICU except
    - Preoperatively, only preductal pulse oximeter readings should be monitored. [E]
    - Arterial blood gasses should be obtained from the UAC or a preductal (right radial) arterial catheter hourly x 3 after initial admission to the NICU. Once parameter targets (see *Ventilator management*) are being met, frequency should shift to Q4-6 hours (and PRN clinical indication / change). [E]
- ***Diagnostic tests***
  - Similar to all infants admitted to the NICU except:
    - An echocardiogram should be obtained between 4-12 hours of life to assess cardiac anatomy and the degree of pulmonary hypertension. [E]
    - A head ultrasound should be obtained to evaluate for intracranial hemorrhage prior to initiating ECMO.[9] [D]
- ***Consults***
  - The Pediatric Surgical team should be notified as soon as possible after the infant is admitted.
  - The Cardiology team should be consulted if the infant is found to have significant pulmonary hypertension (supra-systemic prior to surgery) and may require frequent

echocardiographic evaluation to follow / manage pulmonary hypertension and resulting cardiac dysfunction. [E]
    - A Genetics consult should be obtained if physical examination or associated anomalies raise the suspicion that the CDH may be associated with various genetic abnormities. [E]
- ***Central lines***
    - Arterial access: An umbilical arterial line is preferred, but if one cannot be placed, then a peripheral arterial line should be attempted and preferably pre-ductal (right radial). [E]
    - Central venous access: A 2-3 lumen UVC, a PICC, or a double lumen percutaneous central line should be placed.

- ***Ventilator management (see attached algorithm)***
    - Parameter targets for mechanical ventilation [E]
        - Preductal SaO_2 of 80-95% as long as oxygen delivery is adequate.
        - During the initial stabilization, SaO_2 of >70% may be tolerated for several hours to allow enough time for transition and stabilization.
        - $PaCO_2$: 45-70 mmHg
        - pH: 7.2 - 7.35
        - Adequate oxygen delivery and perfusion:
            - UOP>2cc/kg/hr
            - Lactic acid: < 3 mmol/L (≤ 5 may be tolerated initially)
            - Physical examination (skin color/mottling)
    - Admission ventilator settings [E]
        - Ventilator type: Dragger or Servo-i
        - Mode: Assist Control (Dragger) or Pressure control (Servo-i)
        - PIP: 22cm
        - PEEP: 5cm
        - IMV: 40
        - I-time: 0.35
        - FiO_2: 100%
    - Adjust the ventilator to maintain parameters within range as described above.
        - $PaCO_2$ can be managed by adjusting PIP or back up rate as needed. However, PIP should not be higher than 26 and rate should not be higher than 60. [E]
        - I:E ratios should be monitored and adjusted as needed to avoid air trapping because of inadvertent PEEP in spontaneously breathing on assist control mode of ventilation.
    - Change from SIMV to HFOV [E]
        - The infant should be started on HFOV if
            - Unable to maintain $PaCO_2$ target goals with a PIP of 26 and a rate of 60
            - Unable to maintain oxygenation target goals with a PIP of 26 and a PEEP of 5
            - Initial HFOV settings should be: [E]
                - Starting MAP should be 2 above conventional ventilator MAP but not higher than 15.
                - Starting amplitude may be twice that of MAP or higher to achieve adequate shake (shake down to the level of umbilicus).
                - Frequency of 8-10 Hz as dictated by the last $PaCO_2$.
                - Goal lung expansion for CDH is 8-9 ribs.
    - Management of pulmonary hypertension
        - An echocardiogram should be obtained within 4-12 hours of life. The infant should be stable and in a controlled environment within the NICU.

- Pulmonary hypertension may be treated with the measures below if oxygenation does not respond to mechanical ventilation and pulmonary hypertension has been confirmed by echocardiogram.
- Use of iNO in patients with CDH. There are data to suggest that iNO is ineffective in the treatment of PH associated with CDH. The NiNOS trial showed no benefit and suggested higher need for ECMO or death.[10] Further studies have suggested no benefit in mortality or need for ECMO. Given these data, there is no role for the use of iNO in the preoperative stabilization of CDH infants.
- Treatment of pulmonary hypertension
  - Correct systemic hypotension if present as described below.
  - Consider milrinone (dose per standard NICU dosing)
  - If pulmonary hypertension does not respond to these measures, then proceed to ECMO (if the CDH-PH is manifesting in hypoxia, hypercarbia, and/or compromised perfusion) as described below.
- Other management adjuncts for pulmonary hypertension
  - Inhaled prostacyclin to reduce pulmonary hypertension may be considered in infants who are more than 48 hours old and relatively stable on conventional ventilation with persistent elevated pulmonary pressures. [E]
  - There are case reports in literature about the use of intravenous prostacyclin in the treatment of PPHN [E]
  - Prostaglandins may be used to unload the right ventricle in the case of a restrictive PDA [E].
  - Sildenafil (dose per standard NICU dosing)
  - Such medications should be used after discussion with Pediatric Surgery and Cardiology teams because patients on these medications have to be followed closely with echocardiography.
- Indication for initiating ECMO
  - Conventional management may fail to achieve preoperative targets and the infant may need to be placed on ECMO if one or more of the following conditions are met: [E]
    - The inability to maintain preductal saturations above 80% after institution of HFOV and optimal CDH-PH management
    - Mean airway pressure (MAP) > 15 cm H_2O
    - Oxygenation index consistently (over 2-4 hours) ≥ 40
    - Inadequate oxygen delivery with metabolic acidosis defined as lactate consistently ≥ 5mmol/l and pH < 7.20
    - An increase in $PaCO_2$ > 70 resulting in a respiratory acidosis with pH < 7.20, despite optimization of ventilator management
    - Hypotension resistant to fluid therapy and adequate inotropic support, resulting in a urine output < 0.5 ml/kg/hour
  - ECMO team should be contacted as per unit routine (713.704.ECMO).

o Weaning ventilator support once the infant is clinically stable [E]

- Conventional ventilator
  - Wean PIP before back up rate depending on tidal volume to keep goal $PaCO_2$ as described above. Once the infant is stable on low back up rate then the mode of ventilation may be changed to SIMV.
  - Adjust FiO_2 as needed to maintain pre-ductal SaO_2 as described above.
- High frequency ventilation
  - Wean FiO_2 to achieve goal pre-ductal saturations.

- Wean MAP only if the infant is on less than 60% oxygen and lung expansion is at least 8 ribs.
- Adjust amplitude or frequency to maintain target $PaCO_2$. Increase frequency before amplitude if frequency is <10.

- ***Hemodynamic management***
  - Goal mean blood pressure should be gestational age appropriate.
  - For term and near term infants, the goal MAP should be 40-45 mmHg.
  - If initial MAP is <40mmHg
    - Consider normal saline bolus of 10 ml/kg 1-2 times within the first 2 hours. [E]
    - After the initial 1-2 hours, intravascular volume should be carefully assessed and fluid overload should be avoided. [E]
    - If blood pressure cannot be maintained after NS bolus, then consider starting dopamine and, subsequently, dobutamine according to unit practice. [E]
    - Draw serum cortisol level and consider treatment with hydrocortisone, if cortisol level is low or infant is on high doses of pressers or has other clinical indications. [11] [D]
    - Epinephrine may be added as needed. [E]
    - Echocardiogram should be obtained in patients who are persistently hypotensive to assess left ventricular function and if LV function is poor than milrinone may be considered [O]
- ***Fluid management***
  - The infant should be started on 40-60 ml/kg of maintenance fluid based on blood glucose levels and intake should be adjusted based on fluid balance and weight. [E]
  - Fluid overload should be avoided as much as possible. [E]
  - If the infant is significantly fluid overloaded and is hemodynamically stable with low urine output, then furosemide may be considered, especially prior to operative repair. [X]
- ***Hematological management***
  - Hematocrit should be maintained according to unit guidelines. However, if the infant is on high oxygen and has elevated lactic acid levels, then hematocrit should be kept >40%. [E]
  - A DIC screen should be obtained and treated as needed for infants with clinical bleeding or infants with severe acidosis. [E]
- ***Antibiotics***
  - There is no specific indication for antibiotics for infants with CDH. [E]
- ***Sedation***
  - Sedation may be used as clinically indicated but should be used with caution. [E]
  - Paralysis should generally be avoided and must be initiated with particular caution if the infant is on assist control ventilation. [E]
- ***Surgery for CDH***
  - Surgery may be undertaken after ECMO (if not already repaired on ECMO) or after physiologic stabilization and stabilization of CDH-PH. [D]
  - Infant is considered stable for surgery if: [E]
    - $FiO_2 \leq 0.5$
    - Mean blood pressure normal for gestational age
    - Lactate < 3 mmol/l
    - Stabilization of pulmonary hypertension – a repeat echocardiogram should be obtained prior to surgery – CDH-PH (as measured by estimated RVSP (tricuspid regurgitation jet), RV diameter/wall thickness/function, septal location) should be stable or improved from previous. Echocardiographic evaluation should be

repeated as clinically indicated (*at minimum* an initial and pre-operative ECHO should be obtained) [E]
    - Urine output ≥ 2 ml/kg/hour
- **Abandoned therapies in CDH**
    - Surfactant [D]
    - Inhaled nitric oxide [D]

Evidence Grading Scale

[M]	Meta-analysis/systematic review of RCTs	[O]	Other evidence
[A]	Large randomized trial(s)	[E]	Expert opinion or consensus
[B]	Small randomized trial	[F]	Basic laboratory research
[C]	Prospective cohort study	[L]	Legal requirement
[D]	Retrospective cohort or case control study	[Q]	Decision Analysis
[S]	Review article	[X]	No evidence

References

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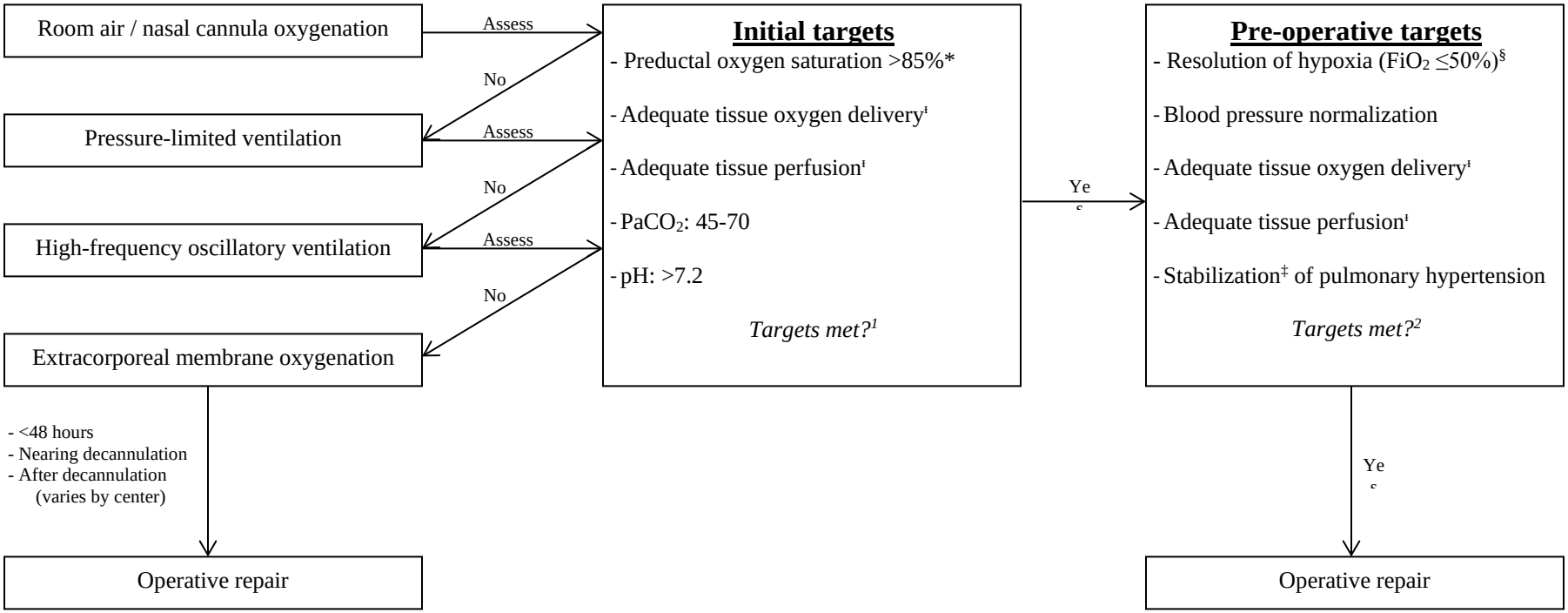
Pulmonary support algorithm for newborn infants with CDH.



Conventional Ventilator Settings:
Start: PIP:20, PEEP:5, FiO2:100%, Rate:40-50
Max: PIP:26, PEEP:5, FiO2:100%, Rate:60

High Frequency Oscillator Settings:
MAP:13-18 (2 above conventional vent MAP)
Frequency:8-15 Hz
Amplitude: ~2x MAP (optimize chest vibration)

*may allow 70-85% briefly
‡assessed by physical exam, UOP, & lactate

§FiO_2 should not be weaned below 40%
‡assessed by physical exam, UOP, & lactate
‡defined by repeated echocardiography and

1. Each mode of ventilatory support should be slowly optimized within designated limitations (see text) to prevent iatrogenic injury. Once the settings reach these limitations, and initial targets are not met, the mode of support should be changed.

2. Support should be decreased in a *gradual, methodical* manner to reach the pre-operative targets. In addition, pre-operative ventilatory and hemodynamic support should allow for a potential post-operative deterioration.

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