Review Article

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An evidence-based treatment algorithm for congenital diaphragmatic hernia

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Abstract

Background: Congenital diaphragmatic hernia (CDH) affects more than 1100 newborns in the United States each year. Severity of clinical presentation is highly variable. Standardized care improves outcomes by promoting consistency in decision-making and clarifying goals of treatment, but CDH management has not yet been standardized.

Methods: We performed a comprehensive literature review with special consideration for—cardiac dysfunction, indications for extracorporeal membrane oxygenation (ECMO), and timing of repair. In collaboration with experts across specialties, we sought to develop and implement a treatment algorithm based on current CDH literature and our own institutional experience.

Results: Left ventricular (LV) hypoplasia and dysfunction is increasingly recognized as an important contributor to the severity of clinical presentation and cardiac dysfunction seen with CDH. Cardiac dysfunction is associated with poor outcomes and increased mortality. CDH-associated severe hypoxic respiratory failure refractory to medical therapy is one of the most common indications for ECMO in the neonatal period. The decision to initiate ECMO and selection of configuration should be shared by members of a multidisciplinary care team. The optimal timing of repair with respect to ECMO has been evolving in the last 3 decades.

Conclusion: Following our review, we recommend (1) timely and detailed cardiac evaluation with echocardiogram after birth, and (2) early repair on ECMO for high-risk patients and delayed repair post-ECMO for low-risk patients with anticipated short ECMO run. This treatment algorithm is a step toward standardization of CDH management practices, which we expect will improve CDH outcomes at our institution and others.

Keywords

CDH congenital Diaphragmatic hernia, ECMO extracorporeal membrane oxygenation, left ventricular dysfunction, timing of repair, treatment protocols

Level III evidence

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Introduction

Approximately 1100 cases of congenital diaphragmatic hernia (CDH), spanning a variable spectrum of disease, are diagnosed in the United States each year.[1] A number of studies suggest that standardized CDH management improves outcomes by promoting consistency in decision-making and clarifying goals of treatment.[2–5] However, standardization of CDH management has not yet been achieved. A 2019 study surveying North American CDH Study Group (CDHSG) and Pediatric Surgical Research Collaborative member institutions revealed that about one third of centers have no clinical practice guidelines and found high variability in content among those that do.[6] Efforts to standardize management across institutions have included the CDH EURO Consortium Consensus treatment protocol originally published in 2010 and revised in 2015; and the 2018 and updated 2023 Canadian CDH Collaborative clinical practice guidelines.[2,7–9] Using these recommendations as a guide and in collaboration with experts across specialties, we sought to develop and implement a treatment algorithm for our institution based on current evidence from the CDH literature and our own institutional experience. Special considerations emphasized in this review include three controversial topics—cardiac dysfunction, indications and contraindications for extracorporeal membrane oxygenation (ECMO), and timing of repair relative to ECMO. Though the survival rate at our institution of approximately 80% is higher than what has been reported in the literature,[6] we anticipate this algorithm will serve to improve patient outcomes across all risk categories and provide a foundation for comparative prospective studies across institutions.

Methods

We performed a systematic literature review to assess current evidence for specific practices and developed our own practice guidelines based on this review. We selected the following questions for our review:

1. What are the treatment considerations for CDH patients with pulmonary vascular disease and left ventricular (LV) hypoplasia/dysfunction?
2. What are the indications and (relative) contraindications for ECMO in CDH patients?
3. What is the optimal timing of CDH repair with respect to ECMO?

We applied Medical Subject Headings (MeSH) search terms in consultation with a health sciences librarian, and searched Medline, Embase, Cochrane, Scopus, and Web of Science (Appendix A). Using EndNote (Clarivate, Philadelphia, PA), duplicates were removed. Titles and abstracts were scanned for relevance, followed by full text. Articles were screened independently by two reviewers using Covidence (Melbourne, VIC, Australia) and disagreements resolved by a third reviewer. The final reference list was limited to English language, non-animal study publications, with available full text (Figure 1). Reference lists of selected papers were also reviewed to expand our final reference list. In cases where multiple studies assessed the same cohort over a given time period, the study with the largest and most complete dataset was included to avoid redundancy. Given substantial variation in study populations and outcomes, qualitative findings were reported, and a meta-analysis was not performed.

Results and discussion

Initial management

For prenatally diagnosed infants with CDH, immediate intubation and gentle ventilation (peak inspiratory pressure $\leq$25 cm H_2O) with permissive hypercapnia to prevent barotrauma is generally accepted and has been routinely practiced at our institution since the 1990s.[2,6,8,10,11] In patients with unclear diagnosis (e.g., possible diaphragm eventration), and possibly even very mild CDH, a trial of spontaneous breathing instead of immediate intubation may be undertaken.[12] Goals of mechanical ventilation include: preductal oxygen saturation (SpO2) 85%–95%, PaCO2 45–60, pH 7.25–7.4. However, escalation to high frequency positive pressure ventilation (HFPPV) as an intermediary mode of rescue ventilation[13] or high frequency oscillatory ventilation (HFOV) might be indicated in patients as who do not achieve these parameters. The results of the Ventilation in Infants with Congenital Diaphragmatic Hernia: an International Randomized Clinical Trial (VICI) trial (n = 171) showed no difference in the combined outcome of mortality or bronchopulmonary dysplasia between patients receiving conventional mechanical ventilation (CMV) and those receiving HFOV as the initial ventilation strategy. However, CMV was associated with shorter ventilation time and decreased need for ECMO.[14] A 2023 systematic review and meta-analysis also demonstrated a higher pooled rate of mortality and incidence chronic lung disease (CLD) in patients who received HFOV versus CMV; however, there was notable heterogeneity regarding indications for HFOV.[15] Current institutional practice includes immediate intubation and CMV with use of HFPPV and/or HFOV for persistent respiratory failure (Figure 2).

Vascular access should be obtained by placing an umbilical arterial line, or if possible, a right radial arterial line to measure preductal SpO2. Early echocardiogram (ECHO) within the first 24 hours of life is necessary to evaluate for structural and functional abnormalities, including assessment of shunting at the level of the atria and ductus arteriosus, ventricular systolic and diastolic function and

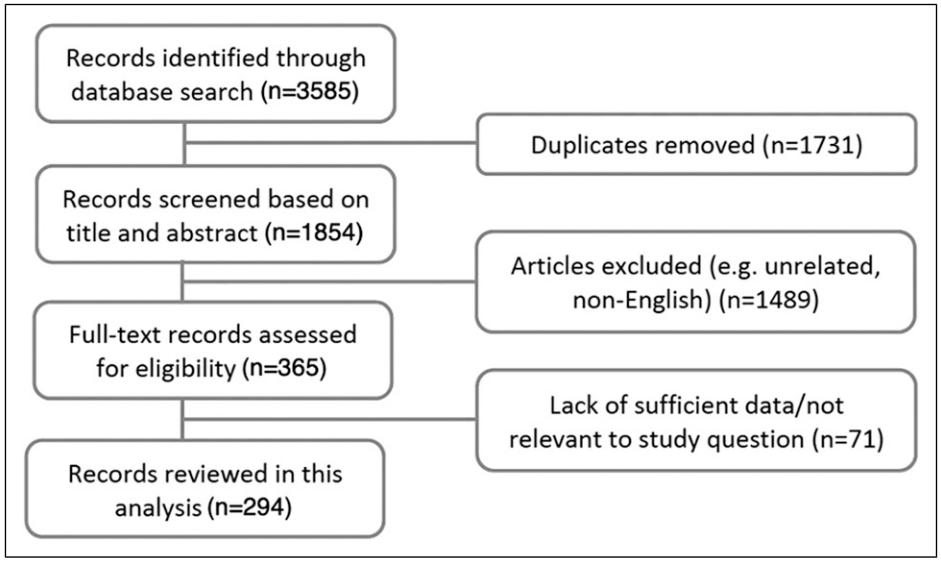

Figure 1. Flowchart of records screened and selected for review.

chamber size, and estimation of pulmonary artery pressure (Table 1).[16,17] The presence of congenital heart disease should be evaluated as this adds an additional layer of complexity, especially if neonatal surgical correction of the cardiac defect is indicated. An estimated 17% of CDH patients have a congenital heart defect at birth, and a 2019 systematic review showed that CDH patients with congenital heart disease have a lower survival rate than those with CDH alone.[18] A head ultrasound should also be performed once the neonate has stabilized.

Cardiac dysfunction

The contribution of LV hypoplasia and dysfunction to CDH severity is being increasingly recognized and should be considered in the CDH treatment algorithm. Siebert et al. first described LV hypoplasia and reduced left atrial return in the CDH population in 1984, and since then, studies have sought to further elucidate this relationship.[19] The three main components of CDH pathophysiology are pulmonary hypoplasia, pulmonary hypertension, and cardiac dysfunction, though management strategies have been primarily directed at the former two components. Proposed mechanisms of LV hypoplasia involve cardiac developmental changes, direct mechanical compression by herniated structures, geometrical shifts favoring blood flow from the ductus venosus toward the right heart, and decreased blood flow to the left heart.[20–22] RV dysfunction is commonly diastolic in nature but is thought to play a role in the development of LV dysfunction through ventricular interdependence as the two structures share muscle fibers, a septum, and pericardium.[22,23] LV hypoplasia, reduced pulmonary blood flow, and the acute increase in afterload in the transitional period are also contributory, working to perpetuate a cycle of cardiac dysfunction and pulmonary vasoconstriction, and ultimately reduced cardiac output, hypoxia, and acidosis.[22,24,25]

Cardiac dysfunction has been associated with poorer outcomes such as increased risk of mortality and may be a better predictor of need for ECMO than PH.[22,26] Independently, RV dysfunction has been shown to be associated with increased mortality, length of hospital stay, and duration of respiratory support.[23] However, Gaffar et al. suggested decreased LV cardiac output was more strongly associated with need for ECMO than PH severity or RV dysfunction.[27] Recently, Dao et al. evaluated 778 patients from the CDH Study Group (CDHSG) registry data with CDHSG defect size A and B who had no structural cardiac or chromosomal abnormalities. They showed that LV dysfunction and severe PH were predictors of adverse outcomes, specifically, ECMO utilization, oxygen requirement at 30 days of life, hospitalization ≥8 weeks, or death.[28] Furthermore, a small right pulmonary artery and LV diastolic diameter, and failure of the heart to return to its normal position after CDH repair have been associated with less favorable outcomes.[29,30]

In our review, studies most commonly compared CDH neonates to normal controls or CDH survivors to non-survivors. However, a major limitation was the variation in echocardiographic parameters used to quantify cardiac dysfunction. This was also an important finding identified in a 2021 systematic review investigating CDH ventricular function by Prasad et al.[31] Measures of LV systolic function included LV ejection fraction (EF) and global longitudinal strain (GLS). For evaluation of RV systolic function, the tricuspid annular plane systolic excursion (TAPSE) and RV pulsed wave tissue Doppler imaging velocity in systole (RV S') were used. In contrast, RV pulsed wave tissue Doppler

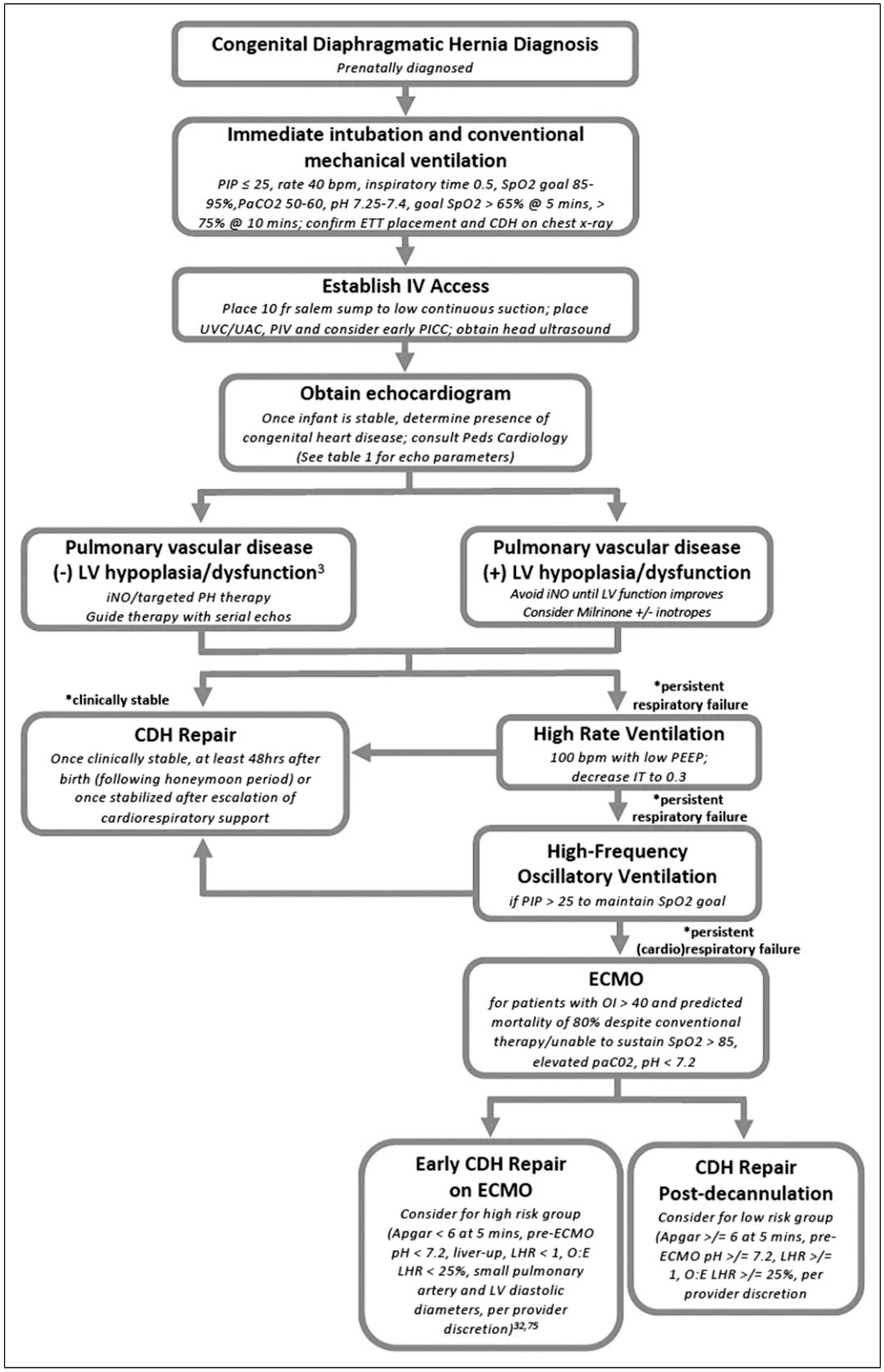

Figure 2. Treatment algorithm for CDH. CDH: congenital diaphragmatic hernia; PIP: peak inspiratory pressure; SpO2: oxygen saturation; PaCO2: partial pressure of carbon dioxide; ETT: endotracheal tube; Fr: French size (1Fr = 0.33 mm); UVC/UAC: umbilical vein/artery catheter; PICC: peripherally inserted central catheter; LV: left ventricular; PH: pulmonary hypertension; PEEP: positive end expiratory pressure; IT: inspiratory time; OI: oxygenation index; LHR: lung head ratio; O:E LHR: observed to expected lung head ratio.

Table 1. Echocardiographic parameters for specific imaging goals. This table provides guidance for which measurements to obtain. Some may not be achievable in all neonates depending on the clinical condition, presence of congenital heart disease, cardiac position, and acoustic windows. Discussion between neonatology, cardiology and pediatric surgery is essential to provide guidance. The essential echocardiographic goals are (1) rule out significant congenital heart disease, (2) assess biventricular systolic and diastolic function, (3) determine presence of pulmonary hypertension, and (4) assess shunting at the atrial septum and patent ductus arteriosus, as these have immediate management implications. Many of the measurements can be done offline if adequate images are available.

Imaging goal	Echocardiographic parameters/measurements
Rule out significant congenital heart disease that needs correction	[a]Evaluate cardiac structure by 2 dimensional imaging, color and spectral Doppler (including valve and vessel measurements)
Evaluate left and right ventricular systolic and diastolic function	[a]1. Qualitative estimation 2. Quantitative analysis (offline): *LV systolic function/dimensions*: [b]- Ejection fraction and LV dimensions by 5/6 area length method and Simpson's method of discs (biplane) [b]- LV dimensions and shortening fraction by M-mode - LV strain *LV diastolic function*: [a]- Mitral valve E and A wave velocities - Pulmonary venous spectral Doppler (all pulmonary veins should be included) *RV systolic function/dimensions*: [b]- Tricuspid annular plane systolic excursion (TAPSE) [b]- RV Fractional area change (FAC) - RV S' wave velocity by tissue Doppler imaging - Myocardial performance index - Strain - RV/LV ratios in systole and diastole on parasternal short axis views *RV diastolic function*: [a]- Tricuspid valve E and A wave velocities - Tissue Doppler imaging of the lateral tricuspid valve annulus - IVC size and collapsibility - Right atrial area and volume
Estimate pulmonary artery pressure	Estimate pulmonary artery pressure [a]1. RV pressure estimate by peak tricuspid regurgitation jet velocity [a]2. Ventricular septal position at end-systole [a]3. Pulmonary regurgitation early diastolic peak velocity and end-diastolic velocity [a]4. Patent ductus arteriosus and/or ventricular septal defect shunt direction and gradient 5. LV eccentricity index at end-systole

Right ventricular (RV), left ventricular (LV).
[a]Priority measurements.
[b]If possible to obtain accurately depending on acoustic windows, any one or more of these measurements can be prioritized.
The remainder of the measurements can be made as the patient's clinical condition and acoustic windows allow.

imaging velocity in diastole (RV E') and the ratio of peak flow velocities across the tricuspid valve in early diastole to late diastole (tricuspid E/A) were used to quantify RV diastolic function. Myocardial performance index (MPI or Tei index) and the ratio of RV systole to diastole duration (SD/DD) were used as composite measures for both systolic and diastolic function.

In their CDHSG registry study, Altit et al. showed no significant difference in LVEF between CDH neonates and normal controls (63.1% vs 65.7%) but showed a significant difference in LV GLS (−13.2% vs −20.8%).[32] Patel et al. also showed a significant difference in LV GLS in CDH neonates compared to normal controls (−14.3% vs −21.2%) and demonstrated an improvement in this measure by 72–120 hours of life.[22] Furthermore, Sernich et al. and Baptista et al. both showed a significant difference in LV MPI (0.38 vs 0.26; 0.23 vs 0.22) and RV MPI (0.53 vs 0.2; 0.28 vs 0.21) in CDH neonates compared to normal controls.[33,34] Following subdivision of their CDH cohorts into survivors and non-survivors, Aggarwal et al. showed significant differences in the LV MPI (0.29 vs 0.47 vs 0.62) and RV MPI (0.25 vs 0.43 vs 0.66) for term controls, CDH survivors, and CDH non-survivors, respectively.[35] However, Naigub et al. showed no significant difference

in RV MPI between survivors and non-survivors ($n = 20$) (0.23 vs 0.26).[36] A recent systematic review and meta-analysis demonstrated the prognostic value of various ECHO parameters. Size of pulmonary arteries, presence of ventricular dysfunction, and severe PH were predictive of survival and use in clinical decision-making for offering ECMO.[37] These variations in findings and the heterogeneity in ECHO parameters highlight the need for the standardization. Standardizing timing of assessment and establishing consensus on optimal ECHO parameters for evaluation of cardiac dysfunction is needed across centers to further improve our understanding of cardiac physiology in CDH patients and their response to treatment intervention. Thus, obtaining a prompt and detailed ECHO, optimally within 24 hours of birth, is a vital component of our proposed treatment algorithm (Figure 2).

Pulmonary vascular disease

Pulmonary hypertension (PH). Severe PH is present in approximately 60% of CDH patients and is associated with high morbidity and mortality.[11] If there is evidence of severe PH on ECHO in the absence of LV dysfunction, treatment with inhaled nitric oxide (iNO) and other pulmonary hypertension targeted therapies may be initiated. Typically, if there is inadequate response or there is worsening pulmonary edema after starting iNO, left heart structural or functional abnormalities should be re-assessed by ECHO. If there is response to iNO but severe PH persists in the absence of left heart dysfunction, additional PH therapies including inhaled iloprost or parenteral prostanoids, should be considered, and other medications including sildenafil (enteral or parenteral) and enteral bosentan may be considered; however, evidence of efficacy in the CDH population is currently limited.[2,38]

It is important to note that right to left shunting at the atrial level is typically observed in the setting of suprasystemic pulmonary vascular resistance (PVR) with adequate LV function, contributing to preductal desaturations. In contrast, left to right atrial shunting may be observed in the setting of LV diastolic dysfunction, and the cause of preductal desaturations in this case would be low pulmonary venous partial pressure of oxygen (PO_2) from intrapulmonary shunt and anastomotic vessels.[25,39] In fact, a recent study ($n = 51$) showed left to right atrial shunting in 82.4% of patients with CDH even in the presence of suprasystemic pulmonary artery pressures.[40] Serial targeted echocardiograms should be performed throughout the course of treatment to assess response to therapy and functional remodeling. Biomarkers such as plasma B-type natriuretic peptide (BNP), vascular endothelial growth factor-A (VEGFA), and placental growth factor (PlGF) have been proposed as indicators of cardiac function but further investigation into their utility is warranted.[41–44]

iNO and vasoactive medications. Over 20 years ago, the Neonatal Inhaled Nitric Oxide Study Group (NINOS) trial, the larger of two randomized controlled trials assessing early iNO therapy in CDH ($n = 53$), reported no difference in death and/or the need for ECMO between the treatment group (20 ppm of iNO) and the control group (100% oxygen).[45,46] However, LV hypoplasia and dysfunction, resulting in pulmonary venous hypertension have been recognized as possible causes of treatment failure.[26,28] The 2015 American Heart Association/American Thoracic Society (AHA/ATS) guidelines caution against the use of iNO in LV dysfunction as this may augment pulmonary venous return to an impaired left ventricle and worsen pulmonary edema.[11,25] A recent retrospective study ($n = 95$) suggested that a subset of CDH patients with PH and preserved LV systolic function may benefit from iNO therapy. Though LV diastolic dysfunction was not evaluated, the authors showed that iNO was associated with improved oxygenation and decreased need for ECMO in this group compared to the LV systolic dysfunction group.[47] Because LV dysfunction is thought to improve over the first few days of life, treatment with iNO might be appropriate once LV function improves.[21,23,24] And, in the setting of hypotension with early LV dysfunction, dobutamine or low-dose epinephrine might be preferable to a fluid bolus.[22,23,25]

Milrinone is often used in the treatment of patients with CDH because it enhances both systolic and diastolic function, has mild pulmonary vasodilator activity, and may lower systemic vascular resistance.[25] In 2012, Patel et al. retrospectively showed an improvement in oxygenation and RV systolic and diastolic function with milrinone use in six neonates with severe pulmonary hypertension.[48] Another study by Kumar et al. ($n = 72$) reported reduced RV pressures and improved EF after milrinone therapy and improvements in oxygenation when administered following favorable response to iNO therapy.[49] More recently, Mears et al. demonstrated no benefit after milrinone use in isolated mild-to-moderate CDH ($n = 87$).[50] A randomized controlled trial assessing the use of milrinone in CDH is remains ongoing (NCT02951130).[51] Prostaglandin-E1 (PGE1) has also been utilized to maintain patency of the ductus arteriosus with the goal of reducing RV afterload and augmenting systemic flow in the context of LV dysfunction. However, as pulmonary pressures normalize, there may be resultant high output heart failure with increased pulmonary blood flow to the hypoplastic lungs.[11,23,24,52,53]

Targeted PH therapy in CDH patients should be reserved for a subset of CDH patients, and therapy should be guided with serial ECHOs to monitor LV function. Research remains ongoing regarding best choice of therapy, mode of therapy (neonatal vs fetal), and timing of therapy, as recent evidence also suggests limited benefit and associated increased risk of mortality and ECLS use with early iNO therapy.[54] There remains a lack of definitive evidence to support any one management strategy for PH in CDH

patients. Current institutional practice involves multidisciplinary decision-making, with use of iNO/targeted PH therapy held until improvement in LV function. Close monitoring of cardiac function with serial ECHOs to guide therapy is integral (Figure 2).

ECMO indications

Severe hypoxic respiratory failure refractory to medical therapy due to CDH is the most common indication for ECMO initiation in the neonatal period.[55–57] In fact, 15–30% of CDH patients require ECMO support.[58] At our center, we have found that 19% of patients with CDH require ECMO. Not surprisingly, entry criteria outlined by the Extracorporeal Life Support Organization (ELSO) and the CDH EURO Consortium Consensus, which include an oxygenation index >40, inability to maintain preductal saturations above 80–85%, pH < 7.15–7.2, and hypotension unresponsive to inotropic support with poor tissue perfusion or urine output <0.5 mL/kg/hr are most commonly cited.[2,53,59] Moreover, ventilator settings are often restricted to a peak inspiratory pressure (PIP) ≤ 26–28 cm H_2O and mean airway pressure (MAP) between 14 and 17 cm H_2O, above which consideration for ECMO is warranted.[14,53] Commonly accepted contraindications include life-limiting chromosomal disorders such as trisomy 13 or 18 or other lethal malformations, Grade III/IV intracranial hemorrhage, irreversible organ and brain damage, uncontrolled bleeding and coagulopathy, gestational age (GA) < 30 weeks, and birthweight < 1 kg.[53,56,57,60] Relative contraindications include prolonged high pressure mechanical ventilation, major cardiac defects, GA between 30 and 34 weeks, and BW between 1 kg and 2 kg.[53,56] These thresholds for BW and GA at delivery exist because of their historical association with poor survival, intracranial hemorrhage, and technical issues with cannulation.[53,56,57] However, mortality risk and exclusion based on these criteria alone have been challenged in recent years.[61–64] A survey of American Pediatric Surgical Association-Critical Care Committee (APSA-CCC) members found significant disagreement among respondents when asked if GA < 34 weeks and birthweight < 2 kg should be considered contraindications to ECMO, but concordance improved when the birthweight limit was lowered to <1800 g and the GA limit to <30 weeks.[65]

Ultimately, the decision to start ECMO and selection of the mode of cannulation should be shared by members of the multidisciplinary care team (e.g., surgeon and neonatologist). Venoarterial (VA) ECMO is more commonly used for reasons including the capacity to provide cardiovascular support, reduced limitations of vessel size for cannulation, fewer flow/positioning challenges, and because it evades the possible need for subsequent emergent mode conversion.[55,57,60,66] Reasons for favoring venovenous (VV) ECMO include preservation of the right common carotid, shorter cannulation time, lower risk of microemboli to the brain, preservation of pulsatile blood flow, decreased risk of cardiac stun, and provision of highly oxygenated blood to the pulmonary artery.[38,57,60,66] Studies have demonstrated similar survival rates for both modes, but VA ECMO has been associated with a higher incidence of neurologic complications, and VV ECMO with an increased likelihood of renal dysfunction.[38,53] A 2018 study applied propensity score matching to ELSO registry data and showed that, although there were no significant differences in mortality between ECMO modes, a lower odds of mortality was observed for patients cannulated to VA ECMO after CDH repair, but with a higher odds of acute severe neurologic events during ECMO.[55] ECMO mode should therefore be chosen based on a combination of patient-specific factors—VV ECMO might be preferred to reduce the risk of neurologic complications, and VA ECMO if cardiac support is anticipated.

Timing of repair

Our understanding of the optimal timing of CDH repair has changed significantly in the last 3 decades. With the 1990s came a shift in management from repairing emergently after delivery to repairing after a period of stabilization.[60,67] Most practitioners today repair CDH after the patient has stabilized, a collaborative decision between neonatology, cardiology, and pediatric surgery. For patients requiring ECMO; however, timing of repair remains controversial, with wide variation in practice between and even within institutions over time. Repair is typically attempted either early after cannulation, later during the ECMO course, or after decannulation, with the optimal management strategy differing based on patient-specific factors. In the absence of recent randomized controlled trials, we have come to rely on retrospective registry and single-institution studies for guidance (Table 2).[78] An important limitation of these types of studies is that they are unable to capture changes in management over time or differences between institutions, and there may be important confounding variables that are not accounted for. The 2015 CDH EURO Consortium recommends that repair on ECMO may be performed but the Canadian CDH Collaborative cautions that surgery should avoided until after decannulation, based on the findings published by Bryner et al. in 2009.[2,8] This CDHSG registry data study ($n = 636$) demonstrated using cox regression that CDH repair post-ECMO was associated with improved survival compared to on-ECMO repair.[79] However, patients who did not undergo repair were not included in the analysis, so the impact on the outcome of those who were not able to be weaned from ECMO is unclear.

Many retrospective studies have addressed this controversial topic in recent years (Table 2). Most studies included the subset of CDH patients who were repaired on ECMO. Overall, the survival rate for patients repaired on ECMO was

Table 2. Recent studies evaluating timing of CDH repair.

Authors	N	Study type	Primary outcomes	Methods	Conclusion
Partridge et al., 2015[68]	61	Retrospective, single-institution	Survival to discharge; operative complications; ECMO duration	Pre-ECMO repair vs on ECMO repair vs post-ECMO repair	Post-ECMO repair is associated with increased survival, fewer surgical bleeding complications, and shorter ECMO runs compared to on-ECMO repair
Kays et al., 2016[69]	45	Retrospective, single-institution	Survival to discharge	Left liver-up, ECMO-eligible with opportunity for pre-ECMO repair vs arriving to ECMO unrepaired	ECMO-eligible left liver-up patients repaired pre-ECMO survive at higher rates compared to those arriving to ECMO unrepaired
Golden et al., 2017[70]	55	Retrospective, single-institution	Mortality; bleeding complications	Late repair on-ECMO vs post-ECMO repair	Patients undergoing post-ECMO repair had fewer complications and better survival compared to late on-ECMO repair
Glenn et al., 2018[71]	668	CDHSG registry	Return to ECMO within 72 hours of repair	Post-ECMO repair	CDH repair after decannulation is associated with a very low risk of return to ECMO within 72 hrs of surgery
Robertson et al., 2018[72]	65	Retrospective, single-institution	In-hospital mortality	Early repair (≤5 days on ECMO) vs late repair (>5 days & after decannulation) protocols	Early repair on ECMO protocol associated with increased hospital mortality and longer ECMO course so a decannulation attempt should be made in those who can be weaned
Dao et al., 2020[73]	136	CDHSG registry	Mortality rate and incidence of non-repair	Quartile stratification of (1) on-ECMO vs after ECMO repair and (2) early vs late on-ECMO repair based on treatment center characteristics and propensity score matching to account for non-repairs	Early repair on ECMO results in a lower rate of non-repair and improved mortality
Delaplain et al., 2019[74]	2224	ELSO registry	Mortality at discharge	On-ECMO vs post-ECMO repair with propensity score matching for severity (does not address non-repairs)	Potential survival benefit associated with delaying repair until after decannulation
Glenn et al., 2019[75]	1170	CDHSG registry	Survival to decannulation; ECMO duration	Early (within 72 hours of cannulation) vs unrepaired on ECMO (includes post-ECMO repairs and never repairs)	Early repair on ECMO results in increased survival to decannulation but does not shorten ECMO course
Steen et al., 2019[76]	33	Retrospective, single-institution	Survival; ECMO duration	Super early repair (<24 hrs) vs early repair (24–72 hrs) on ECMO	Outcomes for repair <24 hrs on ECMO are comparable to repair between 24 and 72 hrs on ECMO

(continued)

Table 2. (continued)

Authors	N	Study type	Primary outcomes	Methods	Conclusion
Smithers et al., 2023[77]	146	Retrospective, single-institution	Survival, bleeding, ECMO duration	Early repair (≤48 hrs) vs delayed repair (>48 hrs) on ECMO	Delayed repair associated with increased ECMO duration and increased surgical site bleeding without significant difference in survival

CDH = congenital diaphragmatic hernia / CDHSG = congenital diaphragmatic hernia study group.
ECMO = extracorporeal membrane oxygen.
ECLS = extracorporeal life support.

53% (244/462) across 20 studies over a study period spanning 1970 to 2017. However, we were unable to reliably compare this survival rate to that of CDH patients repaired prior to ECMO or after ECMO decannulation, and notably unable to delineate differences in survival between patients repaired early on ECMO versus late on ECMO. Moreover, patients who died without repair were inconsistently addressed, limiting our ability to accurately account for this group. In theory, early CDH repair is beneficial because it establishes normal intrathoracic anatomy alleviating mass effect, and allows operative repair prior to the onset of anasarca, using ECMO support to assist in recovery after the physiological insult of surgery.[72,73,80] In 2010, Dassinger et al. (n = 34) noted that surgical repair occurred earlier in their patient cohort (2.4 days vs 7 days after cannulation) in comparison to the CDHSG registry data and reported higher survival (71% vs 50.9%) despite similar ECMO course durations (11.7 vs 13.3 days).[80] Another study from 2013 (n = 46) showed that there were no significant differences in survival among those who were repaired early on ECMO (within 72 hours), late on ECMO (after 72 hours), or after decannulation, 73%, 50%, and 64%, respectively. Those who were repaired early had a shorter ECMO duration and fewer circuit exchanges than the late repair group. However, seven patients from the on-ECMO repair groups experienced intrathoracic bleeding, five of whom did not survive to discharge.[81] A more recent study in 2023 evaluated early (within 48 hrs of ECMO initiation) versus delayed CDH repair (after 48 hrs) on ECMO and showed no difference in overall survival (60% vs 57%, p = 0.737) but demonstrated a lower rate of surgical bleeding in the early ECMO repair group compared to the delayed repair group (5% vs 14%) as well as a shorter duration of ECMO (13 days vs 18 days).[77] It is important to emphasize that perioperative aminocaproic acid infusion was used as an adjunct therapy in all patients, and that surgical bleeding was not associated with higher mortality in this study. This highlights the fact that operative bleeding complications may still have morbid consequences in some cases, and this remains the one major drawback of on-ECMO repair. Antifibrinolytic therapy, however, may serve to mitigate these risks. A demonstrated important advantage of early on-ECMO repair may be a reduction in the rate of non-repair.[73,75]

Glenn et al. found that only 6/663 (0.90%) patients returned to ECMO within 72 hours of their first ECMO run and 13 died (1.9%) within 72 hours. These findings supported the strategy of post-ECMO repair in patients stable enough for decannulation instead of delayed repair on ECMO as a precaution for possible post-surgical decompensation.[71] Guner et al. calculated center-specific standardized mortality ratios (SMRs) and found that post-extracorporeal life support (ECLS/ECMO) repair was two times more common at centers with significantly better mortality ratios compared to those with significantly worse mortality ratios.[82] In contrast, the rate of non-repair was significantly greater for the latter group. Another strategy offered by Kays et al. involves pre-ECMO repair as early as 6 hours after delivery for severe left liver-up patients expected to require ECMO. In their cohort, 22/25 patients were repaired within 60 hours of life prior to ECMO, with a survival rate of 95% compared to 65% for patients arriving to ECMO unrepaired, despite similarities in anatomic and physiological severity. However, this strategy carries significant risks of decompensation during repair, bleeding resulting from rapid transition to ECMO, and the possibility of precipitating the need for ECMO; furthermore, this approach has not been studied in other settings.[69]

Therefore, there are limited repair options to either early repair on ECMO for high-risk patients to prevent the complications associated with late repair on ECMO and to reduce the likelihood of non-repair, and repair after ECMO for low-risk patients who we anticipate will have a short run on ECMO. Observed/expected LHR and pH values are often used in predictive models of outcome in CDH.[69] Delaplain et al. showed that a pH ≤ 7.19 prior to ECMO was predictive of a longer ECMO course.[83] Low pH in addition to anatomically severe CDH based on prenatal imaging might be helpful in identifying patients more likely to benefit from early on-ECMO repair. In conjunction with clinical judgment, the use of risk model calculators such as the Pittsburgh Index for Pre-ECMO risk mortality prediction model (PIPER+) and the on-ECMO risk score may also prove to be useful in identifying these high-risk patients.[84,85] The

impact of timing of surgery on cardiac function should also be elucidated.[22,86] Additionally, repair on ECMO may be associated with adverse neurodevelopmental outcomes later in childhood.[87] Further research in this area is therefore necessary to clarify short and long-term sequelae across risk groups, and how timing of repair may affect these outcomes. Current institutional practices include early CDH repair on ECMO for high-risk patients (Apgar at 5 min less than 6, pre-ECMO pH < 7.2, liver-up on prenatal imaging, LHR <1, O:E LHR <25%, small pulmonary artery and small LV diastolic diameter), carefully weighing the risks and benefits in a multidisciplinary setting. This is congruent with the 2023 update by the Canadian CDH Collaborative, which now recommends early repair for those at risk of failure to wean.[9]

Conclusion

Based on our present review of the literature, there remains a lack of standardized, evidence-based care in the management of CDH. However, from this review, we consider it vital to include early evaluation of cardiac structure and function, to carefully weigh the risks and benefits of ECMO in a multidisciplinary setting using a combination of objective clinical parameters and clinical judgment, and to consider early CDH repair on ECMO for high-risk patients and delayed repair post-ECMO for low-risk patients with anticipated short ECMO run. Our treatment algorithm has been approved by neonatal intensive care unit (NICU) and pediatric surgery leadership and has been implemented in current clinical practice. As we continue to evaluate our institutional outcomes and monitor the effects of implementation through prospective clinical studies, we anticipate future refinement and reiterations as compelling new evidence emerges and ongoing studies further elucidate the etiology of CDH and enable improved risk categorization. This algorithm encapsulates current scientific evidence in CDH and our institutional experience (Figure 2) and is a step toward standardization of management practices in CDH patients. We anticipate this algorithm will serve to inform multi-institutional practices and to improve CDH outcomes across all risk categories at our quaternary care institution and others and contribute to the establishment of standardized best-practice guidelines.

Statements and declarations

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Supplemental Material

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Appendix

Abbreviations

CDH	Congenital diaphragmatic hernia
CDHSG	Congenital diaphragmatic hernia study group
CMV	Convention mechanical ventilation
ECHO	Echocardiogram
ECLS	Extracorporeal life support
ECMO	Extracorporeal membrane oxygenation
HFOV	High frequency oscillatory ventilation
HFPPV	High frequency positive pressure ventilation
LV	Left ventricular
MPI	Myocardial performance index
PH	Pulmonary hypertension
RV	Right ventricular
SpO2	Oxygen saturation
VA	Venoarterial
VV	Venovenous