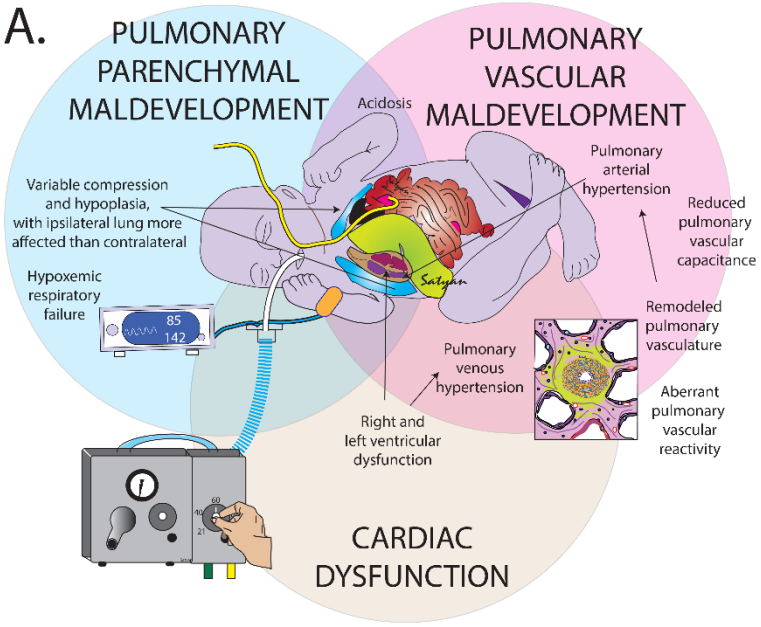
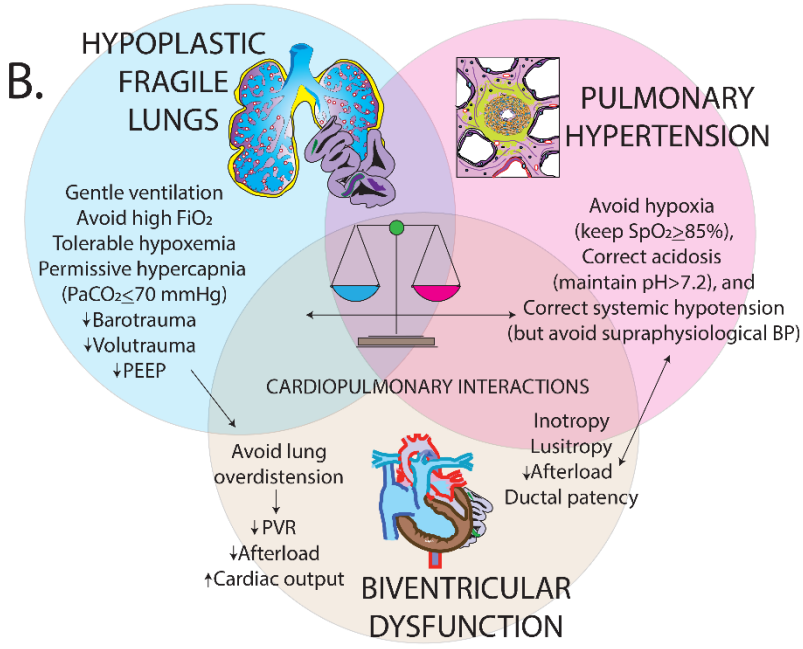
UC DAVIS HEALTH | CHILDREN'S HOSPITAL

Management Guidelines for Congenital Diaphragmatic Hernia (CDH)

A Standardized Approach at the UC Davis Children's Hospital



The following guidelines for "gentle" ventilation and pulmonary vasodilation are provided for reference and are based on three recent reviews (Reiss, Schaible et al. 2010, Keller 2012, Canadian Congenital Diaphragmatic Hernia 2018) (Puligandla, Skarsgard et al. 2023) and based on protocols from various centers including University of Utah. (Yang, Fenton et al. 2020) CDH is characterized by the triad of lung hypoplasia, pulmonary hypertension and cardiac dysfunction.



Collect data from antenatal records and fetal care meetings to assess severity of CDH:

(i) Assessment of lung volume by ultrasound – LHR ratio, observed to expected LHR (O/E LHR), side of the defect, location of liver, associated anomalies, amniotic fluid status etc., An O/E LHR of ≤ 25% with left CDH and O/E LHR of ≤ 50% with right CDH carries a poor prognosis with survival rates ≤ 30%.
(ii) Lung volume assessment by fetal MRI – an O/E total fetal lung

volume (O/E TFLV) < 35% and an intrathoracic liver herniation are associated with low survival.

(iii) Discuss with Obstetric and Maternal Fetal Medicine (MFM) team about feasibility of deferred cord clamping for at least 60 seconds.

(iv) Follow-up genetic workup previous done (if any)

(v) Delivery ~ 39 weeks is optimal if permitted by maternal and fetal status

(vi) Alert the following teams;

a. Pediatric surgery – for all cases
b. Pulmonary hypertension team – the next morning for all cases
c. Cardiology team – if concerns exist and for an echocardiogram
d. PICU ECMO team - if several poor prognostic signs exist based on antenatal assessment or concerns exist for severe hypoxemia or hemodynamic instability

Initial treatment and procedures in the delivery room (table 2, figure 1):

Resuscitation in the delivery room is mainly based on the Neonatal Resuscitation Program and American Academy of Pediatrics / American Heart Association guidelines (Wyckoff, Wyllie et al. 2020) (Aziz, Lee et al. 2020) (Weiner and Zaichkin 2021)

Microcuff endotracheal tubes:

If anesthesia and surgery prefer, consider the use of Microcuff endotracheal tubes. The cuff needs lower pressure (< 10 cm water) and is more cylindrical (instead of spherical) and is thought to exert less mucosal pressure. For the same internal diameter of the endotracheal tube (ETT size in mm), the external diameter of the cuffed tube may be slightly larger than an uncuffed tube and necessary adjustments may need to be made when choosing the right tube. A comparison from two references is shown below. (Hanamoto, Maegawa et al. 2019, Fischer, Grass et al. 2020) The cuff should be deflated prior to insertion and can be left deflated unless ventilation and air leak around the ETT needs to be addressed. The cuff can be inflated by anesthesia during surgery.

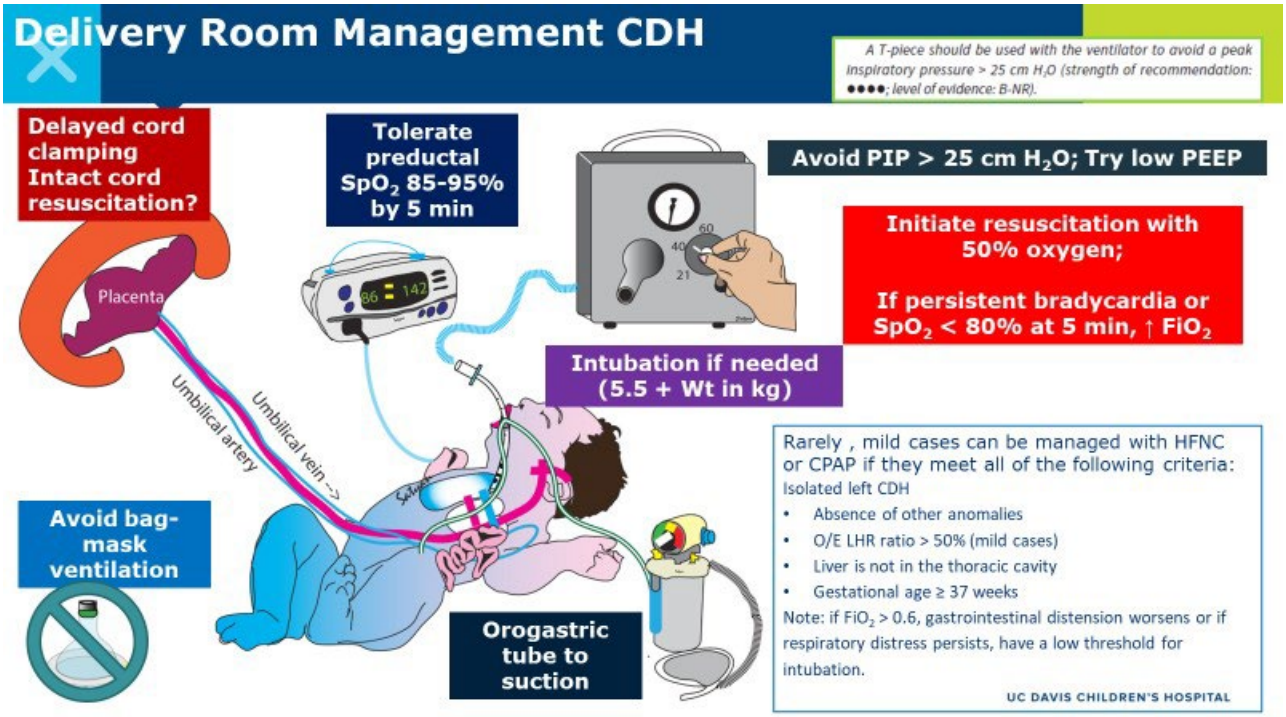
Table 1. Comparison between unuffed and Microcuff endotracheal tubes

ETT size (internal diameter, mm)	Uncuffed ETT external diameter (mm)	Microcuff ETT external diameter (mm)
3.0	4.2	4.3
3.5	4.8	5.0
4.0	5.5	5.6
4.5	6.2	6.3

Table 2. Delivery room procedures for infants with CDH

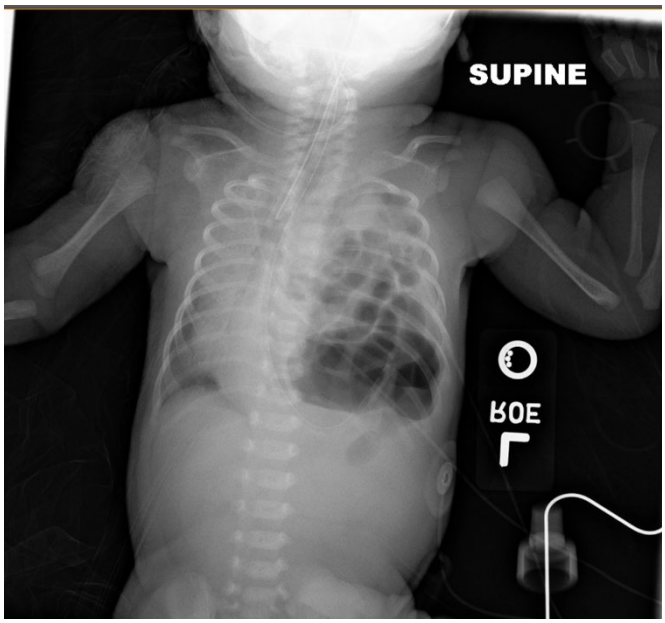
Procedure	Guidelines	Comments
DCC	≥ 60 sec after discussing with Obstetric team	Avoid if non-vigorous and immediate resuscitation is needed (can consider intact umbilical cord milking if the infant is ≥ 35 weeks gestation) (Yamada, Szyld et al. 2024)
Intubation	Appropriate size ETT (uncuffed or a deflated microcuff tube) Distance at the lip – [5.5 cm + estimated weight of the infant in kg]	In mild cases of CDH, consider low-flow nasal cannula, HFNC or CPAP if there is no significant respiratory distress and FiO_2 need is low (≥ 37 weeks gestation and O/E LHR ≥ 50%);
Orogastric suction	Place a orogastric (Replogle or Anderson) tube and aspirate regularly or connect to suction	
Oxygen	Start at 50% and titrate to achieve targets as per NRP	Monitor preductal SpO_2; If HR < 100/min or SpO_2 < 80% at 5 min, consider higher FiO_2
Ventilation	Use a T-piece resuscitator with PIP ~ 20 (max ≤25 cm H_2O) and PEEP of 3 cm H_2O (range 2 to 5)	Avoid volutrauma and barotrauma

Figure 1. Delivery room procedures for infants with CDH



(i) Deferred cord clamping (DCC): Preliminary studies demonstrate that DCC is feasible in infants with CDH. (Foglia, Ades et al. 2020) (Lefebvre, Rakza et al. 2017) Prolonged DCC has been shown to be beneficial in lamb models of CDH. (Kashyap, Hodges et al. 2020) Randomized trials are being planned and conducted to assess DCC in CDH. (Le Duc, Mur et al. 2021, Horn-Oudshoorn, Knol et al. 2022, Gien 2023) If there no contraindications to DCC and infant is not in need of immediate resuscitation, consider ≥ 60 seconds of DCC. Infants ≥ 35 weeks gestation at birth who are non-vigorous may benefit from intact umbilical cord milking. (Yamada, Szyld et al. 2024) However, benefits of umbilical cord milking in CDH are not known.

(ii) Orogastric suction: Infants with CDH or suspected CDH who have respiratory distress are intubated soon after birth and a 10 French Replogle or Anderson tube is placed and suctioned. Bag-mask ventilation should be avoided to prevent stomach distension.



(iii) Pulse oximetry: A preductal pulse oximeter is placed on the right upper extremity as soon as feasible. Oxygen saturation targets are based on neonatal resuscitation program guidelines. Many centers tolerate a lower limit of ≥ 80% saturations after the first 5 min of life in the delivery room.

(iv) Oxygen: Inspired oxygen concentration can be started at 50% and titrated based on preductal pulse oximeter values. (Riley, Antiel et al. 2018) If bradycardia (heart rate HR < 100/min), hypoxemia (SpO2 < 80%) persist at 5 minutes after birth, increase inspired oxygen to 100% and titrate down based on SpO_2 and HR.

(v) Intubation: Majority of infants require intubation. Intubate with a appropriate-sized uncuffed endotracheal tube (ETT). If surgery and anesthesia prefer a cuffed ETT (microcuff ETT), consider placing it before surgery. If intubated with cuffed ETT, do not inflate the cuff prior to surgery.

    (i) Length of ETT: One study suggests that carina is displaced cephalad in infants with CDH. Instead of using 6 + weight in kg (in cm) to determine the length of ETT insertion at the lip, it is recommended that the formula 5.5 + weight in kg (in cm) be used in infants with CDH. Subsequent adjustments can be made after checking a chest X-ray (figure 2). (Gien, Meyers et al. 2018)

    (ii) Note: Majority of infants with CDH require immediate intubation in the delivery room. A small set of infants with CDH may tolerate non-invasive ventilation. (Horn-Oudshoorn, Knol et al. 2022) If the infant meets all of the following criteria, consider non-invasive ventilation

(either CPAP or high-flow nasal cannula – HFNC or low-flow nasal cannula) after placement of a orogastric suction tube.

i. Isolated left CDH
ii. Absence of other anomalies
iii. O/E LHR ratio > 50% (mild cases)
iv. Liver is not in the thoracic cavity
v. Gestational age ≥ 37 weeks
vi. Note: if FiO_2 > 0.6, gastrointestinal distension worsens or if respiratory distress persists, have a low threshold for intubation.

(vi) Peak inflation pressure (PIP): High airway pressures should be avoided and ventilation using a T-piece resuscitator (such as Neopuff®) is preferred. Peak pressures, preferably less than 25 cm H_2O are given to avoid lung damage to the hypoplastic lungs. However, if heart rate is low (<60/min) with inadequate chest rise, it may be appropriate to transiently increase PIP.

(vii) Positive end-expiratory pressure (PEEP): A typical PEEP of 4 cm H_2O is adequate in CDH. Some centers consider using a lower PEEP (2 to 3 cm H2O) to reduce volutrauma and barotrauma. (Guevorkian, Mur et al. 2018) Lower PEEP minimizes the risk of auto-PEEP shifting the pressure volume loop of the infant to the horizontal portion due to the presence of hypoplastic lungs. There are no studies evaluating low PEEP in the delivery room but in postoperative cases of CDH, low PEEP improves gas exchange. (Guevorkian, Mur et al. 2018)

Admission procedures in the NICU:

1) A peripheral (or central – preferably a double-lumen UVC) venous line is inserted to allow administration of fluids and medications.
2) An arterial line is placed for blood pressure monitoring and to draw arterial blood gases. To avoid delays and unnecessary pain and agitation an umbilical arterial line should generally be the first choice.
   a) Right radial arterial line is preductal.
   b) Umbilical arterial line, posterior tibial lines and some left radial lines are postductal.
   c) Total time for line placement should be limited to 1-2 hours.
3) **Blood pressure** levels are maintained at normal values for gestational age. There is no need to increase blood pressure levels to supranormal values if preductal saturations are between 80 to 95%. If there is hypotension and/or poor perfusion, 10 mL/kg bolus (maximum of 2 boluses) of 0.9% NaCl or lactated Ringers (LR) should be administered followed by inotropic and/or vasopressor agents as needed.
4) **Sedation and analgesia:** Sedation and analgesia are initiated with careful monitoring of blood pressure. Routine use of neuromuscular blocking agents is not recommended.
   a) Initiate sedation as soon as possible, as follows:
   b) Give IV morphine ASAP after delivery (IM if unable to quickly place IV) at 0.1 mg/kg
      i) Maintenance: Low dose morphine bolus 0.025 to 0.05 mg/kg PRN q 4-6 hrs
      ii) May also consider low dose morphine infusion 0.025 mg/kg/hr

c) Alternate agent: Fentanyl – 1 to 2 mcg/kg/h infusion
d) Second alternate agent: continuous infusion of IV dexmedetomidine at 0.3 mcg/kg/hr
    i) May adjust to desired sedation effect; maximum dose 1.2 mcg/kg/hr

5) Obtain arterial or capillary blood gas, CBC, and, as indicated, blood cultures
6) Antibiotics may be initiated based on usual sepsis risk factors
    *a) Antibiotic therapy solely because the infant has CDH is **NOT** an indication*
7) Minimal Stimulation: clustered care, Vitals from monitor, CXR's using frame under warmer, eye patches, ear muffs, minimal ETT suction, decreased tactile stimulation, etc.
    a) This does not mean NO stimulation
    b) Position changes to prevent skin pressure injuries is appropriate
8) **Chest X-ray** should be obtained as soon as possible to assess initial condition of the lung and herniated bowel and repeated based on clinical condition and ventilator status.
9) **Surfactant** is not indicated unless the infant is premature and/or has evidence of RDS on chest X-ray. If there is evidence of RDS, consider using half a dose (1.5 ml/kg of Infasurf® or 1 ml/kg of Curosurf) instead of a full dose because of lung hypoplasia.
10) Routine use of **enemas and suppositories** is not recommended.
11) Laboratory investigations:
    a) Blood gases on admission and repeat as needed. Frequent monitoring of blood gases in the first 12 hours of life as the lung is being recruited and the baby is transitioning may be of value in optimizing ventilator settings.
    b) CBC with differential on admission and repeat as needed
    c) Basic metabolic profile (sodium, chloride, potassium, bicarbonate, BUN, creatinine, calcium and glucose), magnesium, phosphate and bilirubin at 12 hours and repeat as indicated.
    d) Type and screen
    e) Lactate
    f) BNP (B-type natriuretic peptide) (optional, can be repeated every 5-7 days if there is persistent pulmonary hypertension).
    g) Echocardiogram – first echocardiogram should be obtained as soon as possible after birth. Repeat echocardiogram 24-72 hours and as needed. Indications for repeat echocardiogram include:
        i) Presence of clinical or biochemical signs of hypoperfusion (lactic acidosis, oliguria etc.,)
        ii) Persistent hypotension (in spite of optimal vasopressor therapy)
        iii) Persistent hypoxemia
        iv) Persistent pulmonary hypertension. Weekly echocardiograms to evaluate progress and guide therapy
    h) Cranial sonogram – baseline soon after admission; repeat as needed

Ventilator management:

The emphasis should be on protecting the lung, changes should be small and deliberate.

(i) **OXYGENATION**: Target preductal **oxygen** saturations are between 91 and 95% in the NICU and maintain FiO_2 < 0.6 if possible (see below for details). Postductal saturations are maintained above 70% if lactate levels are < 2 mM/L and urine output is > 1 ml/kg/h. If oliguria or lactic acidosis occurs, may need to evaluate for hypoperfusion and tissue hypoxia.

- Oxygen titration should be based on preductal oxygen saturations. Inspired oxygen concentration should not be adjusted based on postductal SpO_2 or postductal PaO_2.
- **<u>OXYGENATION BY POSTNATAL AGE</u>**
    i. **Initial 1st hour: ideal preductal SpO_2 is 91-95%;** however, can accept *initial pre-ductal* saturations of <u>≥</u> **75% if FiO_2 is > 0.6**

    ii. Allow SpO_2 to slowly increase w/out aggressive ventilator manipulation

    iii. **Between 1-2 hours: ideal preductal SpO_2 is 91-95%;** accept *pre-ductal* saturations of **80 to 90%**

    iv. **By 2-3 hours:** *Pre-ductal* saturations should be **91-95%**

- ***<u>Post-ductal SpO_2 monitoring can be done but is not recommended</u>***
    i. If used, do not worry over post-ductal SpO_2 split – this is a sign of right-to-left ductal shunting. An echocardiogram to assess right ventricular afterload and direction of shunt at the ductal and atrial level will be helpful in formulating a plan.

- Record highest pre-ductal SpO_2 (also highest post-ductal SpO_2, if measured)
    i. *Record post-ductal SpO2, if monitored*

- **After 3 hours**: Target pre-ductal SpO_2 range is **91-98%. Oxygenation in CDH is a balance of systemic oxygen delivery and pulmonary oxidative stress. So, target SpO_2 is dependent on FiO_2. If FiO_2 is < 0.6, target SpO_2 91-98%. If FiO_2 > 0.6, tolerate preductal SpO_2 88-95%.**
- **Note SpO_2 < 90% cannot be accepted in the presence of the following:**
    i. Lactic acidosis
    ii. Oliguria
    iii. Declining cerebral NIRS ($CrSO_2$)

- Gradually **WEAN** FiO_2 for pre-ductal SpO_2 > 92%
    i. Minimum FiO_2 ~ 0.25 to 0.30 in the 1st 24-hours of life (unless SpO_2 is consistently 99-100% in which case, weaning might be considered)
    ii. Further weaning of FiO_2:
        1. IF stable on FiO_2 0.25 to 0.30 beyond 24-hours w/ pre-ductal SpO_2 consistently 99-100%
        2. *<u>At any time if paO_2 persistently > 100 mmHg</u>*
        3. *There is no benefit to keeping FiO_2 elevated when PaO_2 >100 mmHg, especially with concerns for potential O_2 toxicity*

- **IF Pre-ductal *SpO_2* not > 90%** by 1 hour age consider following:
    i. Obtain CXR to insure no air leak
        1. IF pneumothorax (PTX), MUST be managed PRIOR to any transport
    ii. Insure "optimal" inflation……be careful to NOT overinflate
        1. Typically, if there is adequate lung inflation, further increases in mean airway pressure (Paw) do NOT improve oxygenation
        2. *Sometimes, it is more appropriate to WEAN PAW*
        3. Must be cautious to not over wean Paw leading to atelectasis
    iii. Consider adding pulmonary vasodilator therapy (figure 4 – flow chart):
        1. iNO at 20 ppm
            a. No evidence to support this for most CDH
            b. Does improve oxygenation in the absence of of LV dysfunction
            c. Obtaining an early echocardiogram to look for structural heart disease, RV and LV function, direction of shunts and estimation of RV pressures.
            d. ~ 40% are "responders"
            e. D/C if no improvement in FiO_2, PaO_2, OI within 1 hour
        2. Milrinone at 0.33 mcg/kg/min (range 0.33 to 1.0 mcg/kg/min)
            a. No evidence to support this as effective therapy
            b. Effective pulmonary vasodilator, inotrope, reduces afterload of both ventricles.
            c. Can be associated with hypotension – consider a fluid bolus prior to milrinone
            d. Typically, avoid a loading dose to minimize risk of systemic hypotension
            e. Start at 0.33 mcg/kg/min and escalate to 0.66 mcg/kg/min if no evidence of systemic hypotension
        3. Dobutamine at 2-10 mcg/kg/min
            a. No evidence to support this as effective therapy
            b. No apparent lusitropic effect
            c. Very short ½ life relative to milrinone = more titratable
        4. PGE at 0.01 mcg/kg/min
            a. No evidence from randomized trials to support this as effective therapy
            b. For severe RV strain and supra-systemic RV pressures to keep ductus open and offload the RV
            c. Consider using it as a second or third-line pulmonary vasodilator if there is evidence of RV dysfunction or failure with right-to-left ductal shunt not responding to inhaled NO
            d. IV PGE1 may also be considered in the presence of left ventricular dysfunction or functional aortic obstruction where systemic circulation is dependent on a right-to-left ductal shunt.

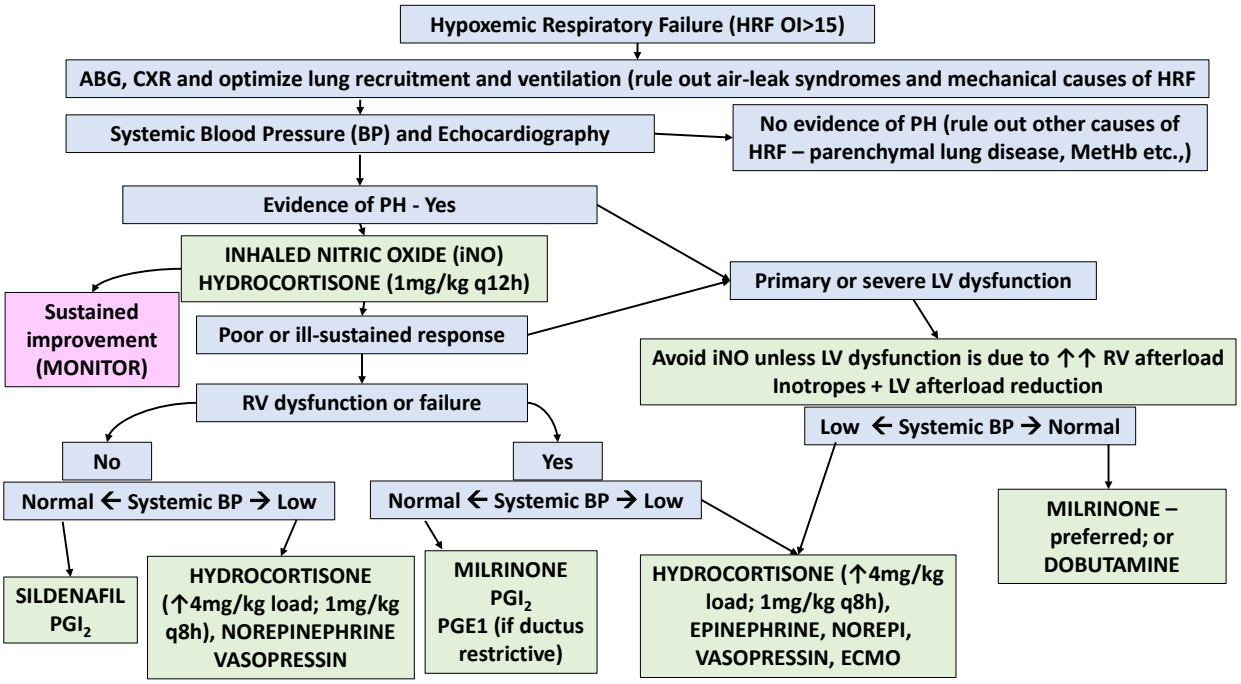


Figure 4- flow chart.

e. Wean iNO once the PDA shunt becomes exclusively left-to-right. (Moore, Keller et al. 2024) Continued use of PGE1 with a left-to-right shunt may result in pulmonary over circulation.

5. Sildenafil – intravenous
   a. Continuous infusion – 0.14mg/kg/h for 3 h followed by 0.07 mg/kg/h continuous
   b. Intermittent – 0.4 mg/kg over 30 min every 6 hours (higher risk of systemic hypotension but may be preferred if central access lines are limited)
   c. Sildenafil – enteral 0.5 mg/kg q 6 hrs – NG (No evidence to support this as effective therapy. Hold NG suction x 30 minutes after dose, Most often used for "chronic" PHTN, or if unable to wean off iNO)
6. Prostacyclin – intravenous
   a. Third-line agent to reduce RV afterload (after iNO and either sildenafil or milrinone)
   b. Risk of systemic hypotension

iv. When to consider Pediatric Pulmonary Hypertension consult:

1. It is better to consult this team soon after delivery of the infant as they will follow this infant throughout the course of hospitalization and as an outpatient.
2. PH team (or Cardiology if PH team is not available must be involved in the following situations)
   a. If "need" for more than 2 systemic vasodilators (including iNO)

b. If complicated by cardiac anomaly (other than ASD, VSD)
c. For "chronic" PHTN requiring vasodilator therapy beyond 4 weeks post-op (See PPHN below)

v. Determine eligibility for ECMO

1) Arterial PCO_2 is maintained between 45 and 60 mmHg (65 mmHg in some centers, **permissive hypercapnia**).
   a) **Initial 2-3 hours:** accept PCO_2 of ≤ 65 torr and pH ≥ 7.20 (correct any metabolic component of acidosis if base deficit is more than negative 10 mEq/L)

   b) Ideal target $paCO_2$ after 3 hours is 45-60 torr

   c) **If at any time, the PCO_2 is > 65 torr** consider following options:
      i) If on HFOV, decrease rate (Frequency/Hz) and/or increase ΔP (Amplitude/Power)
         (1) Make sure there is adequate chest-abdomen vibration
         (2) Consider change to HFJV
      ii) If on HFJV, increase rate and/or increase PIP
         (1) Consider adding/increasing conventional back-up sigh breaths rate at 3-5 bpm
      iii) If on SIMV, consider change to HFV
      iv) Assess for lung over-inflation; if present consider decreasing Paw/PEEP
      v) Assess for under-inflation; if present consider increasing Paw/PEEP
      vi) Some cases of severe CDH with marked pulmonary hypoplasia, $PaCO_2$ cannot be reduced despite effective ventilation. These infants may need ECMO or have lethal pulmonary hypoplasia.

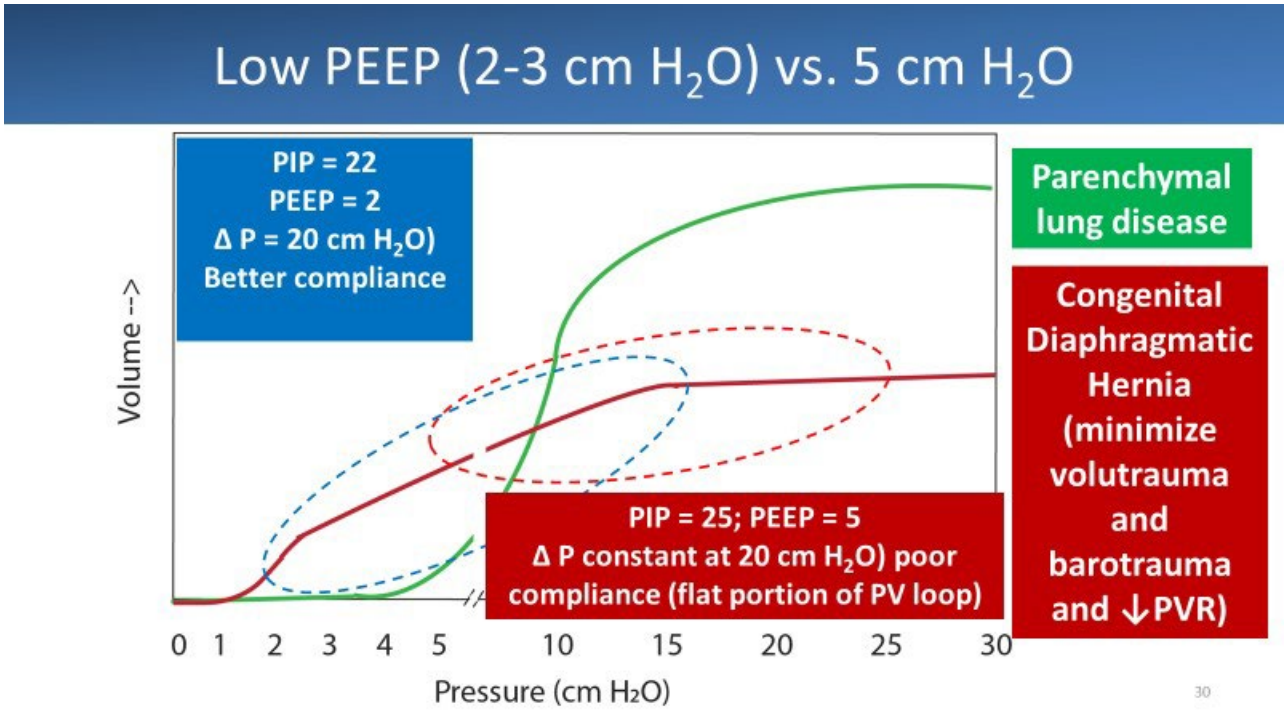
(ii) **Conventional ventilation**: Based on the results from the VICI trial, conventional ventilation may be the preferred mode for initial ventilation in CDH (Snoek, Capolupo et al. 2016) (Snoek, Capolupo et al. 2014). If volume-targeted ventilation is used, tidal volumes should be adjusted (4-5 mL/kg) to account for the lung hypoplasia and limit risk of lung injury. Rather than selecting an arbitrary tidal volume, the minimal volume necessary to provide adequate oxygenation and ventilation should be established. PIP should be limited to 25 cm H_2O or less, PEEP is usually set at 2 to 5 cm H_2O (lower PEEP is often necessary as pulmonary arterial perfusion and compliance is very sensitive to level of PEEP – figure 5). (Guevorkian, Mur et al. 2018) High rates (60/min) are often used to maintain target $PaCO_2$. This may necessitate a shorter inspiratory time (0.3 seconds) than is typical of term infants. Weaning from conventional ventilation should preferentially be by means of decreasing tidal volume first followed by a decrease in rate. If $PaCO_2$ cannot be maintained < 60 – 65 mmHg in spite of using a PIP of 25 to 28 cm H_2O, high frequency oscillatory ventilation (HFOV) should be considered. If the infant needs to be ventilated with a T-piece resuscitator or a bag manually during transport, avoid using peak inspiratory pressures > 25 cm H_2O.

- **Conventional ventilation summary** – A volume-targeted mode is preferred
  i. Set V_T ~ 4-5 ml/kg, PEEP 2-5, RATE 40-60 and I-Time 0.3 seconds
  ii. If pressure mode, start w/ PIP 16-20 cm H_2O, PEEP 2-5, RATE 40, I-Time of 0.3 sec.

1. DO NOT INCREASE PIP ≥ 25 cm H_20…. if needed, consider changing to a HFV mode of ventilation

iii. Target contralateral lung expansion to 9 ribs

Figure 5. Low PEEP



(iii) **High frequency jet ventilation (HFJV)** – This is the preferred mode of high frequency ventilation in CDH. Target mean airway pressure (Paw)~ 10-11 cm H_2O; Set "on"-time at 0.02 seconds, Rate 360-420 bpm, PEEP 6-7 cm H_2O, PIP 24-28 cm H_2O. In preterm infants with CDH, higher Paw may be needed along with surfactant if coexistent RDS is present.

i. Start with 3 conventional back-up sigh breaths
ii. Initiate CMV PIP at 20 cm H_2O
    1. DO NOT INCREASE PIP for back-up sigh breath ≥ 25 cm H_2O
    2. Wean PIP as indicated to keep pressure < 3 cm H_2O of Jet PIP

(iv) **High frequency oscillator ventilator (HFOV):** The initial settings are usually a mean airway pressure of 11-12 cm H_2O, frequency 8-10 Hz, amplitude 24-28 cm H_2O depending on chest wall jiggling and then should be adjusted based on $PaCO_2$ and chest X-ray. Small changes and frequent reassessment are critical. The target mean airway pressure is that needed to achieve adequate oxygenation

(typically 10-13 cm H_2O). If this is possible with an expansion on the contralateral side of 9 ribs, that may be optimal. Some infants will require a 10 rib expansion on the contralateral side to achieve adequate oxygenation, recognizing that both lungs are likely to be abnormal in CDH. HFOV may be considered as the initial ventilator strategy for infants with CDH, ***particularly those with the liver in the chest***. When switching from conventional ventilation to HFOV for respiratory acidosis, consider starting at the same mean airway pressure as on conventional ventilation.

- **Summary of HFOV in CDH:**
- **HFOV** – Begin with Paw 11-12 cm H_2O, Hz 8, ΔP/amplitude 24-28
    i. In general, should NOT increase Paw > 15 cm H_2O; NEVER above 18
        1. Majority of CDH babies do well between 10-13 cm H_2O
        2. Exception may be the preterm infant who also has RDS
            a. In this setting, surfactant therapy may be indicated
    ii. Try to optimize *contralateral* lung inflation at ~ 9-10 ribs
    iii. Unlike babies with RDS/alveolar disease, *increasing PAW for lung hypoplasia almost never improves oxygenation*…. and usually worsens it through adverse effects on PVR & venous return
    iv. However, one must be cautious to not over wean Paw leading to atelectasis

Hemodynamic management:

The goal of hemodynamic management is to provide adequate oxygen delivery to the tissues as determined by monitoring of heart rate, blood pressure, capillary refill (normal < 3 seconds), urine output (normal > 1 mL/kg/h), blood pH (goal ≥ 7.2) and lactate concentration (target < 4.5 mEq/L).

(i) If hypovolemia is suspected, fluid boluses (10 mL/kg) of normal saline or lactated Ringers (LR) are administered. Fluid therapy is followed by vasopressor therapy (norepinephrine and vasopressin, or epinephrine) or inotropy if necessary (e.g. poor contractility on echocardiogram).

(ii) The optimal first line therapy for hypotension is not known. Dopamine is commonly used in the presence of hypotension and cardiac dysfunction. It is important to remember that doses > 10-15 mcg/kg/min can result in systemic *and* pulmonary vasoconstriction. Hence, DOPAmine is not a preferred agent in CDH with PPHN. In the absence of cardiac dysfunction on echocardiogram, norepinephrine and vasopressin (selective systemic vasoconstrictor agents – less inotropy and possibly less pulmonary vasoconstriction) may be preferred. (see table 3 and discussion below).

Table 3. Choice of vasopressor / inotropic agent in CDH

	Cardiac Function	
	Normal	Abnormal
Normal blood pressure	Continue monitoring	Milrinone (preferred) Dobutamine

		Epinephrine
Low blood pressure	Norepinephrine Vasopressin	Epinephrine Dopamine

(iii) Hydrocortisone therapy is considered after conventional therapy has failed to improve blood pressure and perfusion (if there is low risk of infection). Some centers consider early hydrocortisone as infants with CDH commonly have adrenal dysfunction(Kamath, Fashaw et al. 2010). Consider adding hydrocortisone sodium succinate maintenance (1 mg/kg/dose q 12h) early in the course of CDH management. if the infant is not responding to moderate doses of inotropic and/or vasopressor agents, consider high dose hydrocortisone therapy (4 mg/kg load followed by 1 mg/kg/dose q 8 hours).

(iv) In case of cardiogenic shock, as demonstrated by dysfunction of the left and/or right ventricle, inotropic agents should be considered (see table 4 for maintenance doses of inotropic and vasopressor agents). A loading dose for milrinone is 25 mg (preferred) to 50 mcg/kg over 30 min may be considered for a quick onset of action but this load tends to cause systemic hypotension in neonates and hence just starting maintenance dose at 0.33 to 0.66 mcg/kg/min is preferred).

Table 4. Inotropic and vasopressor agents

Agent	Maintenance dose	Comments
Norepinephrine	0.05 to 0.2 mcg/kg/min	Maximum dose 2 mcg/kg/min
Vasopressin	0.1 to 2 milliunits (mU)/kg/min	Wide range – start at lower range and titrate dose – closely monitor urine output and sodium
Dopamine	2 – 20 mcg/kg/min	Preferably through a central vein; doses > 15 mcg/kg/min may cause pulmonary vasoconstriction
Dobutamine	2.5 – 15 mcg/kg/min	May cause hypotension and tachycardia
Milrinone	0.25 – 1 mcg/kg/min	May cause hypotension, especially with loading dose; use lower dose range (0.25 to 0.5 mcg/kg/min) in the presence of mild renal dysfunction. If creatinine is > 2mg/dL or oliguria is present, avoid milrinone. If quick onset of action is needed and systemic blood pressure is normal, consider 25mg/kg load over 30 min.
Epinephrine	0.05 to 0.5 mcg/kg/min	Watch blood glucose levels

It is important to avoid increasing systemic blood pressure above physiologic levels using pharmacologic agents. Supraphysiologic levels of systemic blood pressure may place additional strain on the ventricles. It is recommended to avoid exceeding the values listed in Table 5 when using pressor therapy during

management of PPHN with CDH. In some instances, right to left shunt at the ductal and oval foramen levels may serve as pop-off for the pulmonary vascular circuit. **Do not focus solely on mean BP values. Systolic hypotension is often due to poor contractility and requires inotropes and diastolic hypotension is due to low systemic vascular resistance (or PDA) and requires vasopressors.**

Table 5a. Normal blood pressure ranges in term infants (Nascimento, Xavier et al. 2002) (Note – patients with CDH were not included in this study; values are rounded)

Age	Systolic	Mean	Diastolic
6 to 18 h	80 ± 13	57 ± 12	43 ± 10
18 to 30 h	83 ± 12	60 ± 11	46 ± 10
3 d ± 6 h	84 ± 14	60 ± 12	48 ± 13
7 d ± 1 d	91 ± 15	67 ± 13	52 ± 11

Table 5b. mean – 2 SD as the lower limit of normal values for age from table 3A

Age	Systolic	Mean	Diastolic
6 to 18 h	54	33	23
18 to 30 h	59	38	26
3 d ± 6 h	52	36	22
7 d ± 1 d	61	41	30

For practical purposes, systolic BP of 55 mmHg, Diastolic of 25 mmHg and mean of 35 mmHg may be considered as lower limits of normal during first week in term infants.

Fluid management:

Restrictive fluid management in the first 24 h is useful. Initial maintenance fluid should preferably be our D10 starter TPN at 60 ml/kg/d which provides a GIR of 4.2. Additional volume with boluses of normal saline for intravascular filling may be considered. Thereafter, fluid therapy should be increased based on clinical condition and nutritional needs.

Pulmonary vasodilator therapy:

Table 6. Pulmonary vasodilator therapy in CDH

Typical doses, route of administration of vasodilator medications in the management of CDH:

Drug	Route	Units	Initial dose	Maintenance Dose range
PGE1 – Alprostadil	IV	µg/kg/min	0.05 to 0.1	0.01 to 4
PGE1 – Alprostadil	Inhaled	µg/kg/min	0.15 to 0.3	0.15 to 0.3
Milrinone	IV	µg/kg/min	0.25 to 0.75	0.25 to 1
Dexamethasone	IV	mg/kg/dose	0.05 to 0.6	0.05 to 0.6
Hydrocortisone	IV	mg/kg/dose	1 to 5	0.5 to 5
Nitric oxide (NO)	Inhaled	Ppm	5 to 20	1 to 80

Prostacyclin (Epoprostenol - Flolan)	IV	ng/kg/min	1 to 3	50 to 80
Prostacyclin (Epoprostenol - Flolan)	Inhaled	ng/kg/min	50	25 to 50
Prostacyclin (Treprostinil – Remodulin)	SQ or IV	ng/kg/min	1.25 to 2	50 to 80
Prostacyclin (Treprostinil – Remodulin)	Inhaled	µg/breath	6	
Prostacyclin (Iloprost)	Inhaled	µg/breath	2.5 or 5	
Prostacyclin (Beraprost)	PO	µg	80	80 to 120 (adult dose)
Sildenafil	IV	mg/kg/hour	0.14 mg/kg/h for 3 h	0.07 mg/kg/h
Bosentan	PO	mg/kg/dose	1 to 2	1 to 2

Inhaled nitric oxide (iNO): If pulmonary hypertension persists on echocardiogram after optimizing ventilator and hemodynamic status, most centers consider pulmonary vasodilator therapy. Inhaled nitric oxide (iNO) is often the first therapeutic choice in spite of its association with higher need for ECMO in the NINOS-CDH trial (1997). Inhaled NO is used in 39% of patients with CDH ≥ 36 weeks PMA. Most centers initiate iNO at an OI of 20 – 25 or higher and/ or a pre- and postductal oxygen saturation

difference of ≥ 10%. In many instances, iNO leads to short-term improvement in oxygenation. The usual initial dose of iNO is 20 ppm. Inhaled NO selectively dilates the pulmonary circulation and is not associated with systemic hypotension and can be effective even in the presence of systemic hypotension by reducing right ventricular afterload. Presence of LV dysfunction – both systolic (low ejection fraction or shortening fraction) (Lawrence, Monos et al. 2020) and diastolic dysfunction can worsen outcomes with iNO in CDH. However, if LV dysfunction is secondary to primary RV dysfunction in response to high PVR, iNO may still be helpful. Close discussion with PH and cardiology teams may be needed prior to initiating iNO therapy in CDH.

Prostaglandin infusion: If there is insufficient response to iNO, some centers consider the use of intravenous or inhaled prostacyclin (PGI_2) as an additional pulmonary vasodilator and/ or prostaglandin E1 infusion to reduce the right ventricular afterload by maintaining ductal patency. If the echocardiogram demonstrates right-to-left shunting through the PFO, the right ventricle may be overloaded, as demonstrated by enlargement of the right ventricle and a leftward shift of the interventricular septum. Reopening the ductus and maintaining its patency with intravenous prostaglandin E1 may protect the right ventricle from excessive afterload. Caution should be exercised

as intravenous milrinone and prostaglandins may be synergistic in reducing systemic blood pressure. Cases of gastric outlet obstruction in CDH related to PGE infusion have been reported.

Sildenafil, a phosphodiesterase inhibitor has been used in the treatment of pulmonary hypertension in case reports in newborn infants with CDH. Other pulmonary vasodilators such as endothelin antagonists have been used to manage PPHN associated with CDH. Many experts feel that vasodilators such as sildenafil and bosentan (endothelin antagonist) should be used mainly in the chronic phase of pulmonary hypertension in CDH (Reiss, Schaible et al. 2010) . However, patient's blood pressure should be carefully monitored as intravenous PDE3 (milrinone) and PDE5 inhibitors (sildenafil) may be synergistic in reducing systemic blood pressure.

Extracorporeal membrane oxygenation (ECMO):

In non-randomized trials, ECMO has been reported to improve survival in infants with CDH. The use of ECMO has decreased, and is now more often used in preoperative stabilization. Reports of stabilization and subsequent repair on ECMO have highlighted the benefit of delaying surgery and either performing surgery on ECMO or after ECMO. Early use of ECMO for all infants with CDH with birth weight greater than 2 kg and no lethal anomalies who meet one or more of these criteria in spite of maximal support should be discussed by the neonatology, pediatric surgery, and pediatric intensivist teams:

(i) Oxygenation index is consistently ≥ 40
(ii) Inability to maintain preductal saturations > 85% or postductal saturations > 70%
(iii) Increased $PaCO_2$ and respiratory acidosis with pH < 7.15 despite optimization of ventilator management

(iv) PIP > 28 cm H_2O or mean airway pressure > 17 cm H_2O is required to achieve saturations > 85% and $PaCO_2$ < 65 mmHg

(v) Inadequate oxygen delivery with metabolic acidosis as measured by elevated lactate ≥ 4.5 mEq/L and pH < 7.15

(vi) Pressor resistant hypotension: Systemic hypotension, resistant to fluid and inotropic support, resulting in urine output < 0.5 mL/kg/h for at least 12-24h

Surgical repair:

1. TIMING of Repair

The optimal timing of surgical repair is controversial. Most centers repair the diaphragmatic defect after physiological stabilization, defined as follows:

a. Preductal oxygen saturation of > 85% on inspired oxygen < 50%
b. Low oxygenation index (see below)
c. Stable ventilator settings
d. Mean blood pressure normal for gestation
e. Lactate level < 3 mM/L
f. Urine output ≥ 2 mL/kg/h
g. Oxygenation index (OI) and timing of surgery: If oxygenation index is < 9, the risk of respiratory deterioration after surgery is low.
    i. Pre-op OI typically improves and then stabilizes over the first 24-48 hours of life, with minimal change in most babies after 48 hours
    ii. A pre-op OI < 9 is both sensitive & specific for predicting *survival (Utah)*
        1. 4/190 (2%) subsequently went on ECMO; all 4 survived to d/c
        2. 4/190 died; all survived > 60 days; all died of very late sepsis
h. *Delay of repair* beyond 24 hours after stabilization defined as OI < 9 is associated with increased ventilator days and later discharge age (Utah data)
    i. 80% of CDH patients w/ pre-op OI < 7; median op age = 73 hrs
    ii. 92% of CDH patients w/ pre-op OI < 9; median op age for OI 7 - 9 = 126 hrs

(ii) Repair on ECMO may also be considered.

(iii) The Canadian guidelines are similar except urine output > 1 ml/kg/h, the additional criterion of "estimated pulmonary artery pressures less than systemic pressure" and the following added statement: Failure to meet these criteria within 2 w should prompt consideration of either attempted repair or a palliative approach."

2. VASCULAR ACCESS for surgery

d) Central Venous Access
    i) Place a double-lumen PICC

ii) Once PICC in place, plan to remove the UVC prior to surgery
e) PIV should be in place in case blood products needed during surgery
f) Arterial access
i) Most of Ped Surgeons are OK with UAC in place
ii) BUT, discuss with Peds Surgery 24 hours prior to planned repair if OK to leave
iii) PAL if no UAC, or Peds Surgery requests removal of UAC for operation

2) PRE-OP LABORATORY STUDIES AND BLOOD PRODUCTS
a) Lab: CBC, coagulation studies, and Type and Cross
b) Blood products: Order on call PRBC, FFP and Platelets to bedside or OR

3) POST-OPERATIVE Pain Management (Utah):
a) Operating surgeon will inject 1 ml/kg of 0.25% Marcaine into fascia & skin at end of the operation to assist with post-operative pain control
b) Continue morphine, fentanyl or dexmedetomidine drip and titrate to desired effect;
c) acetaminophen 15 mg/kg/q6hrs for 72 hrs, then prn q 4-12 hrs based on PMA and age
d) Low dose morphine
i) morphine IV drip (0.025 mg/kg/hr) for a MAXIMUM of 24-48hrs
(1) NOTE: If > 25mcg/kg fentanyl given in operating room, infant MAY NOT need IV drip post-operatively; should be determined on a case-by-case basis
ii) PRN IV morphine (0.025 mg/kg) dosing q 4-6 hrs; may increase to 0.05 as needed
iii) Discuss discontinuation of IV morphine drip at 24hr post-op
(1) All attempts should be made to discontinue IV morphine drip by 48hr post-op
(2) Continue morphine 0.025-0.050 mg/kg PRN
(3) Start NWI scoring to assist with weaning analgesics
(4) Goal is to be off all narcotics no later than 7 days post-op
e) Once off morphine drip, wean dexmedetomidine infusion as tolerated; at least daily
i) Consider starting oral clonidine if tolerating oral feeds and unable to taper

Pulmonary and nutritional outcome:

Infants with CDH are at high risk of chronic lung disease / bronchopulmonary dysplasia and may require home oxygen therapy. Some infants need bronchodilator therapy.

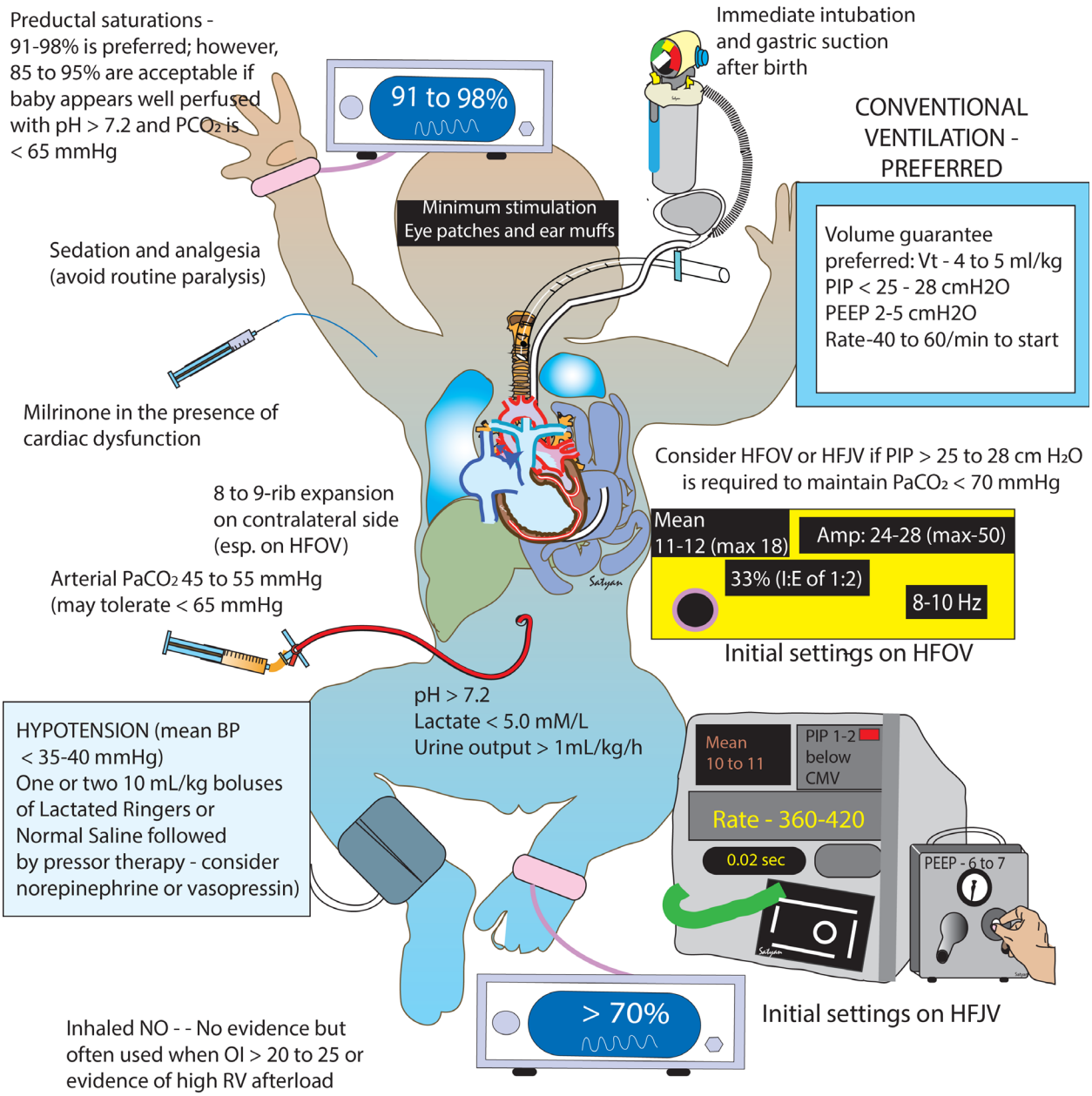
Nutritional morbidity remains a problem in survivors with CDH, particularly gastroesophageal reflux during the first year of life. Reflux may be treated both by antireflux medications and surgical intervention. Some infants suffer from oral aversion and need tube enteral feeding or gastrostomy tube placement.

Discharge and follow-up:

Infants with diaphragmatic hernia treated with either inhaled, intravenous or oral vasodilators during their course in the NICU should be followed up by Cardiology or Pulmonary hypertension clinic at least

for one visit after discharge. Infants who have evidence of pulmonary hypertension on echocardiogram at the time of discharge and/or being discharged on pulmonary vasodilators need close follow-up with Cardiology /pulmonary hypertension services. (Kraemer, Leeuwen et al. 2018) All infants with CDH should be referred for neurodevelopmental testing (ideally at 9-12, 18-24 and 36 months of age).

Figure: 6 Summary



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Aziz, K., et al. (2020). "Part 5: Neonatal Resuscitation: 2020 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care." Circulation **142**(16_suppl_2): S524-S550.

Canadian Congenital Diaphragmatic Hernia, C. (2018). "Diagnosis and management of congenital diaphragmatic hernia: a clinical practice guideline." CMAJ **190**(4): E103-E112.

Fischer, M., et al. (2020). "Cuffed pediatric endotracheal tubes-Outer cuff diameters compared to age-related airway dimensions." Paediatr Anaesth **30**(4): 424-434.

BACKGROUND: Reliable sealing of the pediatric airway requires appropriately sized tracheal tube cuffs. The aim of this study was to compare residual cuff diameters of pediatric tracheal tubes with pediatric airway dimensions. METHODS: Cuff diameters of five different brands of locally marketed pediatric cuffed tracheal tubes with internal diameters of 3.0-7.0 mm were measured at a cuff pressure of 20 cm H(2) O and compared with cuff diameters indicated by their manufacturers. The latter values were compared to tracheal dimensions using the Motoyama and Khine formulas for cuffed tracheal tube size selection. RESULTS: There is considerable heterogeneity in cuff diameters among pediatric tracheal tube brands, except for two brands from different manufacturers (Halyard and Parker Medical) which were identically designed. Cuffs made from polyurethane revealed fewer differences (91%-118%) between measured and manufacturer-indicated values for outer cuff diameters than did those made from polyvinylchloride (91%-146%). Particularly in smaller sized tracheal tubes, cuffs did not reach 100% of the tracheal lateral diameter, while others were oversized in larger tracheal tubes, independent of the two formulas used for cuffed tracheal tube size selection. Cuff diameters indicated by the manufacturer corresponded to 86%-188% of the median and 68%-157% of the maximum mid-tracheal lateral diameter of the corresponding upper age range. CONCLUSION: Our findings show that many of the cuff diameters of currently marketed tracheal tube brands lack an age-related anatomical rationale. A proposal for age-related anatomically based cuff diameters is provided for both recommendations for cuffed tracheal tube size selection in children.

Foglia, E. E., et al. (2020). "Initiating resuscitation before umbilical cord clamping in infants with congenital diaphragmatic hernia: a pilot feasibility trial." Arch Dis Child Fetal Neonatal Ed **105**(3): 322-326.

BACKGROUND: Infants with congenital diaphragmatic hernia (CDH) often experience hypoxaemia with acidosis immediately after birth. The traditional approach in the delivery room is immediate cord clamping followed by intubation. Initiating

resuscitation prior to umbilical cord clamping (UCC) may support this transition. OBJECTIVES: To establish the safety and feasibility of intubation and ventilation prior to UCC for infants with CDH. To compare short-term outcomes between trial participants and matched controls treated with immediate cord clamping before intubation and ventilation. DESIGN: Single-arm, single-site trial of infants with CDH and gestational age >/=36 weeks. Infants were placed on a trolley immediately after birth and underwent intubation and ventilation, with UCC performed after qualitative CO(2) detection. The primary feasibility endpoint was successful intubation prior to UCC. Prespecified safety and physiological outcomes were compared with historical controls matched for prognostic variables using standard bivariate tests. RESULTS: Of 20 enrolled infants, all were placed on the trolley, and 17 (85%) infants were intubated before UCC. The first haemoglobin and mean blood pressure at 1 hour of life were significantly higher in trial participants than controls. There were no significant differences between groups for subsequent blood pressure values, vasoactive medications, inhaled nitric oxide or extracorporeal membrane oxygenation. Blood gas and oxygenation index values did not differ between groups at any point. CONCLUSIONS: Intubation and ventilation prior to UCC is safe and feasible among infants with CDH. The impact of this approach on clinically relevant outcomes deserves investigation in a randomised trial.

Gien, J. (2023). "Timing of umbilical cord clamping in infants with congenital diaphragmatic hernia." Semin Perinatol: 151746.

Congenital diaphragmatic hernia (CDH) is a severe birth anomaly where a defect in the diaphragm allows abdominal organs to herniate into the chest with compression of the intrathoracic structures, specifically the lungs and heart. Pulmonary and left ventricular hypoplasia result in respiratory insufficiency after birth with disordered transition and persistent pulmonary hypertension of the newborn (PPHN). As a result, infants need immediate intervention after birth to support the transition. Delayed cord clamping (DCC) is recommended for all healthy newborns and improves outcomes in infants born preterm and in infants with congenital heart disease; however, DCC may not be feasible in newborns needing immediate intervention after birth. Recent studies have explored resuscitation with intact umbilical cords, to determine feasibility, safety, and efficacy in infants with CDH, with promising results. In this report we discuss the physiologic basis for intact cord resuscitation in infants with CDH and review the above reports with a view to determining optimal timing of umbilical cord clamping in infants with CDH.

Gien, J., et al. (2018). "Assessment of Carina Position Antenatally and Postnatally in Infants with Congenital Diaphragmatic Hernia." J Pediatr **192**: 93-98 e91.

OBJECTIVE: To determine whether endotracheal tube (ETT) insertion depth should be modified in infants with congenital diaphragmatic hernia (CDH) to reduce the risk of main-stem intubation. STUDY DESIGN: The distance from the thoracic inlet to the carina was measured antenatally by fetal magnetic resonance imaging (MRI) between 20-28 weeks' (early) and 30-34 weeks' (late) gestation in 30 infants with CDH and compared

with 12 early and 36 late MRIs in control infants without CDH. Postnatal tube position was assessed by chest radiograph in the same 30 infants with CDH and compared with 20 control infants with postnatal birth depression. RESULTS: The carina position was displaced upward in fetuses and newborns with CDH. Distance from the thoracic inlet to the carina compared with controls was 1.04 +/- 0.1 cm vs 1.42 +/- 0.07 cm on early MRI (P < .05), 1.43 +/- 0.14 cm vs 1.9 +/- 0.04 cm on late MRI (P < .01), and 2.36 +/- 0.07 cm vs 3.28 +/- 0.05 cm on postnatal radiographs (P < .01). Adjusting the ETT depth by 1 cm resulted in a median distance of 1.27 cm from the tip of the ETT to the carina. CONCLUSION: Cephalad displacement of the carina in infants with CDH may predispose them to right main-stem intubation and subsequent development of pneumothorax. We speculate that modifying the ETT insertion depth to 5.5 cm + weight in newborns born at term may prevent pneumothoraces and improve outcomes for infants with CDH.

Guevorkian, D., et al. (2018). "Lower Distending Pressure Improves Respiratory Mechanics in Congenital Diaphragmatic Hernia Complicated by Persistent Pulmonary Hypertension." J Pediatr **200**: 38-43.

OBJECTIVE: To investigate the effects of distending pressures on respiratory mechanics and pulmonary circulation in newborn infants with congenital diaphragmatic hernia (CDH) and persistent pulmonary hypertension (PPHN). STUDY DESIGN: In total, 17 consecutive infants of >/=37 weeks of gestational age with CDH and PPHN were included in this prospective, randomized, crossover pilot study. Infants were assigned randomly to receive 2 or 5 cmH2O of positive end-expiratory pressure (PEEP) for 1 hour in a crossover design. The difference between peak inspiratory pressure and PEEP was kept constant. Respiratory mechanics, lung function, and hemodynamic variables assessed by Doppler echocardiography were measured after each study period. RESULTS: At 2 cmH2O of PEEP, tidal volume and minute ventilation were greater (P < .05), and respiratory system compliance was 30% greater (P < .05) than at 5 cmH2O. PaCO2 and ventilation index were lower at 2 cmH2O than at 5 cmH2O (P < .05). Although preductal peripheral oxygen saturation was similar at both PEEP levels, postductal peripheral oxygen saturation was lower (median [range]: 81% [65-95] vs 91% [71-100]) and fraction of inspired oxygen was greater (35% [21-70] vs 25% [21-60]) at 5 cmH2O. End-diastolic left ventricle diameter, left atrium/aortic root ratio, and pulmonary blood flow velocities in the left pulmonary artery were lower at 5 cmH2O. CONCLUSIONS: After surgical repair, lower distending pressures result in better respiratory mechanics in infants with mild-to-moderate CDH. We speculate that hypoplastic lungs in CDH are prone to overdistension, with poor tolerance to elevation of distending pressure.

Hanamoto, H., et al. (2019). "Age-based prediction of uncuffed tracheal tube size in children to prevent inappropriately large tube selection: a retrospective analysis." BMC Anesthesiol **19**(1): 141.

BACKGROUND: This study aims to validate our previously reported prediction technique for uncuffed tracheal tube (TT) sizes in children younger than 2 years of age based on a calculated outer diameter (OD(Cal), mm) in each patient according to the regression equation OD(Cal) = 0.00223 x age (day) + 4.88 and to investigate a better method to select initial TT sizes to decrease re-intubation frequency, especially since large tubes can damage the trachea. METHODS: We included patients younger than 2 years of age who underwent oral surgery under general anesthesia with tracheal intubation between July 2011 and December 2016 at the Osaka University Dental Hospital. The OD of the actual TT and the age in days were extracted from anesthesia records. Agreement rates, estimated numbers of required tubes, and size reduction frequencies were compared to obtain recommended OD (OD(Rec)) values in 2 selection groups: "average selection" in the range "nearest to the OD(Cal) value (OD(Cal) - 0.35 < OD(Rec) </= OD(Cal) + 0.35)" and "safe selection" in the range "nearest to the value below OD(Cal) (OD(Cal) - 0.7 < OD(Rec) </= OD(Cal))". RESULTS: The agreement rates for an OD(Rec) in the average selection and safe selection groups were 60.8 and 55.1%, respectively (P = 0.001). The estimated number of required tubes per patient were 1.40 +/- 0.51 and 1.47 +/- 0.55 (P < 0.001), respectively. The estimated frequencies of size reductions were 13.3 and 4.0% (P < 0.001), respectively. CONCLUSIONS: Because the size reduction frequency is lower despite a slightly higher number of required TTs, selecting an OD(Rec) based on "safe selection" parameters is desirable to avoid complications due to intubation with larger TTs.

Horn-Oudshoorn, E. J. J., et al. (2022). "Spontaneous breathing approach in mild congenital diaphragmatic hernia: A resuscitation algorithm." Front Pediatr **10**.

<sec>BackgroundInfants with a congenital diaphragmatic hernia (CDH) and expected mild pulmonary hypoplasia have an estimated survival rate of 90%. Current guidelines for delivery room management do not consider the individual patient's disease severity, but an individualized approach with spontaneous breathing instead of routine mechanical ventilation could be beneficial for the mildest cases. We developed a resuscitation algorithm for this individualized approach serving two purposes: improving the success rate by structuring the approach and providing a guideline for other centers.</sec><sec>MethodsAn initial algorithm was discussed with all local stakeholders. Afterwards, the resulting algorithm was refined using input from international experts.</sec><sec>ResultsEligible CDH infants: left-sided defect, observed to expected lung-to-head ratio ≥50%, gestational age at birth ≥37.0 weeks, and no major associated structural or genetic abnormalities. To facilitate fetal-to-neonatal transition, we propose to start stabilization with non-invasive respiratory support and to adjust this individually.</sec><sec>ConclusionsInfants with mild CDH might benefit from an individualized approach for neonatal resuscitation. Herein, we present an algorithm that could serve as guidance for centers implementing this.</sec>

Horn-Oudshoorn, E. J. J., et al. (2022). "Physiological-based cord clamping versus immediate cord clamping for infants born with a congenital diaphragmatic hernia (PinC): study protocol for a multicentre, randomised controlled trial." BMJ Open **12**(3): e054808.

INTRODUCTION: Pulmonary hypertension is a major determinant of postnatal survival in infants with a congenital diaphragmatic hernia (CDH). The current care during the perinatal stabilisation period in these infants might contribute to the development of pulmonary hypertension after birth-in particular umbilical cord clamping before lung aeration. An ovine model of diaphragmatic hernia demonstrated that cord clamping after lung aeration, called physiological-based cord clamping (PBCC), avoided the initial high pressures in the lung vasculature while maintaining adequate blood flow, thereby avoiding vascular remodelling and aggravation of pulmonary hypertension. We aim to investigate if the implementation of PBCC in the perinatal stabilisation period of infants born with a CDH could reduce the incidence of pulmonary hypertension in the first 24 hours after birth. METHODS AND ANALYSIS: We will perform a multicentre, randomised controlled trial in infants with an isolated left-sided CDH, born at >/=35.0 weeks. Before birth, infants will be randomised to either PBCC or immediate cord clamping, stratified by treatment centre and severity of pulmonary hypoplasia on antenatal ultrasound. PBCC will be performed using a purpose-built resuscitation trolley. Cord clamping will be performed when the infant is considered respiratory stable, defined as a heart rate >100 bpm, preductal oxygen saturation >85%, while using a fraction of inspired oxygen of <0.5. The primary outcome is pulmonary hypertension diagnosed in the first 24 hours after birth, based on clinical and echocardiographic parameters. Secondary outcomes include neonatal as well as maternal outcomes. ETHICS AND DISSEMINATION: Central ethical approval was obtained from the Medical Ethical Committee of the Erasmus MC, Rotterdam, The Netherlands (METC 2019-0414). Local ethical approval will be obtained by submitting the protocol to the regulatory bodies and local institutional review boards. TRIAL REGISTRATION NUMBER: NCT04373902.

Kamath, B. D., et al. (2010). "Adrenal insufficiency in newborns with congenital diaphragmatic hernia." J Pediatr **156**(3): 495-497 e491.

Kashyap, A. J., et al. (2020). "Physiologically based cord clamping improves cardiopulmonary haemodynamics in lambs with a diaphragmatic hernia." Arch Dis Child Fetal Neonatal Ed **105**(1): 18-25.

OBJECTIVE: Lung hypoplasia associated with congenital diaphragmatic hernia (CDH) results in respiratory insufficiency and pulmonary hypertension after birth. We have investigated whether aerating the lung before removing placental support (physiologically based cord clamping (PBCC)), improves the cardiopulmonary transition in lambs with a CDH. METHODS: At approximately 138 days of gestational age, 17 lambs with surgically induced left-sided diaphragmatic hernia (approximately d80) were delivered via caesarean section. The umbilical cord was clamped either immediately prior to ventilation onset (immediate cord clamping (ICC); n=6) or after achieving a

target tidal volume of 4 mL/kg, with a maximum delay of 10 min (PBCC; n=11). Lambs were ventilated for 120 min and physiological changes recorded. RESULTS: Pulmonary blood flow (PBF) increased following ventilation onset in both groups, but was 19-fold greater in PBCC compared with ICC lambs at cord clamping (19+/-6.3 vs 1.0+/-0.5 mL/min/kg, p<0.001). Cerebral tissue oxygenation was higher in PBCC than ICC lambs during the first 10 min after cord clamping (59%+/-4% vs 30%+/-5%, p<0.001). PBF was threefold higher (23+/-4 vs 8+/-2 mL/min/kg, p=0.01) and pulmonary vascular resistance (PVR) was threefold lower (0.6+/-0.1 vs 2.2+/-0.6 mm Hg/(mL/min), p<0.001) in PBCC lambs compared with ICC lambs at 120 min after ventilation onset. CONCLUSIONS: Compared with ICC, PBCC prevented the severe asphyxia immediately after birth and resulted in a higher PBF due to a lower PVR, which persisted for at least 120 min after birth in CDH lambs.

Keller, R. L. (2012). Management of the infant with congenital diaphragmatic hernia. The newborn lung. E. Bancalari and R. A. Polin. Philadelphia, Elsevier Saunders: 381-406.

Kraemer, U. S., et al. (2018). "Characteristics of Infants With Congenital Diaphragmatic Hernia Who Need Follow-Up of Pulmonary Hypertension." Pediatr Crit Care Med **19**(5): e219-e226.

OBJECTIVES: Pulmonary hypertension is one of the main causes of mortality and morbidity in patients with congenital diaphragmatic hernia. Currently, it is unknown whether pulmonary hypertension persists or recurs during the first year of life. DESIGN: Prospective longitudinal follow-up study. SETTING: Tertiary university hospital. PATIENTS: Fifty-two congenital diaphragmatic hernia patients admitted between 2010 and 2014. INTERVENTIONS: None. MEASUREMENTS AND MAIN RESULTS: Pulmonary hypertension was measured using echocardiography and electrocardiography at 6 and 12 months old. Characteristics of patients with persistent pulmonary hypertension were compared with those of patients without persistent pulmonary hypertension. At follow-up, pulmonary hypertension persisted in four patients: at 6 months old, in three patients (patients A-C), and at 12 months old, in two patients (patients C and D). Patients with persistent pulmonary hypertension had a longer duration of mechanical ventilation (median 77 d [interquartile range, 49-181 d] vs median 8 d [interquartile range, 5-15 d]; p = 0.002) and hospital stay (median 331 d [interquartile range, 198-407 d) vs median 33 d (interquartile range, 16-59 d]; p = 0.003) than patients without persistent pulmonary hypertension. The proportion of patients with persistent pulmonary hypertension (n = 4) treated with inhaled nitric oxide (100% vs 31%; p = 0.01), sildenafil (100% vs 15%; p = 0.001), and bosentan (100% vs 6%; p < 0.001) during initial hospital stay was higher than that of patients without persistent pulmonary hypertension (n = 48). At 6 months, all patients with persistent pulmonary hypertension were tube-fed and treated with supplemental oxygen and sildenafil. CONCLUSIONS: Less than 10% of congenital diaphragmatic hernia patients had persistent pulmonary hypertension at ages 6 and/or 12 months. Follow-up for pulmonary hypertension should be reserved for congenital diaphragmatic hernia patients with echocardiographic signs

of persistent pulmonary hypertension at hospital discharge and/or those treated with medication for pulmonary hypertension at hospital discharge.

Lawrence, K. M., et al. (2020). "Inhaled Nitric Oxide Is Associated with Improved Oxygenation in a Subpopulation of Infants with Congenital Diaphragmatic Hernia and Pulmonary Hypertension." J Pediatr **219**: 167-172.

OBJECTIVES: To determine which patients with congenital diaphragmatic hernia (CDH) and pulmonary hypertension (PH) benefit from inhaled nitric oxide (iNO) treatment by comparing characteristics and outcomes of iNO responders to nonresponders. STUDY DESIGN: We performed a retrospective chart review of infants with CDH treated at our center between 2011 and 2016. In a subset of patients, iNO was initiated for hypoxemia or echocardiographic evidence of extrapulmonary right to left shunting. Initial post-treatment blood gases were reviewed, and patients were classified as responders (increased PaO2 >20 mm Hg) or nonresponders. Baseline characteristics, echocardiograms and outcomes were compared between groups with Fisher exact tests and Mann-Whitney t tests, as appropriate. RESULTS: During the study period, 95 of 131 patients with CDH (73%) were treated with iNO. All patients with pretreatment echocardiograms (n = 90) had echocardiographic evidence of PH. Thirty-eight (40%) patients met treatment response criteria. Responders had significant improvements in PaO2 (51 +/- 3 vs 123 +/- 7 mm Hg, P < .01), alveolar-arterial gradient (422 +/- 30 vs 327 +/- 27 mm Hg, P < .01), and PaO2 to FiO2 ratio (82 +/- 10 vs 199 +/- 15 mm Hg, P < .01). Nonresponders were more likely to have left ventricular systolic dysfunction (27% vs 8%, P = .03) on echocardiogram. Responders were less likely to require extracorporeal membrane support (50 vs 24%, P = .02). CONCLUSIONS: iNO treatment is associated with improved oxygenation and reduced need for ECMO in a subpopulation of patients with CDH with PH and normal left ventricular systolic function.

Le Duc, K., et al. (2021). "Efficacy of Intact Cord Resuscitation Compared to Immediate Cord Clamping on Cardiorespiratory Adaptation at Birth in Infants with Isolated Congenital Diaphragmatic Hernia (CHIC)." Children (Basel) **8**(5).

Resuscitation at birth of infants with Congenital Diaphragmatic Hernia (CDH) remains highly challenging because of severe failure of cardiorespiratory adaptation at birth. Usually, the umbilical cord is clamped immediately after birth. Delaying cord clamping while the resuscitation maneuvers are started may: (1) facilitate blood transfer from placenta to baby to augment circulatory blood volume; (2) avoid loss of venous return and decrease in left ventricle filling caused by immediate cord clamping; (3) prevent initial hypoxemia because of sustained uteroplacental gas exchange after birth when the cord is intact. The aim of this trial is to evaluate the efficacy of intact cord resuscitation compared to immediate cord clamping on cardiorespiratory adaptation at birth in infants with isolated CDH. The Congenital Hernia Intact Cord (CHIC) trial is a prospective multicenter open-label randomized controlled trial in two balanced parallel groups. Participants are randomized either immediate cord clamping (the cord will be clamped

within the first 15 s after birth) or to intact cord resuscitation group (umbilical cord will be kept intact during the first part of the resuscitation). The primary end-point is the number of infants with APGAR score <4 at 1 min or <7 at 5 min. One hundred eighty participants are expected for this trial. To our knowledge, CHIC is the first study randomized controlled trial evaluating intact cord resuscitation on newborn infant with congenital diaphragmatic hernia. Better cardiorespiratory adaptation is expected when the resuscitation maneuvers are started while the cord is still connected to the placenta.

Lefebvre, C., et al. (2017). "Feasibility and safety of intact cord resuscitation in newborn infants with congenital diaphragmatic hernia (CDH)." Resuscitation **120**: 20-25.

BACKGROUND: Starting resuscitation before clamping the umbilical cord at birth may progressively increase pulmonary blood flow while umbilical venous blood flow is still contributing to maintenance of oxygenation and left ventricle preload. OBJECTIVE: To evaluate the feasibility, safety, and effects of intact cord resuscitation (ICR) on cardiorespiratory adaptation at birth in newborn infants with CDH. STUDY DESIGN: Prospective, observational, single-center pilot study. METHODS: Physiologic variables and outcomes were collected prospectively in 40 consecutive newborn infants with an antenatal diagnosis of isolated CDH. RESULTS: Infants were managed with immediate cord clamping (ICC group) from 1/2012 to 5/2014 or the cord was clamped after initiation of resuscitation maneuvers (ICR group) from 6/2014 to 4/2016 (20 in each group). Ante- and postnatal markers of CDH severity were similar between groups. Resuscitation before cord clamping was possible for all infants in the ICR group. No increase in maternal or neonatal adverse events was observed during the period of ICR. The pH was higher and the plasma lactate concentration was significantly lower at one hour after birth in the ICR than in the ICC group (pH=7.17+/-0.1 vs 7.08+/-0.2; lactate=3.6+/-2.3 vs 6.6+/-4.3mmol/l, p<0.05). Mean blood pressure was significantly higher in the ICR than in the ICC group at H1 (52+/-7.7 vs 42+/-7.5mmHg), H6 (47+/-3.9 vs 40+/-5.6mmHg) and H12 (44+/-2.9 vs 39+/-3.3mmHg) (p<0.05). CONCLUSION: Commencing resuscitation and initiating ventilation while the infant is still attached to the placenta is feasible in infants with CDH. The procedure may support the cardiorespiratory transition at birth in infants with CDH.

Moore, S. S., et al. (2024). "Congenital Diaphragmatic Hernia: Pulmonary Hypertension and Pulmonary Vascular Disease." Clin Perinatol **51**(1): 151-170.

This review provides a comprehensive summary of the current understanding of pulmonary hypertension (PH) in congenital diaphragmatic hernia, outlining the underlying pathophysiologic mechanisms, methods for assessing PH severity, optimal management strategies, and prognostic implications.

Nascimento, M. C., et al. (2002). "Arterial blood pressure of term newborns during the first week of life." Braz J Med Biol Res **35**(8): 905-911.

The progressive behavior of the blood pressure of term newborns during the first week of life was assessed by the simultaneous use of oscillometric and Doppler methods. A total of 174 term neonates born at the Municipal Hospital Odilon Behrens in Belo Horizonte, from March 1996 to February 1997, were prospectively assessed. The oscillometric and Doppler ultrasonic methods were simultaneously used for four consecutive recordings obtained at 12 +/- 6, 24 +/- 6 and 72 +/- 24 h and on the 7th +/- 1 day of life. The combined use of the two methods simplified the procedure, with automatic cuff inflation and deflation, and speed was properly controlled with an automatic pressure monitor. The procedure was performed using a Y-connection to the mercury sphygmomanometer, with blood pressure being recorded with an automatic device and systolic blood pressure being measured simultaneously by Doppler ultrasound. The newborns were awake, not crying and in the supine position. A statistically significant increase in systolic and diastolic blood pressure was observed between the first and second, and the third and fourth measurements by Doppler and oscillometric methods. No significant correlation between birth weight, length, ponderal index and blood pressure was observed. The technique used represents a simpler and more accurate procedure for blood pressure measurement.

Puligandla, P., et al. (2023). "Diagnosis and management of congenital diaphragmatic hernia: a 2023 update from the Canadian Congenital Diaphragmatic Hernia Collaborative." Arch Dis Child Fetal Neonatal Ed.

OBJECTIVE: The Canadian Congenital Diaphragmatic Hernia (CDH) Collaborative sought to make its existing clinical practice guideline, published in 2018, into a 'living document'. DESIGN AND MAIN OUTCOME MEASURES: Critical appraisal of CDH literature adhering to Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology. Evidence accumulated between 1 January 2017 and 30 August 2022 was analysed to inform changes to existing or the development of new CDH care recommendations. Strength of consensus was also determined using a modified Delphi process among national experts in the field. RESULTS: Of the 3868 articles retrieved in our search that covered the 15 areas of CDH care, 459 underwent full-text review. Ultimately, 103 articles were used to inform 20 changes to existing recommendations, which included aspects related to prenatal diagnosis, echocardiographic evaluation, pulmonary hypertension management, surgical readiness criteria, the type of surgical repair and long-term health surveillance. Fifteen new CDH care recommendations were also created using this evidence, with most related to the management of pain and the provision of analgesia and neuromuscular blockade for patients with CDH. CONCLUSIONS: The 2023 Canadian CDH Collaborative's clinical practice guideline update provides a management framework for infants and children with CDH based on the best available evidence and expert consensus.

Reiss, I., et al. (2010). "Standardized postnatal management of infants with congenital diaphragmatic hernia in Europe: the CDH EURO Consortium consensus." Neonatology **98**(4): 354-364.

Congenital diaphragmatic hernia (CDH) is associated with high mortality and morbidity. To date, there are no standardized protocols for the treatment of infants with this anomaly. However, protocols based on the literature and expert opinion might improve outcome. This paper is a consensus statement from the CDH EURO Consortium prepared with the aim of achieving standardized postnatal treatment in European countries. During a consensus meeting between high-volume centers with expertise in the treatment of CDH in Europe (CDH EURO Consortium), the most recent literature on CDH was discussed. Thereafter, 5 experts graded the studies according to the Scottish Intercollegiate Guidelines Network (SIGN) Criteria. Differences in opinion were discussed until full consensus was reached. The final consensus statement, therefore, represents the opinion of all consortium members. Multicenter randomized controlled trials on CDH are lacking. Use of a standardized protocol, however, may contribute to more valid comparisons of patient data in multicenter studies and identification of areas for further research.

Riley, J. S., et al. (2018). "Reduced oxygen concentration for the resuscitation of infants with congenital diaphragmatic hernia." J Perinatol **38**(7): 834-843.

OBJECTIVE: To evaluate whether infants with congenital diaphragmatic hernia (CDH) can be safely resuscitated with a reduced starting fraction of inspired oxygen (FiO2) of 0.5. STUDY DESIGN: A retrospective cohort study comparing 68 patients resuscitated with starting FiO2 0.5 to 45 historical controls resuscitated with starting FiO2 1.0. RESULTS: Reduced starting FiO2 had no adverse effect upon survival, duration of intubation, need for ECMO, duration of ECMO, or time to surgery. Furthermore, it produced no increase in complications, adverse neurological events, or neurodevelopmental delay. The need to subsequently increase FiO2 to 1.0 was associated with female sex, lower gestational age, liver up, lower lung volume-head circumference ratio, decreased survival, a higher incidence of ECMO, longer time to surgery, periventricular leukomalacia, and lower neurodevelopmental motor scores. CONCLUSION: Starting FiO2 0.5 may be safe for the resuscitation of CDH infants. The need to increase FiO2 to 1.0 during resuscitation is associated with worse outcomes.

Snoek, K., et al. (2014). "O-223 The Vici-trial: an international multicenter randomized clinical trial comparing HFO and CMV as initial ventilation strategy in congenital diaphragmatic hernia." Arch Dis Child **99: A110**.

Background Congenital diaphragmatic hernia (CDH) is a life-threatening anomaly with significant mortality and morbidity. The lungs have a high susceptibility for oxygen and ventilation damage resulting in a high incidence of chronic lung disease (CLD).

Aim To establish the optimal initial ventilation strategy in CDH.

Methods In a prospective, randomised international multicenter trial initiated by the CDH Euroconsortium (VICI-trial, NTR 1310), prenatally diagnosed CDH neonates born between November 2008 and December 2013, were randomised for either conventional mechanical ventilation (CMV) or high-frequency oscillation ventilation (HFO) as initial ventilation mode. Primary outcome measure was death or CLD (Jobe and Bancalari, 2001) at day 28 analysed by multiple logistic regression analysis corrected for centre, lung-to-head ratio, liver position and side of defect. Secondary outcome was corrected for centre.

Results Of the 171 included patients, 91 (53.2%) initially received CMV (median gestational age 38.1 weeks) and 80 (46.8%) HFO (median gestational age 38.0 weeks). In total, 21 (23.1%) patients ventilated by CMV died and 25 (31.3%) in HFO. Of the survivors, 21 (23.1%) had CLD in CMV and 18 (22.5%) in HFO. Primary outcome measure showed that in CMV 41 (45.1%) died or had CLD at day 28 and in HFO 43 (53.8%), OR 0.6, 95% CI [0.12–2.54]. Results of secondary outcome are shown in Table 1.

Conclusions Although the primary outcome was statistically not significant, CDH patients initially ventilated by CMV were ventilated less days, received inotropics less days, and received less often nitric oxide, sildenafil and ECMO compared to HFO.

Snoek, K. G., et al. (2016). "Conventional Mechanical Ventilation Versus High-frequency Oscillatory Ventilation for Congenital Diaphragmatic Hernia: A Randomized Clinical Trial (The VICI-trial)." Ann Surg **263**(5): 867-874.

OBJECTIVES: To determine the optimal initial ventilation mode in congenital diaphragmatic hernia. BACKGROUND: Congenital diaphragmatic hernia is a life-threatening anomaly with significant mortality and morbidity. The maldeveloped lungs have a high susceptibility for oxygen and ventilation damage resulting in a high incidence of bronchopulmonary dysplasia (BPD) and chronic respiratory morbidity. METHODS: An international, multicenter study (NTR 1310), the VICI-trial was performed in prenatally diagnosed congenital diaphragmatic hernia infants (n = 171) born between November 2008 and December 2013, who were randomized for initial ventilation strategy. RESULTS: Ninety-one (53.2%) patients initially received conventional mechanical ventilation and 80 (46.8%) high-frequency oscillation. Forty-one patients (45.1%) randomized to conventional mechanical ventilation died/ had BPD compared with 43 patients (53.8%) in the high-frequency oscillation group. An odds ratio of 0.62 [95% confidence interval (95% CI) 0.25-1.55] (P = 0.31) for death/BPD for conventional mechanical ventilation vs high-frequency oscillation was demonstrated, after adjustment for center, head-lung ratio, side of the defect, and liver position. Patients initially ventilated by conventional mechanical ventilation were ventilated for fewer days (P = 0.03), less often needed extracorporeal membrane oxygenation support (P = 0.007), inhaled nitric oxide (P = 0.045), sildenafil (P = 0.004), had a shorter duration of

vasoactive drugs (P = 0.02), and less often failed treatment (P = 0.01) as compared with infants initially ventilated by high-frequency oscillation. CONCLUSIONS: Our results show no statistically significant difference in the combined outcome of mortality or BPD between the 2 ventilation groups in prenatally diagnosed congenital diaphragmatic hernia infants. Other outcomes, including shorter ventilation time and lesser need of extracorporeal membrane oxygenation, favored conventional ventilation.

The Neonatal Inhaled Nitric Oxide Study Group, N. (1997). "Inhaled nitric oxide and hypoxic respiratory failure in infants with congenital diaphragmatic hernia. The Neonatal Inhaled Nitric Oxide Study Group (NINOS)." Pediatrics **99**(6): 838-845.

OBJECTIVE: We designed and conducted a randomized, double-masked, controlled multicenter study to determine whether inhaled nitric oxide (INO) in term and near-term infants with congenital diaphragmatic hernia (CDH) would reduce the occurrence of death and/or the initiation of extracorporeal membrane oxygenation (ECMO). PATIENTS AND METHODS: Infants of 34 weeks gestation or more, <14 days of age with CDH, without known structural heart disease, requiring assisted ventilation for hypoxemic respiratory failure with two oxygenation indices (OIs) of 25 or more at least 15 minutes apart, were eligible for this trial. Infants were centrally randomized and then received masked treatment with 20 ppm NO or 100% oxygen as control. Infants with less than a full response to 20 ppm NO (increase in PaO2 > 20 Torr) after 30 minutes were evaluated at 80 ppm NO/control study gas. RESULTS: The 28 control and 25 treated infants enrolled by the 13 participating centers were not significantly different at randomization for any of the measured variables including prerandomization therapies and initial OIs (45.8 +/- 16.3 for controls, 44.5 +/- 14.5 for INO). Death at <120 days of age or the need for ECMO occurred in 82% of control infants compared with 96% of INO infants (ns). Death occurred in 43% of controls and 48% of the INO group (ns), and ECMO treatment was used for 54% of control and 80% of INO-treated infants. There was no significant improvement in PaO2 (delta PaO2 7.8 +/- 19.8 vs 1.1 +/- 7.6 Torr, ns) nor significant reduction in OI (-2.7 +/- 23.4 vs 4.0 +/- 14.8, ns) associated with INO treatment. Mean peak nitrogen dioxide (NO2) concentration was 1.9 +/- 1.3 ppm and the mean peak methemoglobin was 1.6 +/- 0.8 mg/dL. No infant had study gas discontinued for toxicity. There were no differences between the control and INO groups for the occurrence of intracranial hemorrhage, specific grades of intracranial hemorrhage, periventricular leukomalacia, brain infarction, and pulmonary or gastrointestinal hemorrhages. CONCLUSIONS: Although the immediate short-term improvements in oxygenation seen in some treated infants may be of benefit in stabilizing responding infants for transport and initiation of ECMO, we conclude that for term and near-term infants with CDH and hypoxemic respiratory failure unresponsive to conventional therapy, inhaled NO therapy as used in this trial did not reduce the need for ECMO or death.

Weiner, G. M. and J. Zaichkin (2021). Textbook of Neonatal Resuscitation, American Academy of Pediatrics.

Wyckoff, M. H., et al. (2020). "Neonatal Life Support 2020 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science With Treatment Recommendations." Resuscitation **156**: A156-A187.

This 2020 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science With Treatment Recommendations (CoSTR) for neonatal life support includes evidence from 7 systematic reviews, 3 scoping reviews, and 12 evidence updates. The Neonatal Life Support Task Force generally determined by consensus the type of evidence evaluation to perform; the topics for the evidence updates followed consultation with International Liaison Committee on Resuscitation member resuscitation councils. The 2020 CoSTRs for neonatal life support are published either as new statements or, if appropriate, reiterations of existing statements when the task force found they remained valid. Evidence review topics of particular interest include the use of suction in the presence of both clear and meconium-stained amniotic fluid, sustained inflations for initiation of positive-pressure ventilation, initial oxygen concentrations for initiation of resuscitation in both preterm and term infants, use of epinephrine (adrenaline) when ventilation and compressions fail to stabilize the newborn infant, appropriate routes of drug delivery during resuscitation, and consideration of when it is appropriate to redirect resuscitation efforts after significant efforts have failed. All sections of the Neonatal Resuscitation Algorithm are addressed, from preparation through to postresuscitation care. This document now forms the basis for ongoing evidence evaluation and reevaluation, which will be triggered as further evidence is published. Over 140 million babies are born annually worldwide (https://ourworldindata.org/grapher/births-and-deaths-projected-to-2100). If up to 5% receive positive-pressure ventilation, this evidence evaluation is relevant to more than 7 million newborn infants every year. However, in terms of early care of the newborn infant, some of the topics addressed are relevant to every single baby born.

Yamada, N. K., et al. (2024). "2023 American Heart Association and American Academy of Pediatrics Focused Update on Neonatal Resuscitation: An Update to the American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care." Circulation **149**(1): e157-e166.

This 2023 focused update to the neonatal resuscitation guidelines is based on 4 systematic reviews recently completed under the direction of the International Liaison Committee on Resuscitation Neonatal Life Support Task Force. Systematic reviewers and content experts from this task force performed comprehensive reviews of the scientific literature on umbilical cord management in preterm, late preterm, and term newborn infants, and the optimal devices and interfaces used for administering positive-pressure ventilation during resuscitation of newborn infants. These recommendations provide new guidance on the use of intact umbilical cord milking, device selection for

administering positive-pressure ventilation, and an additional primary interface for administering positive-pressure ventilation.

Yang, M. J., et al. (2020). "Left-sided congenital diaphragmatic hernia: can we improve survival while decreasing ECMO?" J Perinatol **40**(6): 935-942.

BACKGROUND: Mortality and ECMO rates for congenital diaphragmatic hernia (CDH) remain ~30%. In 2016, we changed our CDH guidelines to minimize stimulation while relying on preductal oxygen saturation, lower mean airway pressures, stricter criteria for nitric oxide (iNO), and inotrope use. We compared rates of ECMO, survival, and survival without ECMO between the two epochs. DESIGN/METHODS: Retrospective review of left-sided CDH neonates at the University of Utah/Primary Children's Hospital NICUs during pre (2003-2015, n = 163) and post (2016-2019, n = 53) epochs was conducted. Regression analysis controlled for defect size and intra-thoracic liver. RESULTS: Following guideline changes, we identified a decrease in ECMO (37 to 13%; p = 0.001) and an increase in survival without ECMO (53 to 79%, p = 0.0001). Overall survival increased from 74 to 89% (p = 0.035). CONCLUSION(S): CDH management guideline changes focusing on minimizing stimulation, using preductal saturation and less aggressive ventilator/inotrope support were associated with decreased ECMO use and improved survival.

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