Diagnosis and management of congenital diaphragmatic hernia: a 2023 update from the Canadian Congenital Diaphragmatic Hernia Collaborative

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ABSTRACT

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.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Congenital diaphragmatic hernia (CDH) is a developmental defect that requires intensive cardiorespiratory support in the perioperative period.
⇒ The exemplar anomaly in CDH is pulmonary hypoplasia, which manifests as postnatal pulmonary hypertension of variable severity; however, infants with CDH also experience additional multisystem morbidity.
⇒ Multisystem morbidity extends into childhood and adolescence and necessitates long-term health surveillance.

WHAT THIS STUDY ADDS

⇒ This study builds on existing care recommendations published in 2018 that address all phases of CDH care from prenatal diagnosis, to in-hospital care, to post-discharge health surveillance.
⇒ Twenty existing recommendations have been revised, and another 15 new CDH care recommendations have been developed, especially in the area of pain control and analgesia.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study provides a framework for CDH management that continues to reduce unwanted variability in CDH care as well as improve patient outcomes.
⇒ The updated care recommendations provide a pragmatic approach to CDH care that are applicable to all stakeholders involved in CDH care globally.
⇒ The updated care guidelines still allow for innovation and continued advancement in CDH care.

INTRODUCTION

In 2018, the Canadian Congenital Diaphragmatic Hernia (CDH) Collaborative produced a clinical practice guideline (CPG) for the diagnosis and management of CDH.[1] Leveraging national, interdisciplinary expertise and the best available evidence, this guideline reflected a pragmatic approach to optimal CDH management that sought to minimise variations in care. In order to further increase the guideline's uptake and utilisation, we developed a free smartphone application providing ready access to CDH care recommendations and the evidence that informed them.[2] Knowledge synthesis related to care of CDH has been ongoing since 2018, and an update that assimilates recent best evidence using a rigorous appraisal methodology is timely.

The scope of this project involved the appraisal and assimilation of the accumulated, best available evidence since 2017 into the existing CPG. As with the original version, the recommendations encompass all phases of CDH care from prenatal diagnosis to in-hospital management to post-discharge health surveillance. This update represents another collaborative effort among CDH experts and thought leaders across Canada and is relevant not only to users in North America, but around the world.

METHODS

Online supplemental appendix 1 provides a detailed description of the methods used by the CDH Collaborative to update the 2018 guidelines, including: (1) the steering committee and working group composition (2) the literature search conducted from 1 January 2017 to 30 August 2022 (figure 1 and online supplemental materials); (3) the evidence appraisal process using Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology[3] (figure 1 and online supplemental appendix 2); (4) the iterative process of evidence assessment leading to modification of existing recommendations or the creation of new ones; (5) the taxonomy used to assign strength of recommendation (figure 2); (6) the modified Delphi endorsement process which established consensus on new or modified guidelines using predetermined thresholds (figure 3); and (7) the management of competing interests. As with the original version, these recommendations encompass all phases of CDH care from prenatal diagnosis to in-hospital management to post-discharge health surveillance.

The following subject areas informed the literature search. If no new evidence was found to compel a significant change to the 2018 recommendations, that subject area's recommendations are 'unchanged'. Recommendations from 2018 that were modified based on new evidence are designated as 'updated' or 'new' based on degree of novelty. Two new subject areas (*management of gastro-oesophageal reflux*, and *analgesia, sedation and neuromuscular blockade*) have been added to the updated guidelines:

1. Prenatal diagnosis and treatment.
2. Fetal therapy.
3. Ventilation.
4. Fundamentals of haemodynamic support.
5. Role of echocardiography.

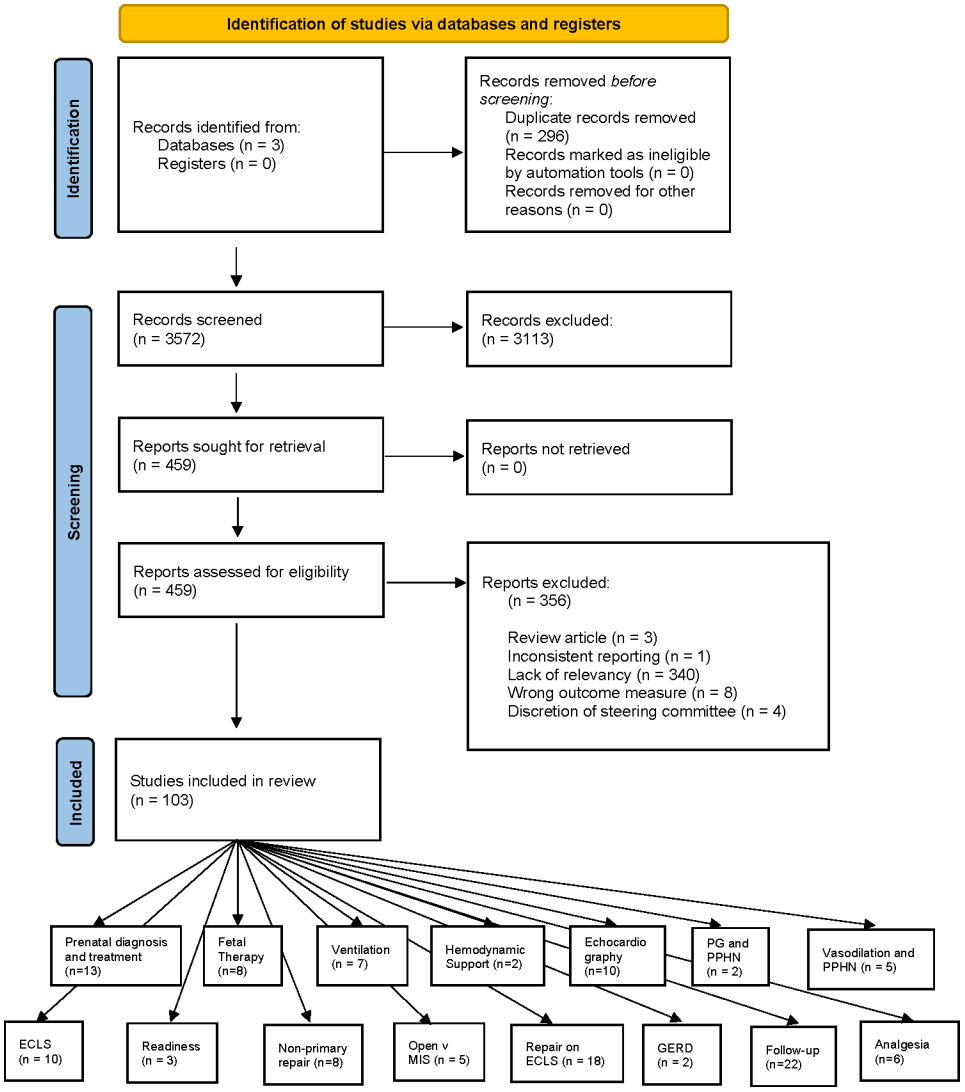

Figure 1 PRISMA flow diagram. ECLS, extracorporeal life support; GERD, gastro-oesophageal reflux disease; MIS, minimally invasive surgery; PG, prostaglandin; PPHN, persistent pulmonary hypertension of the newborn; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Level A
· High-quality evidence from more than 1 RCT · Meta-analyses of high-quality RCTs · One or more RCTs corroborated by high-quality registry studies
Level B-R (Randomized)
· Moderate-quality evidence from 1 or more RCTs · Meta-analyses of moderate-quality RCTs
Level B-NR (Non-randomized)
· Moderate-quality evidence from 1 or more well-designed, well-executed nonrandomized studies, observational studies, or registry studies · Meta-analyses of such studies
Level C-LD (Limited data)
· Randomized or nonrandomized observational or registry studies with limitations of design or execution · Meta-analyses of such studies · Physiological or mechanistic studies in human subjects
Level C-EO (Expert Opinion)
· Consensus of expert opinion based on clinical experience

Figure 2 Taxonomy of the levels of evidence used to grade recommendations.[1] RCTs, randomised controlled trials.

6. Role of prostaglandins in the management of CDH-associated pulmonary hypertension.
7. Targeted pulmonary vasodilation in CDH-associated pulmonary hypertension.
8. Role of extracorporeal life support (ECLS).
9. Surgical readiness.
10. Options for non-primary surgical repair.
11. Open versus minimally invasive surgical repair.
12. Surgical repair on ECLS.
13. Management of gastro-oesophageal reflux.
14. Long-term follow-up.
15. Analgesia, sedation and neuromuscular blockade.

RESULTS

Twenty CDH care recommendations were updated, and 15 new recommendations were added. These are presented below, categorised by the 15 care areas in CDH management.

Prenatal diagnosis and management

Prenatally diagnosed CDH is associated with additional structural and genetic anomalies in 30–40% of cases,[4 5] most commonly cardiovascular malformations.[6] All antenatally detected cases of CDH should undergo a detailed anatomical survey and fetal echocardiogram in a tertiary fetal medicine centre. All affected pregnancies should be offered invasive genetic testing with chromosomal microarray analysis (CMA) given a 10–13% risk of CMA abnormality in isolated CDH.[7 8] Expanded genomic analysis (eg, exome sequencing, RNA analysis) will likely increase this diagnostic yield further[9 10] (table 1).

Antenatal sonographic predictors of neonatal survival include the observed-to-expected lung-to-head ratio (o/e LHR)[11–13] and intrathoracic liver herniation.[13–15] The o/e LHR should be measured with the trace method (figure 4) between 22 and 32 weeks' gestational age (GA)[13 16 17] in experienced centres.[18 19] Severe pulmonary hypoplasia is predicted by an o/e LHR of ≤25% in left CDH and o/e LHR ≤50% for right CDH,[20] with estimated survival of ≤30%[11 12 21] and 20%[20] for left and right CDH, respectively. Moderate pulmonary hypoplasia is defined as an o/e LHR of 26–34% in left CDH. Intrathoracic liver herniation may be challenging to recognise sonographically. As such, stomach position classification has been proposed as a surrogate,[22–25] and has been shown to correlate with neonatal mortality and morbidity.[23 24 26] Although promising in its simplicity, this prognosticator requires further prospective validation.

Fetal magnetic resonance imaging (MRI) provides additional prognostic information by assessing the o/e total fetal lung volume (o/e TFLV)[27] and quantifying liver herniation.[28 29] An o/e TFLV<35% and intrathoracic liver herniation are significant predictors of mortality.[11 13 27–29] When compared with ultrasound (US), MRI is more reproducible and is not limited by maternal habitus or fetal position. Additionally, MRI parameters perform better, with greater sensitivity and specificity for survival prediction.[30] Based on the protocol from the TOTAL trial,[21] as well as current practice in most centres performing fetal tracheal occlusion, the ideal timing for MRI appears to be around 26 weeks since earlier timing may lead to inaccurate measurements. Combined, o/e TFLV and liver herniation demonstrate better predictive value for mortality and need for ECLS.[29] Although MRI may be advantageous for prenatal prognostication, US assessment is likely to remain the cornerstone of antenatal prognostication due to its widespread availability. Both imaging modalities should be used together, particularly in high-risk fetuses.

Agreement with recommendation:
1) Strongly agree
2) Somewhat agree
3) Neither agree or disagree
4) Somewhat disagree
5) Strongly disagree

Level of Consensus	Description
4	**STRONG AGREEMENT** with recommendation: >80% #1 or #5
3	**GOOD AGREEMENT** with recommendation: >80% of #1 + #2 or #4 + #5 but >50% of the votes as #1 or #5
2	**WEAK AGREEMENT** with recommendation: >80% of #1 + #2 or #4 + #5 but <50% of the votes as #1 or #5
1	**NO CONSENSUS**

Figure 3 Consensus framework.[1]

Table 1 Updated and new recommendations regarding prenatal diagnosis and management of CDH[7–10 13 16 18 20 26 32 152–154]

Updated recommendations	Strength of consensus	Level of evidence
1.1 Ultrasound measurement of o/e LHR using the trace method should be obtained between 22 and 32 weeks' GA, in consultation with a regional fetal medicine/therapy programme.	4	B-NR
1.2 Observed/expected LHR cut-offs of ≤25% and ≤50% should be used to predict poor outcome for left and right CDH, respectively.	4	B-NR
1.3 MRI for the assessment of o/e TFLV and liver herniation should be considered in all fetuses with CDH, and is strongly recommended in fetuses with severe or moderate CDH by o/e LHR, ideally in collaboration with a fetal therapy programme.	4	B-NR
New recommendations	**Strength of consensus**	**Level of evidence**
1.4 Due to the increased risk of associated structural anomalies, a detailed anatomy assessment and a fetal echocardiogram should be performed in a tertiary fetal medicine centre for all pregnancies with prenatally diagnosed CDH.	3	B-NR
1.5 Invasive antenatal genetic testing, ideally with chromosomal microarray analysis, should be offered in all CDH pregnancies.	4	B-NR
1.6 Delivery at ~39 weeks gestation should be considered, with delivery planning in a tertiary centre experienced in the management of CDH with NICU, PICU and paediatric surgery expertise. Mode of delivery should be determined based on standard obstetric indications.	4	B-NR

CDH, congenital diaphragmatic hernia; GA, gestational age; NICU, neonatal intensive care unit; NR, non-randomised; o/e LHR, observed-to-expected lung-to-head ratio; o/e TFLV, observed-to-expected total fetal lung volume; PICU, paediatric intensive care unit.

Delivery is recommended in a tertiary care centre with neonatal intensive care unit (NICU) and paediatric surgery expertise in CDH management, as outborn delivery is a significant predictor of mortality.[31] Mode of delivery should be determined on usual obstetric grounds, and should be considered between 38 and 39 weeks' gestation due to reportedly improved survival at 28 days with term delivery.[32]

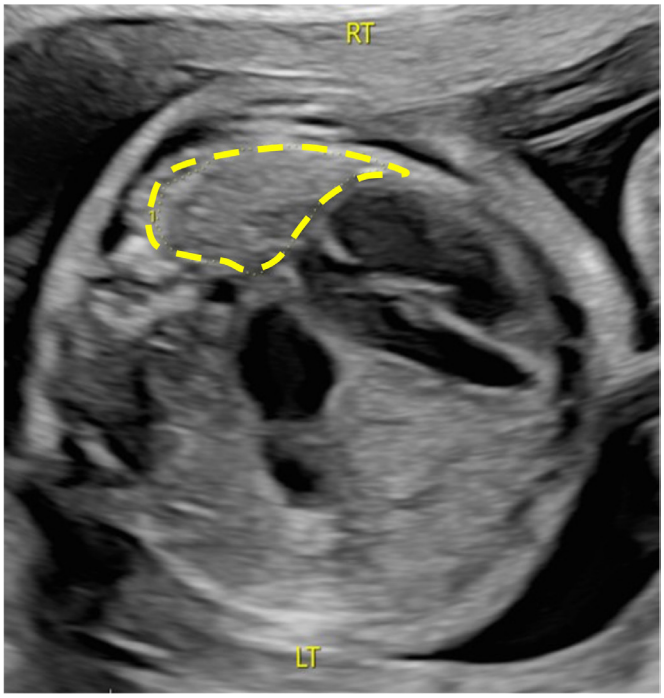

Figure 4 Axial section of the fetal chest demonstrating sonographic measurement of the right (RT) lung area using the 'trace' method in a fetus with left CDH. The lung area is obtained on a well-optimised cross-section of the fetal chest at the level of the four-chamber view of the heart, by manually tracing the lung perimeters. The lung area is combined with the fetal head circumference to obtain an observed-to-expected lung-to-head ratio. CDH, congenital diaphragmatic hernia; LT, left.

Fetal therapy in CDH

Due to the significant morbidity and mortality associated with CDH, fetal interventions aimed at improving lung development in utero have been investigated.[33–35] Fetal endoscopic tracheal occlusion (FETO), a minimally invasive percutaneous procedure that prevents egress of fetal fluid and consequent accelerated airway and pulmonary vessel growth, has shown promise.[36] In both multicentre and single-centre cohort studies, FETO has demonstrated statistically improved survival for left and right CDH.[20 37–40] The Tracheal Occlusion to Accelerate Lung growth (TOTAL) randomised controlled trials (RCTs) evaluated the impact of FETO on survival in isolated left CDH predictive of both moderate (o/e LHR 25–35% or o/e LHR 35–45% with liver herniation)[41] and severe (o/e LHR <25%) pulmonary hypoplasia, in comparison with standard neonatal management.[21] In the 'severe' trial, a significant improvement in survival to discharge (40% vs 15%; p=0.009) was noted with FETO insertion at 27–29 weeks' gestation compared with expectant management, despite an increased incidence of preterm premature rupture of membranes (PPROM; 47% vs 11%) and preterm birth (75% vs 29%). Despite later FETO at 30–32 weeks' gestation in the moderate trial, there was also an increased incidence of PPROM (44% vs 12%) and preterm birth (64% vs 22%), without an improvement in survival (63% vs 50%; p=0.06).[41] Pooled data from both trials were reanalysed to evaluate the heterogeneity of treatment effect by o/e LHR and GA at balloon insertion, and found no evidence of effect by o/e LHR. Rather, the differences in results between trials were likely due to later balloon insertion in the moderate trial[42] (table 2).

Table 2 New recommendations regarding fetal therapy in CDH[20 21 39–42 44 45]

New recommendations	Strength of consensus	Level of evidence
2.1 Fetal endoscopic tracheal occlusion (FETO) should be considered a treatment option and discussed with parents for all cases of severe CDH.	4	A
2.2 FETO may be considered as a treatment option for moderately severe CDH.	4	B-R

CDH, congenital diaphragmatic hernia; R, randomised.

Based on these studies, FETO is an option for severe, and possibly moderate risk CDH in selected patients, with more research required for its use in infants with moderate CDH. Discussions regarding FETO lend themselves to a shared decision-making approach with families. It is important to consider potential burdens and issues of healthcare access for family and caregivers related to maternal risks, distance and displacement from home for the duration of treatment (since FETO is only offered in very select centres with extensive fetoscopic experience), and the impact on the family unit, particularly with respect to disruption of the support structure, occupation and wages/income. Further studies are also needed to evaluate the impact of prematurity on neonatal morbidity and long-term outcomes following FETO therapy.

Research addressing the prevention of pulmonary hypertension using antenatal sildenafil has been promising, with animal studies demonstrating some rescue of the pulmonary vascular bed and improved airway morphometry with transplacental sildenafil therapy.[43 44] Trials are ongoing to evaluate the transplacental transfer and safety of sildenafil in humans,[45] which may lead to a randomised trial of antenatal sildenafil for pulmonary hypertension mitigation.

Ventilation in CDH

Airway management at birth

The neonatal resuscitation guideline from the American Heart Association and the American Academy of Pediatrics supports immediate endotracheal intubation for neonates with a known diagnosis of CDH and the avoidance of bag–valve–mask ventilation.[46] A small, retrospective audit found that a spontaneous breathing approach was successful in 40% of infants with mild CDH (o/e LHR >50%), although half of the successful cases required non-invasive ventilation with its attendant risk of hollow visceral insufflation.[47] Survival to discharge and total duration of postoperative ventilation were identical regardless of whether or not the trial of spontaneous breathing was successful. This new evidence is insufficient to lead to a revision of the current recommendation (table 3).

Mode of ventilation

The VICI trial[48] attempted to provide level I evidence regarding the initial ventilatory mode in CDH. Analysis of the 171 of 356 targeted patients showed similar rates of mortality and bronchopulmonary dysplasia between groups initially managed with conventional mechanical ventilation (CMV) versus high-frequency oscillatory ventilation (HFOV).

Two retrospective studies comparing conventional ventilation with high-frequency ventilation (HFV) were unable to show any difference in survival, need for inhaled nitric oxide (iNO), duration of mechanical ventilation or oxygen requirement at discharge. The study by Derraugh *et al*[49] was based on experience at a single non-ECLS centre over a 25-year period. The HFV group included patients managed with both high-frequency jet ventilation and HFOV. A Japanese CDH Study Group analysis compared 250 HFOV with 77 CMV CDH patients.[50] Both studies suggested that physicians are more likely to choose HFV in sicker, higher-risk patients.

Individual, single-centre retrospective studies have demonstrated that high-frequency positive pressure ventilation,[51] neurally adjusted ventilatory assist[52 53] and heliox admixture with oxygen[54] hold some promise for future CDH management.

Fundamentals of haemodynamic support

In the setting of haemodynamic instability, treatment to optimise perfusion is centred around very judicious fluid resuscitation and early inotropic support to prevent pulmonary oedema. Indeed, ventricular dysfunction is a major contributor to persistent hypotension which will only be exacerbated by excessive fluid resuscitation. While the choice of inotropic agent depends on the clinical state of the infant with CDH, dopamine, epinephrine and norepinephrine are still considered the first-line choices for cardiac or vasopressor support.[55] Higher dosing of epinephrine may cause adverse events such as tachyarrhythmia, hyperglycaemia and lactic acidosis due to a dose-dependent shift from beta to alpha-receptor agonist. Norepinephrine only has vasomotor effects and increasing afterload could further impair already precarious cardiac function. Furthermore, norepinephrine may also potentially increase pulmonary arterial resistance. While there is some recent evidence suggesting that dopamine may be an inferior choice based on experience extrapolated from infants with non-CDH persistent pulmonary hypertension,[56] dopamine is still the most extensively used inotropic medication in the neonatal literature, and possesses a well-documented safety profile.[57] As such, there is no conclusive evidence demonstrating the superiority of lesser-studied agents over dopamine in the population with CDH. However, vasopressin is showing promise in supporting systemic haemodynamics in catecholamine-resistant shock states without affecting pulmonary haemodynamics based on a small, retrospective study of 13 infants with CDH.[58] Cardiovascular management, as well as the introduction, discontinuation and precise titration of each agent, should occur within a framework of targeted haemodynamic management. Treatment will need to be individualised to meet the unique requirements and responses of each neonate and their specific cardiovascular status (table 4).

There is accumulating evidence that the underlying cardiovascular phenotype may vary among different patients with CDH.

Table 3 Unchanged recommendations regarding ventilation in CDH[47 49–54]

Unchanged recommendations	Strength of consensus	Level of evidence
3.1 All newborns with CDH who require respiratory support should be intubated (for assisted ventilation) immediately after birth.	4	C-EO
3.2 A T-piece on the bag–valve mask, or a ventilator, should be used to rigorously avoid a peak inspiratory pressure (PIP) greater than 25 cm H_2O from the first breaths onwards in all newborns with CDH.	4	B-NR
3.3 Gentle intermittent mandatory ventilation (IMV) should be the initial mode of ventilation for all newborns with CDH requiring respiratory support. High-frequency oscillatory ventilation or high-frequency jet ventilation should be used as rescue therapy when the PIP required to control hypercapnia using IMV exceeds 25 cm H_2O.	4	B-R
3.4 An arterial pCO_2 (partial pressure of carbon dioxide) between 45 and 60 mm Hg and a pH between 7.25 and 7.40 should be targeted in all newborns with CDH.	4	B-NR
3.5 Supplemental oxygen should be titrated to achieve a preductal saturation of at least 85%, but not >95%.	4	C-EO

CDH, congenital diaphragmatic hernia; EO, expert opinion; NR, non-randomised; R, randomised.

Table 4 Unchanged recommendations regarding the fundamentals of haemodynamic support in CDH[65 67]

Unchanged recommendations	Strength of consensus	Level of evidence
4.1 If poor perfusion persists, cardiac function should be assessed by echocardiography.	4	B-NR
4.2 Hydrocortisone should be used to treat hypotension that responds inadequately to intravenous volume and vasopressor therapy.	4	B-NR
Updated recommendations	**Strength of consensus**	**Level of evidence**
4.3 Treatment of poor perfusion (any combination of capillary refill >3 s, lactate >3 mmol/L, urine output <1 mL/kg/hour) and blood pressure below norms for age should include: a. Very judicious administration of crystalloid, if any, and generally not exceeding 20 mL/kg. b. Inotropic agents such as dopamine, epinephrine or norepinephrine.	4	B-NR

CDH, congenital diaphragmatic hernia; NR, non-randomised.

This phenotype may evolve during the early acute phase of hospital admission, underscoring the need for continuous, multidisciplinary vigilance and the utilisation of multimodal clinical information that includes bedside echocardiography.[59 60] Nevertheless, although diverse phenotypes have been documented, no trials within CDH cohorts have delineated the benefits of employing specific cardiovascular management strategies for acute pulmonary hypertension, right ventricular dysfunction, left ventricular dysfunction or biventricular dysfunction in this population. Hence, clinicians should tailor their therapy based on their best assessment of the patient's underlying physiology.[61–63]

Acute kidney injury (AKI) is defined and staged using the Neonatal Modified Kidney Disease: Improving Global Outcomes[64] Serum Creatinine criteria. A few retrospective studies confirmed that AKI is common among infants with CDH.[65–67] Among those with AKI, survival in these series ranged from 37% to 47%, and an increasing stage of AKI was associated with decreased survival. The authors found that AKI in patients with CDH was associated with prenatal risk factors, including lower antenatal lung volumes, liver herniation and postnatal factors such as vancomycin, corticosteroids and diuretic use, abdominal closure surgery, hypotension and elevated plasma-free haemoglobin. The situation is further complicated in patients receiving ECLS who are prone to fluid overload and a systemic inflammatory response that can also lead to AKI. Infants who remain unstable despite fluid and vasopressor therapy should receive hydrocortisone as well as echocardiographic assessment of cardiac function.

The role of echocardiography in CDH

Echocardiography is recommended shortly after birth, not only to verify suspected cardiac anomalies based on fetal echocardiography but also to (a) assess cardiac dimensions and ventricular function, (b) estimate pulmonary arterial pressures, (c) assess for shunt physiology and (d) guide/adjust cardiovascular support. A minimum of two standardised echocardiograms are recommended. The first should occur within the first 24–48 hours of life (or preoperatively), with earlier evaluation recommended for high-risk infants or in the context of severe postnatal cardiorespiratory instability as it may dictate additional interventions or the timing of surgery. This may be particularly important in anticipation of ECLS candidacy.[68 69] Interestingly, Yang *et al*[68] demonstrated reduced inotrope usage, lower ECLS rates, repair at earlier age and improved survival using a care bundle that deferred echocardiography until after 24 hours (or alternatively a time-limited assessment) to avoid excessive manipulation during the critical first 24 hours of physiological transition. The second echocardiogram should occur at 2–3 weeks of life, to assess for persistence of pulmonary hypertension or cardiac dysfunction. Additional studies may be conducted as clinically indicated (eg, pre-surgery or pre-discharge). This is especially relevant in the presence of significant pulmonary hypertension or cardiac dysfunction since this has been associated with adverse outcomes and may affect surgical and anaesthetic preparation.[70–72] Two single-centre studies highlight a possible prognostic role for pulmonary artery acceleration time to right ventricular ejection time (PAAT/ET) for early risk assessment in neonates with CDH. PAAT/ET values at the baseline echocardiogram are significantly lower in ECLS patients compared with non-ECLS patients. Additionally, ECLS non-survivors demonstrate lower PAAT/ET values at 5–7 days of life when compared with ECLS survivors.[73 74] These results suggest the utility of echocardiography at 5–7 days of life during ECLS support (table 5).

The measurement of brain natriuretic peptide (BNP) or N-terminal BNP may serve as adjunct biomarkers to detect underlying cardiac strain[75]; increasing trends in these biomarkers have been

Table 5 Updated and new recommendations regarding the use of echocardiography in CDH[68–77]

Updated recommendations	Strength of consensus	Level of evidence
5.1 A minimum of two standardised echocardiograms should be performed, one within 24–48 hours of life (or preoperatively) and another at 2–3 weeks of life, to assess pulmonary hypertension and cardiac function. Additional studies may be conducted as clinically indicated.	4	B-NR
5.2 While initial echocardiography may be deferred after 24 hours to avoid excessive manipulation during the critical period of pulmonary vascular adaptation, early (<24 hours) echocardiography should be considered in the context of severe cardiorespiratory instability.	4	B-NR
New recommendation	**Strength of consensus**	**Level of evidence**
5.3 Repeat echocardiography on days of life 5–7, especially when on ECLS support, may be indicated to assess progression or improvement of pulmonary hypertension.	4	C-LD

CDH, congenital diaphragmatic hernia; LD, limited data; NR, non-randomised.

Table 6 Updated recommendations regarding the role of prostaglandin E1 (PGE1) in the medical management of pulmonary hypertension associated with CDH[78 79]

Updated recommendations	Strength of consensus	Level of evidence
6.1 PGE1 infusions should be used: a. If pulmonary or systemic blood flow is dependent on patency of the ductus arteriosus. b. In the presence of a concomitant anatomical cardiac lesion.	4	B-NR
6.2 PGE1 infusions may be considered: a. In the presence of supra-systemic right ventricular pressures. b. In the presence of right ventricular failure. c. If right-to-left ductal shunting exceeds left-to-right shunting.	4	C-LD
6.3 PGE1 should be considered to maintain ductal patency in CDH if there is left ventricular dysfunction or functional aortic atresia in the context of systemic right ventricular or pulmonary artery pressures.	4	C-EO

CDH, congenital diaphragmatic hernia; EO, expert opinion; LD, limited data; NR, non-randomised.

associated with adverse CDH outcomes (death or respiratory support at 56 days of life).[76 77] However, institutional availability of these markers may vary and there is a paucity of data indicating improvement of outcomes solely based on biomarker surveillance.

The role of prostaglandins in the management of CDH-associated pulmonary hypertension

Two small, retrospective studies reviewed the impact of prostaglandin E1 (PGE1) in the management of severe pulmonary hypertension in CDH and were the basis for changes to existing recommendations. Le Duc *et al* noted improvement in preductal and post-ductal saturations, as well as increased ductal blood flow and a reduction in fractional inspired oxygen with PGE1.[78] Lawrence *et al*[79] demonstrated improved echocardiographic indices as well as reduced BNP levels in 57 patients with PGE1.[79] Both studies supported the use of PGE1 in the context of a restrictive ductus arteriosus, severe pulmonary hypertension and impending right ventricular failure (table 6).

The use of 'targeted' pulmonary vasodilation in the management of CDH-associated pulmonary hypertension

The use of targeted pulmonary vasodilator therapy is recommended in the context of CDH-associated pulmonary hypertension when standard cardiorespiratory manoeuvres fail to maintain adequate oxygenation or cardiac function. iNO may be considered as part of the treatment regimen but only in the context of demonstrable echocardiographic and clinical evidence of improvement, which, if lacking, should lead to its cessation. Milrinone is a lusitropic medication that theoretically enhances diastolic function while also causing pulmonary and systemic vascular dilation. It undergoes renal excretion and can offer assistance to a compromised left ventricle. Milrinone is recommended for its pulmonary arterial vasodilator properties based on experience extrapolated from non-CDH, cardiac infants with pulmonary hypertension,[1] with caution for its use in the context of hypotension. The results of an ongoing RCT should clarify milrinone use in the population with CDH.[80] Prostaglandins (such as treprostinil and epoprostenol) and vasopressin[81] may be considered as rescue therapy for pulmonary hypertension in newborns with CDH prior, during or after ECLS.[77 82–84] Responders to these therapies have been reported, although it should not delay the initiation of other life-saving strategies (such as ECLS) in infants with severe hypoxic respiratory failure already meeting criteria (table 7).

The role of ECLS in the management of CDH

A recent guideline statement from the Extracorporeal Life Support Organization (ELSO) was published without clear adherence to GRADE methodological standards.[69] ELSO generated 26 recommendations in relation to CDH management, many of which overlap considerably with recommendations included here. The Collaborative's author group specifically endorses the ELSO indications for initiation of ECLS based on hypoxic or hypercapnic respiratory failure, circulatory failure or acute clinical deterioration[69] (table 8).

There continues to be sparse evidence that ECLS confers a survival advantage in CDH. A large retrospective cohort study demonstrated that overall mortality was higher when ECLS was used in CDH. A survival advantage was only observed in a

Table 7 Updated and new recommendations regarding targeted pulmonary vasodilation in the management of CDH-associated pulmonary hypertension[77 82–84 155]

Unchanged recommendations	Strength of consensus	Level of evidence
7.1 In the context of echocardiographic confirmation of supra-systemic pulmonary arterial hypertension in the absence of left ventricular dysfunction, a trial of inhaled nitric oxide (iNO) should be used, providing that lung recruitment is adequate. If there is no iNO response based on echocardiographic assessment or other parameters (clinical or laboratory), iNO should be stopped.	4	B-NR
7.2 Milrinone should be used to treat cardiac dysfunction, particularly if it is associated with pulmonary hypertension.	4	B-NR
7.3 The use of sildenafil may be considered in patients with refractory pulmonary hypertension (ie, unresponsive to iNO) or as an adjunct when weaning iNO.	3	B-NR
New recommendation	**Strength of consensus**	**Level of evidence**
7.4 The use of prostacyclin (such as treprostinil and epoprostenol) may be considered as rescue therapy prior, during or after ECLS in infants with severe and refractory pulmonary hypertension.	3	C-LD

CDH, congenital diaphragmatic hernia; ECLS, extracorporeal life support; LD, limited data; NR, non-randomised.

Table 9 Unchanged and new recommendations regarding surgical readiness criteria for CDH[94–96]

Unchanged recommendations	Strength of consensus	Level of evidence
9.1 The following criteria should be met prior to surgery: urine output >1 mL/kg/hour, FiO_2 <0.5, preductal oxygen saturation between 85% and 95%, normal mean arterial pressure for gestational age, lactate <3 mmol/L and estimated pulmonary artery pressures less than systemic.	4	B-NR
9.2 Surgery should be reconsidered if a patient fails to meet surgical readiness criteria after 2 weeks.	4	C-LD
New recommendation	**Strength of consensus**	**Level of evidence**
9.3 In patients who have achieved physiological stability, there is no benefit in delaying operative repair.	4	C-LD

CDH, congenital diaphragmatic hernia; FiO_2, fractional inspired oxygen; LD, limited data; NR, non-randomised.

subgroup of high-risk patients and only in high-volume centres. This and another small centre series suggest that high-risk patients with CDH might have lower mortality when ECLS is used.[85 86] Two recent studies have considered the cost and societal implications of prolonged ECLS runs for CDH, arguing strongly against indefinite run length.[87 88]

There is accruing evidence regarding current age (<34 weeks' gestation) and weight (<1.7–2 kg) exclusion criteria for ECLS, suggesting they be reconsidered under special circumstances. A systematic review of all premature patients treated with ECLS demonstrated that survival rates for premature babies with CDH supported with ECLS, although rarely offered, were similar to survival in the prematurely born infant with CDH without ECLS.[89 90] The most recent ELSO dataset demonstrates an overall survival of 50% (n=7564), with a modest decline in infants <34 weeks' GA (44%); survival is even lower in those infants <2 kg (29%). Given the high risk of death and neural impairment associated with ECLS use in this population,[91] the provision of ECLS to populations with CDH with traditional relative contraindications should remain experimental and only contemplated at high-volume ECLS centres.

Two recent investigations reviewed repeat ECLS for CDH, with a combined total n=31.[92 93] Both papers endorsed repeat ECLS, with cannulation criteria remaining similar to the criteria used for the index cannulation. While it is clear that patients with CDH who undergo ECLS have inferior developmental/cognitive outcomes than a non-ECLS cohort, it is unknown whether a second run further compounds this impairment.

Surgical readiness criteria

Delaying surgical repair until 'physiological stability' has been achieved (usually interpreted as cardiorespiratory function and oxygenation sufficient to avoid lactic acidosis with evidence of subsystemic pulmonary artery pressure) appears to optimise CDH outcome. A recent retrospective, single-centre study of 158 neonates with CDH studied temporal trends in oxygenation index (OI) as a proxy for physiological stability. OI measurements in the first 24 hours of life corresponded with mean preoperative OI values suggesting that early OI could be used to determine the timing of operative repair in CDH. An OI <9.4 correlated with survival, and any delay in surgical repair after an OI of <9.4 was achieved led to increased ventilator days and delayed hospital discharge.[94] These findings suggest that there is no benefit to delaying surgical repair once clinical stability has been attained. A smaller prospective study from China (n=30) also concluded that delaying thoracoscopic repair beyond 48 hours was of no benefit for mild-moderate CDH (LHR >1)[95] (table 9).

One additional study demonstrated that meaningful survival can be achieved in high-risk patients and reinforced the importance of avoiding non-repair whenever possible. In their study exploring differences in outcomes at high-volume centres, Harting *et al*, noted that centres that had low rates of non-repair had higher survival than those centres with high rates of non-repair (suggesting survivability of repaired, highest-risk patients).[96]

Table 8 Updated recommendation regarding the use of ECLS in CDH[69 85–93]

Updated recommendation	Strength of consensus	Level of evidence
8.1 ECLS may be considered in populations with CDH with traditional size/age or comorbidity contraindications under special circumstances.	2	C-LD

CDH, congenital diaphragmatic hernia; ECLS, extracorporeal life support; LD, limited data.

Options for non-primary repair

Although there is no clearly preferred prosthetic (synthetic or biological) patch material for the repair of defects not amenable to primary repair,[97–101] recent studies describe success with defect closure using autologous muscle flaps. Two studies of 97 (in aggregate) neonates with CDH with large defects closed with oblique muscle flaps recorded 5-year recurrence rates of 3% and 3.5%.[102 103] Rates of repair on ECLS were similar to those undergoing patch repair (39% vs 31%) and complication rates, including bleeding on ECLS, were similar between groups—an observation made separately in another publication.[104] Three earlier publications reported an additional 50 muscle flap repairs, from which there were 3 reported recurrences (6%).[105–107] Long-term musculoskeletal outcomes (scoliosis, chest wall deformities) were equivalent in patch versus muscle flap groups[107] (table 10).

Open versus minimally invasive repair

Any consideration of a minimally invasive approach to CDH repair must acknowledge its higher recurrence rate compared with open and the importance of selecting patients based on favourable ventilatory and pulmonary hypertension preoperative parameters. Five recent cohort studies (totalling 137 patients) have reported recurrence rates of 7–21% after thoracoscopic repair (TR) of neonatal CDH.[108–111] Low-quality evidence suggests that use of a biological mesh underlay for primary and prosthetic mesh repairs reduces both the risk of recurrence and adhesive bowel obstruction[112] (table 11).

An earlier multicentre study of 37 infants undergoing TR identified preoperative OI >3 as independently predictive of

Table 10 Unchanged and new recommendations regarding non-primary repair in CDH[97–104]

Unchanged recommendation	Strength of consensus	Level of evidence
10.1 For diaphragmatic defects that are not amenable to primary repair, oversized, tension-free polytetrafluoroethylene (GORE-TEX) patches should be used.	4	C-LD
New recommendation	**Strength of consensus**	**Level of evidence**
10.2 Oblique muscle flap repair may be considered if technical expertise with the procedure exists.	4	C-LD

CDH, congenital diaphragmatic hernia; LD, limited data.

treatment failure, defined as need for conversion or the development of a serious postoperative complication.[113]

Surgical repair on ECLS

Survival to discharge for infants with CDH who require ECLS is approximately 50%, with single centres reporting rates approaching 70%.[86] Complications of repair on ECLS are predominantly metabolic, circuit related or haemorrhagic (including surgical site), which occurs in 25% of cases and is only partially offset by surgical technique and modified anticoagulation.[114] CDH non-repair rates in infants who receive ECLS are approximately 15%,[115] a rate which could be reduced by an on-ECLS repair strategy (table 12).

Two large registry studies have investigated the relationship between on or after ECLS CDH repair and survival. A Congenital Diaphragmatic Hernia Study Group (CDHSG) study of propensity-matched patients showed a survival advantage (HR 0.54 (0.38, 0.77)) to repair on ECLS, with high-volume centres disproportionately represented in this group.[116] However, if non-repairs were excluded, the survival benefit was reversed. An ELSO registry study of >2200 propensity-matched patients which excluded non-repairs demonstrated a threefold increased mortality and a run duration-dependent increased risk of severe neurological injury in the on-ECLS repair group.[117] A comparative study from Ann Arbor demonstrated the highest survival rate (94%) in infants who were decannulated prior to repair.[118]

Studies have explored outcomes according to early or late repair on ECLS with conflicting results. Two studies from CDHSG have shown improved survival with early repair, defined as <72 hours, or within the shortest time to repair quartile range.[116 119] In addition, a single-institution study of 33 patients comparing repair within 24 hours of cannulation versus repair between 24 hours and 72 hours demonstrated improved survival in the <24-hour group.[120] Conversely, a single-institution study comparing early (≤5 days) versus late (>5 days) repair protocols demonstrated that early repair was independently predictive of mortality (HR 3.48, CI 1.28 to 9.45).[118]

A single-centre study recently reported 2-year neurocognitive outcomes in CDH survivors repaired on ECLS versus after or without ECLS. While the entire CDH cohort had neurocognitive scores that were significantly lower than population norms in all domains, those repaired on ECLS had lower cognitive and motor scores compared with those repaired after ECLS.[121]

These analyses suggest that the relationship between survival and timing of repair relative to the ECLS run is confounded by whether mortality associated with non-repair (which will be more likely in high-risk patients) is excluded or attributed to the after-ECLS group. Patients with adverse prenatal predictors who go onto ECLS with severe cardiopulmonary derangement represent the greatest risk of non-repair. Consideration should be given to early repair in these patients.

Management of gastro-oesophageal reflux in CDH

Gastro-oesophageal reflux disease (GERD) is extremely prevalent with formal impedance testing demonstrating persistence of GERD in >60% of infants with CDH beyond 1 year of age.[122] This has led to consideration of 'preventative' fundoplication, which was explored in a prospective, multi-institutional study from France in which select institutions performed preventative fundoplication (n=27; 11%) versus no fundoplication for

Table 11 Updated recommendation regarding the type of surgical repair in CDH[108–112]

Updated recommendation	Strength of consensus	Level of evidence
11.1 Although recurrence rates for minimally invasive repairs of CDH continue to be higher than open repairs, minimally invasive repair may be considered in patients: a. Who easily achieve preoperative ventilatory targets. b. With infrasystemic pulmonary artery pressures and normal cardiac function. c. If the surgical team is technically proficient and the anaesthetic team is experienced and able to continuously monitor and manage intraoperative hypercarbia and acidosis.	3	C-LD

CDH, congenital diaphragmatic hernia; LD, limited data.

Table 12 Unchanged and updated recommendations regarding surgical repair on ECLS[86 114 116–120]

Unchanged recommendation	Strength of consensus	Level of evidence
12.1 For patients on ECLS, surgery should be avoided until after decannulation.	3	B-NR
Updated recommendation	**Strength of consensus**	**Level of evidence**
12.2 Patients with a low probability of survival based on prenatal predictors or the severity of cardiopulmonary derangement at cannulation are at risk of failure to wean and may benefit from early repair.	3	B-NR

ECLS, extracorporeal life support; NR, non-randomised.

Table 13 Updated recommendation regarding the management of gastro-oesophageal reflux in CDH[122 123]

Updated recommendation	Strength of consensus	Level of evidence
13.1 Routine 'preventative' fundoplication is not indicated at the time of diaphragm repair.	4	B-NR

CDH, congenital diaphragmatic hernia; NR, non-randomised.

high-risk cases at the time of CDH repair with prosthetic patch.[123] The rate of redo fundoplication in the preventative group was higher than the rate of subsequent fundoplication for medically refractory GERD in the no fundoplication group. Moreover, preventative fundoplication patients experienced significantly longer hospital stays and additional morbidity including oral aversion and the need for tube feeding >6 months. Thus, there is no advantage to fundoplication at the time of CDH repair; it should only be considered in the context of failed medical management (table 13).

Long-term follow-up in CDH

Studies continue to deepen our understanding of the long-term sequelae of CDH beyond the initial NICU admission along a number of biophysical domains, including cardiopulmonary,[124–131] gastrointestinal/nutrition/growth,[127 132–136] neurodevelopmental,[126 128 132 137–140] musculoskeletal[128 141] and all-cause late mortality.[142] These findings reinforce the importance of longitudinal follow-up by a team with CDH-specific expertise in accordance with the American Academy of Pediatrics guidelines. Finally, there is a significant knowledge gap in the optimal transitioning of patients with CDH from a paediatric to adult care context (table 14).

Pain, analgesia and neuromuscular blockade management in CDH

A systematic review and subsequent clinical guidelines for analgesia and sedation in term and near-term infants requiring mechanical ventilation made recommendations for infants with severe respiratory failure, which apply to patients with CDH: (1) a validated pain score[143] should be used to titrate opioid dose (strong recommendation); (2) fentanyl as a continuous infusion (CI) is preferred over morphine in presence of hypotension or renal failure (conditional recommendation); (3) when tolerance with one agent has occurred, opioids should be rotated (conditional recommendation); (4) use of short-acting benzodiazepine as bolus or CI can help reduce dose of opioid or need for muscle relaxant (conditional recommendation).[144] Use of fentanyl as a CI is also supported by a neonatal RCT that demonstrated favourable pharmacokinetics and equivalent pain scores versus intermittent bolus dosing[145] (table 15).

There is increasing evidence supporting use of intravenous and enteral acetaminophen or paracetamol in postoperative CDH management. Its use was reported in 48% of post-repair patients in the Children's Hospital Neonatal Consortium (CHNC) CDH Database.[146] A Cochrane review demonstrated that use of paracetamol decreased opioid utilisation in infants undergoing painful procedures or following invasive surgery.[147] An RCT and subsequent implementation cohort study demonstrated reduced opioid utilisation and equivalent pain scores in patients undergoing non-cardiac surgery managed postoperatively with opioids combined with either paracetamol or placebo.[148 149] A recent quality improvement study demonstrated that a standardised protocol which combined intravenous acetaminophen, education and standardised pain handover reduced postoperative opioid use and duration of intubation in patients with CDH.[150]

Table 14 Updated and new recommendations regarding long-term follow-up in CDH[124–142]

Updated recommendations	Strength of consensus	Level of evidence
14.1 We recommend standardised multidisciplinary follow-up for children with CDH to provide surveillance and screening, optimal and timely diagnosis and clinical care adjusted to the level of risk.	4	B-NR
14.2 We recommend identifying the subset of CDH survivors at high risk of long-term morbidity as comprising those infants and children who require extracorporeal life support, who have been repaired with a patch or muscle flap or who require respiratory support at 30 days of life.	4	B-NR
New recommendation		
14.3 Where possible, the following members should constitute the longitudinal multidisciplinary follow-up team for CDH survivors: paediatrics, developmental paediatrics, nutrition/dietary sciences, paediatric surgery, paediatric respirology and paediatric cardiology. Additional subspecialties or allied health professionals should be engaged as needed.	4	B-NR

CDH, congenital diaphragmatic hernia; NR, non-randomised.

Table 15 New recommendations regarding pain, analgesia and neuromuscular blockade management in CDH[143–147 149 150]

New recommendations	Strength of consensus	Level of evidence
15.1 All infants with CDH requiring mechanical ventilation should have personalised analgesic/sedation management that is guided by a clinically applicable and appropriately validated pain/sedation scoring tool.	4	B-NR
15.2 Intravenous opioid (morphine or fentanyl) should be administered as a CI in combination with a short-acting benzodiazepine, which may reduce opioid dosing requirements.	3	B-NR
15.3 Routine neuromuscular blockade should be avoided in preoperative stabilisation, but its use should be considered for infants with escalating severity of pulmonary hypertension or if ventilation targets are difficult to achieve.	4	C-LD
15.4 Postoperative use of intravenous acetaminophen should be considered as a means of reducing overall opioid requirements.	3	B-NR

CDH, congenital diaphragmatic hernia; CI, continuous infusion; LD, limited data; NR, non-randomised.

There is little evidence to address the role of neuromuscular relaxation in preoperative stabilisation of infants with CDH. A prospective cohort study of 15 mechanically ventilated infants with CDH demonstrated a significant decrease in compliance after the administration of pancuronium.[151] Furthermore, a multicentre registry review found that prolonged use of sedation and/or muscle relaxation was associated with longer lengths of stay and a higher mortality rate, which mirrors findings from the CHNC Database where the use of neuromuscular relaxation pre-repair occurred with nearly twice the frequency in non-survivors versus survivors (87% vs 48%).[146] These data appear to suggest that neuromuscular paralysis is added when patients with severe disease fail to stabilise.[146]

DISCUSSION AND CONCLUSION

In creating this update, the Canadian CDH Collaborative has sought to maintain its CPG as a 'living document' by updating and adding recommendations to care areas where new evidence has emerged. This updated CPG provides an evidence-based and consensus-driven management framework that aims to improve outcomes and encourage synthesis of new knowledge through targeted research and quality improvement efforts.

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Contributors A three-member steering committee (PP, ES, RB) was formed to oversee the CDH Collaborative's guideline development process, to finalise the guideline panel membership and contributors to the literature reviews, to critically appraise all materials generated during the evidence review process, oversee the final guidelines endorsement process and prepare the manuscript. PP acted as guarantor. They were specifically involved in the preparation of sections on haemodynamics (PP), ECLS (RB), non-primary surgical repair (ES), type of surgical repair (ES), repair on ECLS (ES/PP), and pain control and analgesia (ES). EG was the research director for the project who oversaw its design, the literature search and screening, as well as the editing of the final revised version of the manuscript and supplemental materials. AD was involved with the literature search and abstract screening, the critical appraisal and preparation of the section on surgery on ECLS, as well as the revision of the final submitted manuscript. OG was involved with the literature search and abstract screening, the critical appraisal and preparation of the section on haemodynamics, as well as the revision of the final submitted manuscript. NA was involved with the critical appraisal and preparation of the sections on prenatal diagnosis and fetal therapy, as well as revision of the final submitted manuscript. GA was involved with the literature search and abstract screening, the critical appraisal and preparation of the sections on echocardiography, role of PGE and target pulmonary vasodilator therapy, as well as the revision of the final submitted manuscript. MB was involved with the literature search and abstract screening, the critical appraisal and preparation of the section on surgical readiness, as well as the revision of the final submitted manuscript. SF was involved with the literature search and abstract screening, the critical appraisal and preparation of the section on type of surgical repair, as well as the revision of the final submitted manuscript. SD was involved with the literature search and abstract screening, the critical appraisal and preparation of the section on ventilation, as well as the revision of the final submitted manuscript. HF was involved with the critical appraisal and preparation of the section on gastro-oesophageal reflux as well as the revision of the final submitted manuscript. AH was involved with the literature search and abstract screening, the critical appraisal and preparation of the sections on echocardiography, role of PGE and target pulmonary vasodilator therapy, as well as the revision of the final submitted manuscript. RK was involved with the literature search and abstract screening, the critical appraisal and preparation of the section on ECLS as well as the revision of the final submitted manuscript. MO was involved in the concept and design of the work, as the facilitator for our Delphi consensus process, as well as the revision of the final submitted manuscript. DP was involved with the literature search and abstract screening, the critical appraisal and preparation of the section on role of ECLS, as well as the revision of the final submitted manuscript. GR was involved with the critical appraisal and preparation of the sections on prenatal diagnosis and fetal therapy, as well as the revision of the final submitted manuscript. MT was involved with the literature search and abstract screening, the critical appraisal and preparation of the section on ventilation, as well as the revision of the final submitted manuscript. AZ was involved with the literature search and abstract screening, the critical appraisal and preparation of the section on ECLS as well as the revision of the final submitted manuscript. PC was involved with the literature search and abstract screening, the critical appraisal and preparation of the section on long-term follow-up, as well as the revision of the final submitted manuscript.

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Appendix 1

i) Steering Committee and Panel Composition:

Steering Committee: A three-member Steering Committee (PP, ES, RB) was formed to oversee the CDH Collaborative's guideline development process, to finalize the guideline panel membership and contributors to the literature reviews, to critically appraise all materials generated during the evidence review process, oversee the final guidelines endorsement process and prepare the manuscript, which was reviewed and approved by the Collaborative.

Guideline Panel Composition: Specialists in the fields of pediatric surgery, maternal fetal medicine, pediatric anesthesia, neonatal intensive care, pediatric intensive care, neonatal follow-up and pediatric cardiology were recruited, including both new and original members from the 2018 CDH Collaborative.

*Pramod S. Puligandla	Pediatric Surgery/PICU	Montreal Children's Hospital
*Erik D. Skarsgard	Pediatric Surgery	British Columbia Children's Hospital
*Robert G. Baird	Pediatric Surgery	British Columbia Children's Hospital
Elena Guadagno	Research Director	Montreal Children's Hospital
Alexandra Dimmer	Trainee	Montreal Children's Hospital
Olivia Ganescu	Trainee	Montreal Children's Hospital
Nimrah Abbasi	Maternal Fetal Medicine	Mount Sinai Hospital (Toronto)
Gabriel Altit	Neonatology	Montreal Children's Hospital
Mary Brindle	Pediatric Surgery	Alberta Children's Hospital
Sairvan Fernandes	Trainee	British Columbia Children's Hospital
Shyamala Dakshinamurthi	Neonatology	Winnipeg Children's Hospital
Helene Flageole	Pediatric Surgery	McMaster Children's Hospital
Audrey Hebert	Neonatology	Centre Hospitalier Université Laval
Richard Keijzer	Pediatric Surgery	Winnipeg Children's Hospital
Martin Offringa	Neonatology	Hospital for Sick Children (Toronto)
Dylan Patel	Trainee	Montreal Children's Hospital
Greg Ryan	Maternal Fetal Medicine	Mount Sinai Hospital (Toronto)
Michael Traynor	Pediatric Anesthesia	British Columbia Children's Hospital
Augusto Zani	Pediatric Surgery	Hospital for Sick Children (Toronto)
Priscilla Chiu	Pediatric Surgery	Hospital for Sick Children (Toronto)

*Steering Committee members

All authors listed above made substantial contributions to the conception or design of this work, as well as the acquisition, analysis and interpretation of the data used to create this work. The authors were also involved in drafting the document and revising the final version to be published. All authors are accountable for all aspects of this work in ensuring that any questions

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related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

ii) Literature search

A senior medical librarian conducted an update to the existing CDH guideline published in 2018.[1] The PRISMA guideline[2] for conducting systematic reviews was used. The following databases were searched from January 1, 2017 to August 30, 2022: Medline (Ovid), Embase (Ovid), and Cochrane (Wiley). The search strategy used variations in text words found in the title, abstract or keyword fields, and relevant subject headings to retrieve articles looking very broadly at all congenital diaphragmatic hernia literature. The search excluded editorials, letters to the editor, review articles, case reports involving less than 3 patients, and animal studies, where applicable (See "Supplementary Material" for search strategy). The PRISMA-S[3] extension for searching was used for reporting and is included in the Supplementary material. EndNote X9^{TM} was used for duplicate removal. Initial title and abstract screening was performed by at least two independent reviewers (PP and a combination of OG, EG, DP and/or AD) with a third reviewer resolving the discrepancies using the online platform Rayyan.[4] The primary reason for exclusion was documented in a Google spreadsheet. Selected articles were then segregated according to their potential relevance to each of the 15 CDH care areas.

iii) Evidence appraisal process

The process for updating the existing CDH clinical practice guidelines adhered to GRADE methodology.[5] Work groups were provided the screened articles associated with their area of interest in order to complete their full manuscript critical appraisal for new evidence. Articles could be excluded at this stage if they were deemed irrelevant or if they did not include at least one outcome measure pertinent to the CDH care area under review. The work groups created Population-Intervention-Comparison-Outcome (PICO) tables based on their review of each article (**Appendix 2**). This information was then used to inform changes to existing guidelines or the need to develop new care recommendations.

iv) Recommendation generation and/or modification

Work groups provided evidence summaries supporting the care amendments and then provided the level of evidence for each recommendation using the previously published taxonomy (Figure 2[1]). Recommendations were categorized as "unchanged", "updated" or "new" based on the existence or degree of novelty of evidence emerging since the creation of the 2018 guidelines. Based on the search outcomes, a new set of recommendations were created for analgesia, sedation and neuromuscular blockade, a care area not addressed by the 2018 guidelines.

v) Strength of recommendation

The strength of recommendation and supporting level of evidence were achieved and displayed according to GRADE recommendations[5] in each section's table of recommendations (see **Tables 1-15**)

vi) Modified Delphi endorsement process

The new and updated CDH care recommendations, including the evidence summaries and PICO tables that supported them, were packaged into a single document that was shared with all Collaborative members and guideline contributors for review. Concomitantly, a survey (Survey Monkey™) was delivered to each member explicitly asking if they agreed with each care recommendation as written. Following the consensus framework previously used (**Figure 3**),[1] care recommendations not meeting the predetermined consensus (>80% agreement) thresholds of good or strong were then marked for further discussion. If consensus could not be reached after further discussion, the final level of consensus was noted and this item identified for future discussion by Steering Committee members.

vii) Management of competing interests

Members of the Canadian CDH Collaborative performed their tasks voluntarily. All members reported conflict of interest/commitment declarations, and no conflicts were encountered.

viii) Funding

This project received no external or internal funding.

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Appendix 1: PICO Tables Informing New CDH Care Recommendations

Table 1: Summary table for evidence supporting revisions in CDH prenatal diagnosis and management

Author	Population	Intervention	Comparison	Outcome	Class of Evidence
Kammoun (2018)[1]	Cohort of 120 fetuses with isolated CDH (L, R, B/L)	Targeted massively parallel sequencing of 143 human and mouse CDH causative and candidate genes	NA	10% pathogenic or likely pathogenic CNVs	B-NR
Zhu (2018)[2]	196 CDH (96 isolated, 80 non-isolated, remaining insuff. data) Vs. 987 healthy, unaffected controls	CMA (customized aCGH platform designed covering 140 known and candidate CDH regions)	NA	Up to 13% pathogenic variants (9.7% if large CNVs excluded) *Comparison to controls *no prenatal data	B-NR
Schwab (2022)[3]	22 parent-offspring trios	none	CDH fetus and parents	Exome sequencing increases the diagnostic yield in CDH	C-LD
Sferra (2022)[4]	SR/MA of 5 studies (150 eligible patients)	Integrated postnatal care (ECLS) after FETO	Non-integrated postnatal CDH care (no ECLS) after FETO	Survival increased OR 2.97 (1.69-4.26) with integrated care and ECLS access	B-NR
Wild (2022)[5]	411 patients	none	none	43% of syndromic and 98% of non-syndromic/isolated CDH did not have genetic abnormality identified; need expanded genomic	C-LD

				analysis	
Danzer (2022)[6]	CDHSG 156 (of 2510) RCDH	none	none	Cannot use LCDH prenatal imaging criteria to predict outcome for RCDH	C-LD
Abbasi (2019)[7]	Determine antenatal lung area measurement method with highest inter-rater agreement in NAFTNet	48 imaging specialists 13 CDH fetal US studies	NA	Trace highest inter-rater agreement and lowest bias among experienced and inexperienced NAFTNet centres	B-NR
Russo (2021)[8]	RCDH 214 isolated RCDH 86 Expect mgmt. 128 FETO Retrospectiv e multicentre review		Survival comparison between expectant and fetal therapy.	Neonatal survival/ LOS in NICU predicted by o/e LHR US and o/e TFLV MRI In fetuses with o/e-LHR ≤45% treated with FETO, survival rate was higher than in those with similar lung size managed expectantly (49/120 (41%) vs 4/27 (15%); P = 0.014), despite higher PTB (GA at birth: 34.4 ± 2.7 weeks vs 36.8 ± 3.0 weeks; P < 0.0001). With FETO, GA at birth = only predictor of survival Best o/e LHR for prediction of survival = 50%	B-NR
Bouchghoul (2021)[9]	Optimal timing of delivery Isolated L CDH No FETO Retrospectiv	Kaplan–Meier method \ used to calculate cumulative survival at	NA	213 L CDH Median GA 38 +2 (37-39+1) Delivery <37 wks., significant lower survival rate Kaplan–Meier	B-NR

	e study	28 days after birth according to GA at delivery. Adjustment for liver position, o/e LHR, management center and mode of delivery. Association also evaluated according to severity of CDH/ o/e LHR (mild/ mod/ sev)		analysis higher survival at 28 days when delivery between 37 + 0 and 38 + 6 wks. vs. delivery at or after 39 + 0 wks. ($p<0.001$) For mod CDH, the 28-d & 6 mo. survival significantly higher with delivery between 37 + 0 - 38 + 6 wks. vs. delivery at/ after 39 wks. (not (81.5% *vs* 61.5%; *P* = 0.03 for 28 d survival). *? Worsening PHTN. Not seen with mild/ sev. CDH ? power* Survival rate did not differ according to mode of delivery at 28 d, trend towards lower survival with CS (survival lower with emergency CS). Isolated mod CDH—delivery should be considered between 38-9 wks. Mode of delivery-- standard Ob indications	
Wang (2022)[10]	94 CDH	none	none	Mediastinal shift angle predicts outcomes and LV hypoplasia	C-LD
Weller (2022)[11]	101 CDH	none	none	Stomach position predicts need for increased PH	C-LD

				management (and can predict increased defect size)	
Oluyomi-Obi (2017)[12]	Prenatally diagnosed CDH (L+R) 22 studies (prospective & retrospective) included in metanalysis evaluating prenatal US and MRI parameters & prediction of survival (1ry outcome), and use of ECLS (2ry)	Prenatally diagnosed CDH survivors	Prenatally diagnosed CDH non-survivors	o/e LHR and o/e TFLV performed best in prediction of survival (o/e TFLV AUC 0.8 and o/e LHR 0.78 with longest diameter and slightly higher with trace method AUC 0.85).Thresholds of <25% for o/e LHR and o/e TFLV more specific for neonatal mortality. Liver herniation by US and MRI also significant predictors of mortality (present/ absent by US and quantitatively by MRI). Odds of survival 0.21 with liver herniation by US. LiTHR AUC 0.72 %HL AUC 0.75 for prediction of mortality. LHR<1 predictive of need for ECLS	B- NR
Senat (2018)[13]	305 LCDH	Predictive value of o/e LHR for survival at 28d and 6 months in high volume centres (>/=14 CDH cases, 82 CDH cases	Low volume centres (<14 CDH cases; 223 cases in 29 centres)	Survival at 28 days, for specificity of 0.3 Sensitivity 0.71 in larger centres and 0.55 in smaller centres.	B-NR

		in 2 centres)			

Table 2: Evidence summary for updated recommendations regarding fetal therapy in CDH

Author	Population	Intervention	Comparison	Outcome	Class of Evidence
Belfort (2017)[14]	Isolated severe LCDH	FETO LHR <1 & liver herniation (n=11)	9 expect. mgmt. "Historical controls"	1/11 FETO not technically feasible Improved survival in FETO vs. expect mgmt.: 6 mo. (80% vs. 11%), 1 yr. (70% vs. 11%) and 2yr (67% vs. 11%) survival Reduced ECMO (30 vs. 70%)	C-NR
Baschat (2020) [15]	CDH Mod-sev CDH Non-isolated	FETO o/e LHR <30% n=14 Associated anomalies CCAM (n=2) TOF (n=1) Normal genetic testing	Feasibility study, no control group	Neonatal survival 93% Survival to discharge 86% PPROM 30% Median gestational age at birth was 39 2/7 wks. (range 33 6/7–39 4/7) *(*PRG, Tocolysis, pessary, amnioreduction, needle puncture balloon?)*	C-NR
Deprest(2021)[16]	Isolated moderate CDH	Moderate isolated LCDH (o/e LHR 25-35%, 35-45% liver up) RCT 1:1 Primary outcome: Infant survival to discharge from a NICU and survival	40 expect. mgmt.	FETO at 30-32 wks. did not result in a significant benefit in survival (63 vs. 50%) FETO increased PPROM (44 vs. 12%) and PTB <37 wk. (64% vs. 22%)	A-R

		without 02 at 6 mo.			
Deprest (2021)[17]	Isolated severe CDH	Severe isolated LCDH (o/e LHR <25%) RCT 1:1 primary outcome: Infant survival to discharge from NICU	98 expect. mgmt.	FETO at 27 to 29 wks. resulted in a significant benefit over expectant care with survival to discharge (40% vs. 15%) and survival at 6 months. FETO increased PPROM (47 vs. 11%) and PTB <37 wks. (75% vs. 29%)	A-R
Van Calster (2021)[18]	Isolated LCDH mod + sev (pooled data NEJM)	Data from 2 NEJM trials pooled to study the heterogeneity of the treatment effect by o/e LHR and explore the effect of GA at balloon insertion		aOR of FETO with early balloon insertion was 2.73 (95% CI, 1.15-6.49). Results for survival to 6 months and survival to 6 months without 02 were comparable. FETO increases survival for both moderate and severe lung hypoplasia. Difference between the results for the TOTAL trials, when considered apart, may be because of the difference in the time point of balloon insertion. The effect of the time point of balloon insertion could not be robustly assessed	A-R

				because of a small sample size and the confounding effect of disease severity.	
Russo(2016)[19]	Transplacental sildenafil in rabbit model DH Determine therapeutic dosing without toxicity and assess pulmonary effects of sildenafil	DH fetuses were randomly exposed to transplacental placebo or sildenafil 10 mg/kg/ day from gestational day 24 until examination at term (day 30). Efficacy measures were ipsilateral pulmonary vascular and airway morphometry, micro-CT-based branching analysis, Doppler flow in the main pulmonary artery and postnatal lung mechanics.	DH fetuses without transplacental sildenafil	Sildenafil-exposed DH fetuses, had a medial and adventitial thickness in peripheral pulmonary vessels in the normal range and normal vascular branching. Fetal pulmonary artery Doppler showed a reduction of pulmonary vascular resistances Sildenafil also reversed the mean terminal bronchiolar density to normal and improved lung mechanics, yet without measurable impact on lung-to-bodyweight ratio. **In the rabbit model for diaphragmatic hernia, maternally administered sildenafil reverses all the pathological changes in lung peripheral vessels and also results in a morphological**	B-NR

				and functional improvement in lung parenchyma without obvious fetal and maternal toxicity, except for fetuses with normally developed lungs in whom it seems to decrease vascular branching.	
Russo (2018)[20]	Sildenafil SToP-PH Trial (ongoing)	Randomized, investigator-blinded, double-armed, parallel-group, phase I/IIb study with as a primary objective to measure the in-vivo transplacental transfer of sildenafil in women in T2 & early T3 Participants undergoing termination of pregnancy will be randomized to two different sildenafil doses: 25 or 75 mg (single dose or 3 doses prior to delivery). Maternal and			A-R (ongoing)

		fetal blood samples will be collected. Markers of fetal pulmonary vasodilation will also be measured.			
Russo (2021)[8]	RCDH 214 isolated RCDH 86 Expect mgmt. 128 FETO Retrospective multicentre review		Survival comparison between expectant and fetal therapy.	Neonatal survival/ LOS in NICU predicted by o/e LHR US and o/e TFLV MRI In fetuses with o/e-LHR ≤45% treated with FETO, survival rate was higher than in those with similar lung size managed expectantly (49/120 (41%) vs 4/27 (15%); P = 0.014), despite higher PTB (GA at birth: 34.4 ± 2.7 weeks vs 36.8 ± 3.0 weeks; P < 0.0001). With FETO, GA at birth = only predictor of survival Best o/e LHR for prediction of survival = 50%	B-NR

*One article (Russo et al) was excluded as it was a review article ineligible for data abstraction.

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Table 3 – Evidence summary informing changes to ventilation strategies in CDH

Author	Population	Intervention	Comparison	Outcome	Class of Evidence
Gerall (2021)[21]	77 CDH (2005-2019)	CMV to HFPPV to HFOV	CMV to HFOV	HFPPV to HFOV group experienced higher survival, earlier surgical repair, less ECLS/iNO, less need for oxygen and decreased need for PHTN medications	Retrospective C-LD
Cochius-den Otter (2020)[22]	Retrospective review of 71 CDH infants with 18 classified as mild severity and underwent spontaneous breathing approach (SBA)	Spontaneous breathing	Received respiratory support	6/15 were successful with SBA; 3 were excluded due to no plan for SBA	C-LD
Derraugh (2020)[23]	Propensity analysis of 80 CDH infants (1991-2015) receiving HFV or CMV at time of surgery	HFV (39 patients)	CMV (41 patients)	Raw analysis suggested increased oxygen dependence and death with HFV but propensity analysis demonstrated no difference	C-LD
Fuyuki (2021)[24]	327 patients stratified based on initial mode of ventilation (250 HFV, 77 CMV) using Japanese CDH Study Group	HFV	CMV	Adjusted odds of death (0.98,CI 0.57-1.67) or BPD (1.66, CI 5.49) were no different between groups	C-LD
Kurland (2021)[25]	18 of 130 CDH (2011-2019) selected	NAVA while intubated	Standard IMV while intubated	NAVA tolerated in 16, not tolerated in 2. Lower PIP, lower	C-LD Retrospective single-centre

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	by clinician. 32 matched controls			MAP and decreased sedative/analgesia use on NAVA	
Meinen (2021)[26]	10 CDH patients (2015-2018) selected by clinician.	NAVA for wean from IMV	Standard wean from IMV	Successful wean to NIV in 6, unsuccessful in 4. Lower PIP, lower MAP and decreased use for supplemental O2 on NAVA.	C-LD Retrospective single-centre
Wise (2018)[27]	45 CDH (2011-2015). 28 instances of heliox use for hypercapnia (clinician discretion).	Heliox as rescue for hypercapnia	Standard ventilation strategy using air/O2	Significant, sustained decrease in FiO_2, PIP, and $PaCO_2$ after switch to heliox	C-LD Retrospective single-centre

Table 4: Evidence summary informing changes to fundamentals of hemodynamic support

Author	**Population**	**Intervention**	**Comparison**	**Outcome**	**Class of Evidence**
Acker et al (2014)	13 CDH infants	vasopressin		Vasopressin was effective in 6/13 patients (improved BP, reduced pulmonary/systemic pressure ratio	C-NR
Ryan (2020)	54 CDH neonates (CDH registry from 2011-2017)			Development of AKI – 37% - risk factors include patch repair, vancomycin, diuretics, corticosteroids	C-NR

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Liberio (2021)[28]	CDH neo (single center)		Infants developing AKI n=34 vs those with no AKI n=34.	The overall survival rate of infants with CDH in this cohort was 79%. Survival was 47% for those with AKI, while no AKI experienced a 98% survival	C-LD
Arattu Thodika (2022)[29]	CDH infants admitted to tertiary care center from 2011 – 2021, including FETO infants Infants with renal anomalies excluded	N/A	Infants developing AKI (n=59) vs. no AKI (n =35)	Infants undergoing FETO had increased incidence of AKI (49.1% vs. 18.8%, p=0.005) AKI not an independent predictor of survival, hospital duration, or length of ventilation or ICU stay	C-LD

Table 5: Evidence summary informing changes to the role of echocardiography in CDH

Author	**Population**	**Intervention**	**Comparison**	**Outcome**	**Class of Evidence**
Ferguson (2021)[30]	CDH neo	Echocardiography – PH severity	PH severity categorized using echocardiographic findings: none, mild (RVSP detectable but <2/3 systemic), moderate (RVSP ≥2/3 systemic and ≤systemic), or severe (supra-systemic RVSP).	Increased PH severity over time correlated with worse late outcomes, including overall in hospital mortality and a composite outcome of mortality or oxygen support at discharge/transfer	C-LD

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Gupta (2021)[31]	CDH neo	Pro-BNP values	Association between pro-BNP values and ventricular dysfunction	Patients with any ventricular dysfunction on their initial echo had higher proBNP values than patients with normal ventricular function. For all patients whose proBNP value improved over time, their echo either showed normal ventricular function or improvement in cardiac function at discharge	C-LD
Yang (2020)[32]	CDH neo	CDH Protocol adoption Delaying echo at 24 hours of life	Pre and post epochs of guidelines adoption	Decrease in ECMO and increase in survival without ECMO	C-LD
Altit (2017)[33]	CDH neo	Echocardiography	ECMO vs Non-ECMO	Decreased left and right ventricular performance were significantly associated with need for ECMO	C-LD
Guslits (2021)[34]	CDH	Pro-BNP values	Respiratory status at 56 days	BNP cutoffs that maximized correct outcome classification decreased over time from 285 pg/mL at 3 weeks to 100 pg/mL at 4 weeks and 48 pg/mL at 5 weeks.	C-LD
Avitabile (2020)[35]	CDH neo	Pro-BNP and echocardiography	BNP-echo pairing preop and post-op	BNP and strain abnormalities were associated with an ECMO	C-LD

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				requirement. Higher BNP level in recovery was associated with greater mortality. Abnormal strain in recovery had high sensitivity for detection of mortality	
Aggarwal (2022)[36]	CDH neonates	Echocardiography measures of the relationship between right ventricular contractility and pulmonary hypertension	Echo parameters combining RV function and PH severity were compared among survivors and those who died or required ECMO	Non-survivors and those requiring ECMO had lower PAAT/PET, TASPE/PAAT and TAPSE/RSVP compared to survivors without ECMO	C-LD
Kipfmueller (2022)[37]	CDH neonates	Echocardiography measures calculating the pulmonary artery acceleration time to the right ventricular ejection time (PAAT/ET)	PAAT/ET were compared between non-ECMO survivors, ECMO-surviovors and non-survivors	Baseline PAAT/ET values were significantly lower in ECMO patients ECMO survivors had similar PAAT/ET values to non-survivors at baseline and DOL2, but non-survivors had significantly lower values at DOL 5-7	C-LD
Guner (2021)[38]	CDH neonates ELSO practice guidelines	N/A	N/A	Recommend early echo (4-12 hours of life) to assess cardiac anatomy & function	B-NR
Patel (2019)[39]	CDH neonates Multicenter prospective	Assessment of cardiac function from	Survival compared amongst	Survival varied by category: normal function, 80%;	C-LD

	study (CDHSG registry)	early echo (first 48 hours of life)	infants with normal function, RV dysfunction only, LV dysfunction only or combined RV & LV dysfunction	RV_{dys}, 74%; LV_{dys}, 57%; and $RV\&LV_{dys}$, 51% ($P < 0.001$).	

One study (Prasad et. al) excluded. This was a systematic review and attempted meta-analysis. 11 studies were included, without consistent data reporting among the 11 studies, with different outcomes examined. No definitive conclusions were drawn in this article.

6 studies were reviewed for full text and excluded, due to relevancy.

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Table 6: Evidence summary supporting existing care recommendations for the role of prostaglandins in the management of CDH-associated pulmonary hypertension

Author	Population	Intervention	Comparison	Outcome	Class of Evidence
Le Duc (2022)[40]	18	PGE in CDH	Pre-Post study	FiO2, pre-post ductal SpO2, blood flow via ductus.	C-LD
Lawrence (2019)[41]	57	PGE	Pre-post study	BNP levels, echocardiographic estimates of severe PH improved.	C-LD

Table 7: Evidence summary supporting care recommendations regarding targeted pulmonary vasodilation in the management of CDH-associated pulmonary hypertension.

Author	Population	Intervention	Comparison	Outcome	Class of Evidence
Joshi et al (2022)	10	vasopressin		Reduction in oxygenation index, improvement in BP, averted ECLS in 50%	C-NR
Jozefkowicz (2020)[42]	18	Treprostinil	Clinical data were compared before and after treprostinil treatment.	Before treatment, median OI 20 (IQR: 12–27). Suprasystemic PH in 8/17 patients; the rest were systemic. After 1 week of treatment, 15/17 patients were alive and median OI was 8 (IQR: 5–12, p 0.0089). Echocardiogram still showed suprasystemic PHT in 20% of patients	C-LD
Turbenson (2020)[43]	3 with CDH out of 5	Transitioning From	Description of transition from	Rapid high-dose transition from IV	C-LD

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		Intravenous to Subcutaneous Prostacyclin Therapy	IV epoprostenol to subQ Treprostinil	epoprostenol to IV treprostinil and then to SQ treprostinil is well tolerated in neonates, with minimal adverse effects.	
Carpentier (2017)[44]	14 CDH	Treprostinil	Oxygenation parameters and ECHO pre and post introduction.	Post-ductal SpO2 increased and the difference between the pre- and post-ductal SpO2 decreased after starting Treprostinil. Mean blood flow velocities in the LPA and RPA increased after beginning treprostinil ($p<0.05$). The score for the curvature of the IVS decreased after starting Treprostinil.	C-LD
Lawrence (2018)[45]	164 CDH – 17 with treprostinil	Retrospective cohort - treprostinil for severe pulmonary hypertension.	Pre-Post treprostinil	Infants treated with treprostinil were more likely to be treated with additional pulmonary hypertension therapies and ECMO. They were also more likely to have a longer length of hospital stay and longer duration of mechanical ventilation. Over the same period of time that BNP	C-LD

				decreased, there was also an improvement in pulmonary hypertension as assessed by echocardiogram.	
Guslits (2021)[34]	CDH	Pro-BNP values	Respiratory status at 56 days	BNP cutoffs that maximized correct outcome classification decreased over time from 285 pg/mL at 3 weeks to 100 pg/mL at 4 weeks and 48 pg/mL at 5 weeks.	C-LD

5 full-text articles were reviewed and excluded due to relevancy.

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Table 8: Evidence summary supporting revised recommendations regarding the use of ECLS in the management of CDH

Author	Population	Intervention	Comparison	Outcome	Class of Evidence
Jancelewicz (2022)[46]	CDH neo	ECLS		Overall mortality higher with ECLS (47.8% vs 21.8% OR 3.3) Survival advantage in subgroup of high-risk patients (64.2% vs 84.4% OR 0.33), this was only observed in high CDH volume centres	C-LD
Delaplain (2017)[47]	CDH neo	ECLS	<34 weeks gestation <2 kg	No mortality difference <34 weeks gestation OR 2.11 for mortality in <2 kg	C-LD
Guner (2021)[38]	CDH and ECLS guideline	Interim consensus guideline		No change in timing If possible delay repair till after ECLS High risk might benefit from early repair while on ECLS	B-NR
Mesas Burgos (2020)[48]	CDH neo	Re-ECLS	Primary vs re-ECLS	Same indications and similar long term outcomes	C-LD
Gien (2022)[49]	CDH neo (n=13)	ECLS	N/A – observational study of severe CDH managed with ECLS and early repair	77% survived ECMO and 69% survived to discharge. 22% underwent tracheostomy.	C-LD
Zheng (2022)[50]	CDH neo	Cost-effectiveness of ECLS >2 weeks	ECLS < 2 weeks	ECLS duration of 2-3 weeks is more cost effective than > 3 weeks in 68.6% of simulations	C-LD
Snyder (2021)[51]	CDH neo	ECLS	CDH without ECLS	11.2% of infants received ECLS. Newborns with CDH on ECMO had a survival of 46%	C-LD

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				(61/133) compared to 85.5% without ECMO (903/1056)	
Burgos (2022)[52]	Systematic Review of CDH neo	ECLS in early (<34 weeks) prematurity	ECLS in late (37 weeks) prematurity	Risk of ICH and death has declined in ECLS group <34 weeks and is comparable to premature infants without ECLS. GA < 34 weeks may no longer be considered a contraindication to ECLS	C-LD
Guner (2022)[53]	CDH and ECLS guideline	Interim consensus guideline		GA ≤ 32 weeks and weight ≤ 1.7–2 kg should be considered relative contraindications Concomitant severe congenital heart disease and CDH may be considered a contraindication for ECLS based on severity of the cardiac defect; multidisciplinary communication is mandatory in such patients Major genetic abnormalities or syndromes are commonly considered relative contraindications for ECLS	B-NR
Herco (2022)[54]	CDH neo	ECLS (1 vs. 2 runs)	Comparison of Neurodevelop mental outcomes in CDH without ECLS, 1 run of ECLS, and 2 runs of	Survival of ECMO patients was 50%, with 48% of single run and 57% of repeat run patients surviving to discharge. CDH neonates who	C-LD

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			ECLS	underwent ECMO (single or repeat runs) were more likely to have lower cognitive, language, and motor composite scores as compared with CDH neonates who had not required ECMO. Motor composite scores were significantly lower in repeat ECMO run neonates as compared with single ECMO run but there were no further deficits noted in language or cognitive domains.	

*One article (Abdulhai et al) was excluded due to outcome measurement as this was a survey of pediatric surgeons.

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Table 9: Evidence summary supporting revised recommendations surgical readiness criteria

Author	Population	Intervention	Comparison	Outcome	Class of Evidence
Harting (2018)[55]	CDH neo (CDHSG database)	Repair at high volume sites with low or high rates of repair	Patients treated at high volume centers with low rates of non-repair (n=1105) Patients treated at high volume centers with high rates of non-repair (n=1125)	For every 100 CDH patients, high volume centers with a low rate of non-repair have at least 2.7 additional survivors beyond high volume centers with a high rate of non-repair	C-LD
Liu (2021)[56]	CDH neo (single center)	Thoracoscopic repair of mild to moderate left-sided CDH (early vs. delayed)	Patients repaired early (within 48 hours) n =15 Patients repaired later n=15	Delaying thoracoscopic repair was of no benefit for mild-moderate CDH (LHR > 1)	B-R
Cox (2022)[57]	CDH neo (retrospective single center)	Analysis of repeated measures of oxygenation index (OI)	Delay in surgical repair beyond initial stability (OI < 9.4)	A pre-operative OI of ≤9.4 (AUC 0.95) was predictive of survival. Surgical delay after an OI ≤9.4 resulted in increased ventilator days (1.4, 95% CI 1.1–1.9) and discharge age (1.5, 95% CI 1.2–2.0).	C-LD

One paper (Kotb et al) was excluded due to relevance. One paper (Abdulhai et al) was excluded due to outcome measurement as this was a survey of pediatric surgeons.

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Table 10: Evidence summary supporting care recommendations regarding options for non-primary repair

Author	Population	Intervention	Comparison	Outcome	Class of Evidence
Ruhrnschopf (2021)[58]	CDH neo	Patch repair (synthetic)	SIS-18 PTFE-25	CDH recurrence: SIS-50% PTFE-4%	C-LD
Suply (2020)[59]	CDH neo	Patch repair (synthetic)	Patch-107 NP-96	Recurrence: Patch-9.3% NP-4.2% (p=NS)	C-LD
Long (2019)[60]	CDH neo	Patch repair (synthetic, biologic)	Synthetic (Goretex, PP, Polyester) n=34 Biologic (bovine or porcine collagen) n=19	Recurrence: Synthetic-12% Biologic-11% (p=NS)	C-LD
Heiwegen (2021)[61]	CDH neo (meta, SR of 25 studies)	Patch repair (1254)	No outcomes comparison by type of patch	Recurrence, SBO, chylothorax higher in patch repair	B-NR
*Aydin (2020)[62]	CDH neo	Non-primary repair (patch or muscle flap)	Synthetic P-n=34 Muscle flap-n=57	Recurrence: Synthetic-9% Muscle flap-3.5% (p=NS)	C-LD
*Dewberry (2019)[63]	CDH neo	Non-primary repair (patch or muscle flap)	Synthetic P-n=30 Muscle flap-n=40	Recurrence: Synthetic-10% Muscle flap-3% (p=NS)	C-LD
Kamal (2022)[64]	CDH (<16 y) Meta, SR of 47 studies	Patch repair	Synthetic (760) Biologic (226)	Recurrence rates: 16.7% synthetic vs. 30.3% biologic	B-NR
Nolan (2019)[65]	CDH neo, on-ECLS repairs	Patch repair (n=13)	Muscle-flap repair (n=16)	Seven patch (53.8%) and 9 flap (56.2%) patients survived to	C-LD

				discharge (p = 0.596). On-ECLS bleeding complications are the same for both flap and patch repair.	

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Table 11 – Evidence summary informing care recommendations regarding open vs. minimally-invasive repair

Author	Population	Intervention	Comparison	Outcome	Class of Evidence
Bawazir (2021)[66]	CDH neo (single center)	Repair	Thoracoscopic-n=11 Open-n=30	Recurrence: Thoracoscopic-9.1% Open-0% F/U period-not provided	C-LD
Vandewalle (2019)[67]	CDH neo (single center)	MIS (thoracoscopic) repair	Thoracoscopic 1^{o} repair-n=28 Thoracoscopic repair w biologic mesh underlay-n=15	Recurrence: 1^{o} repair-21.4% Repair with biologic mesh underlay-6.6% F/U $\geq$5y	C-LD
Okawada (2021)[68]	CDH neo (multicenter)	Repair	Open repair-n=467 Thoracoscopic repair-n=47	Recurrence: Open repair-3% Thoracoscopic repair-7% F/U period-not provided	B-NR
Elbarbary (2021)[69]	CDH neo and late presenters (single center)	MIS (thoracoscopic) case series *modified closure technique*	N=36 (No comparison group)	Recurrences 5 (16%) F/U mean 29m	C-LD
Kotb (2021)[70]	CDH neo (single center)	Thoracoscopic 1^{o} repair in selected patients (n=39)	No comparison group	5 conversions 2 recurrences (median F/U 12 months)	C-LD

Table 12: Evidence summary for updated recommendations regarding surgical repair on ECLS

Author	Population	Intervention	Comparison	Outcome	Class of Evidence
Stewart (2022)[71]	CDH Newborns who require ECMO (Columbia)	CDH repair on ECMO (n=54)	none	61% survival 70% complication rate (metabolic, mechanical, hemorrhage (22%)	C-LD
Gien (2022)[49]	Newborns (n=19) with severe CDH: O/E LHR<25%) (Denver)	CDH repair on ECMO (11/12 within 72h of cannulation	none	Survival 10/12 Bleeding complication 2/13 11/13 rectus abdominus flap	C-LD
Dao (2021)[72]	CDH NB who require ECMO (CDHSG registry (PS matched)	Repair on (early or late) or after ECMO	1) On vs After 2) Early vs late (on ECMO repair predominates in high volume centres	1) With non-repairs excluded, on ECMO repair assoc with lowest mortality. 2) Early and Mixed on ECMO repair survival superior late on ECMO repair. No difference if non-repairs excluded	B-NR
Glenn (2019)[73]	CDH NB who require ECMO (CDHSG)	Repair on ECMO within 72h (n-248)	Unrepaired at 72h (n=922)	Improved survival in early repair (87.1 vs 78.4%), but longer ECMO duration	B-NR
Steen (2019)[74]	CDH NB who require ECMO and undergo repair within 72h (Baylor)	Repair on ECMO within 24h (n=14) "super-early"	Repair on ECMO between 24-72h (n=19)	Improved survival (71.4 vs 59.7%) in super early group	B-NR

Delaplain (2019)[75]	CDH NB who require ECMO (ELSO). PS matched	Repair on ECMO	Repair off ECMO	3-fold increase in mortality; 1.5 fold increase in severe neurologic injury in on ECMO repair group	B-NR
Robertson (2018)[76]	CDH NB who require ECMO (Ann Arbor)	"Early" (≤5d) Repair on ECMO	"Late" (>5d) repair on ECMO	Early repair independent predictor of mortality and days on ECMO.	B-NR
Danzer (2018)[77]	CDH NB who require ECMO (CHOP)	Repaired on ECMO	No ECMO, repaired pre-ECMO, repaired post-ECMO	Repaired on ECMO group had poorer cognitive, motor (fine and gross) scores by Bayley Scales testing (22m)	B-NR

3 full-text articles were reviewed and excluded from analysis due to relevance.

Table 13: Evidence summary for the management of gastroesophageal reflux in CDH

Author	**Population**	**Intervention**	**Comparison**	**Outcome**	**Class of Evidence**
Montalva (2022)[78]	CDH neo	Preventive Fundoplication	No fundoplication during CDH repair	Preventive fundoplication not recommended	B-NR
Zanini (2018)[79]	All CDH	pH-metry study at age 1 in CDH patients	pH-metry study at age 1 in EA patients and children without congenital anomalies but GERD sx	Routine assessment for GERD should be performed regardless of sx	B-NR

6 full-text articles were reviewed and excluded as they did not contain the primary outcome measure of interest.

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Table 14: Evidence summary for long-term follow-up in CDH

Author	Population	Intervention	Comparison	Outcome	Class of Evidence
Henzler (2017)[80]	Prospective CDH 2-year olds (n=29)	Assessment of cerebral blood flow by pulsed arterial spin labeling (pASL) MRI and angiography following ECMO with RCCA cannulation	non-ECMO CDH patients	14 patients had RCCA occlusion 4/14 had >20% reduction in right hemisphere perfusion Collateral circulation restored perfusion to the right hemisphere in RCCA occluded circulation. No focal lesions	B-NR
Wong (2018)[81]	Retrospective study of CDH patients (n=160)	Assessing the use of tube feed supplementation in CDH patients		20% of patients required tube feeds at discharge 5 patients (4%) started TF after discharge due to FTT Need for TF correlated with patch repair, ECMO, prolonged ICU stay, initial arterial pH < 7.25, ventilator days and days to first feed In LTFU, 50% discontinued TF by 3 years	C-LD
Bojanic (2017)[82]	CDH neo (n=38)	Retrospective study of CDH infants treated with ECMO	CDH infants treated without ECMO	8/38 infants required ECMO 30/38 patients survived including 6/8 ECMO patients	B-NR

				who had more chronic lung, GI/nutrition and neurodevelopmental problems at follow-up	
Haliburton (2017)[83]	CDH neo (n=33)	Retrospective single-center review of CDH infants who underwent indirect calorimetry and PFTs		Sampled patients had elevated pREE and negative FEV1, FVC z-scores; they also had lower BMI z-scores that correlated with their lower FEV1 and FVC z-scores but not their FEV1/FVC z-scores of pREE	C-LD
Koh (2021)[84]	CDH infants at 5 y old (n=28)	Assessment of lung function by PFT and CT chest (TLV)		1/3 of CDH patients had lung dysfunction correlating with smaller morphometric markers at birth (HC and abdominal circumference) than those with normal lung function (2/3). CT chest volumetric studies did not correlate with standard CDH severity categories other than longer ventilation days for TLV <50% and correlated with PFT results showing "lung dysfunction'.	C-LD
Ramaraj (2021)[85]	CDH neo (n=69)	Assessment of aspiration with oral feeding		8 patients had documented aspiration with feeds while inpatients and 17 as	C-LD

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				outpatients using VFSS, requiring interventions including altering consistency, feeding volume or tube feeds. Aspiration did not correlate with severity of CDH.	
Moawd (2020)[86]	CDH children (n=40)	Single-center RCT for respiratory muscle training exercises and impact on respiratory function, exercise capacity, functional performance and QoL	No training exercises (incentive spirometer only)	Training group compared to control group performed better on standard PFT's over time. Study group also had higher QoL scores and higher exercise capacity/functional performance scores**.**	B-R
Antiel (2017)[87]	CDH survivors (n=84)	CDH survivors assessed at age 12 months with BSID-III and growth trajectory		51% scored 1 SD below mean in at least 1 domain (cognitive, language, motor) and growth (weight, length, HC z-scores) grouped as "high" or low" trajectory cohorts. Correlation between HC z-scores with motor scores- "high" cohort score higher on motor testing than "low" cohort. Lower motor scores correlated with longer LOS, length of ventilation and d/c on tube feeds.	C-LD

Wong (2019)[88]	CDH infants (n=42)	Assessment of pulmonary hypertension and lung perfusion defects in patients assessed up to age 5		PH in this cohort generally improved as indicated by serial echo assessments but lung perfusion bias did not "normalize".	C-LD
Terui (2021)[89]	CDH neo (n=109)	Multi-centre retrospective study (Japanese CDHSG) assessing weight gain velocity	Severe vs. non-severe cohorts	WGV negative in early infancy (age 1-3 months for all CDH infants but worse in severe (Terui's risk stratification) compared to non-severe group. Both groups were slow to gain weight but non-severe patients with also more affected. Patients on home O2 also had lower WGV.	B-NR
Schwab (2021)[90]	CDH neo (n=101)	Retrospective study of gastrostomy tube use (n=38)		GT use correlated with severe CDH such as lower APGAR, patch repair, longer LOS and ventilation days, delayed oral feeding. GT's generally removed (median age 26 mo) with some drop of weight post removal.	C-LD
Leeuwen (2017)[91]	CDH survivors (n=172)	Single-centre prospective study to assess growth up to age 12 years	ECMO (n=43) vs. non-ECMO (n=129)	1/3 had documented GERD and 12% were symptomatic requiring Nissen. All CDH patients exhibited lower weight-for-height metrics but ECMO patients were lowest, this gap	B-NR

				narrows from age 8-12 years for ECMO patients. All growth metrics negatively correlated with ECMO support, LOS, patch repair, tube feeding and fortification requirement, especially at early age points. Increased nutritional and growth monitoring with dietary consultation and interventions required in LTFU.	
Bevilacqua (2017)[92]	CDH neo (n=49)	Single-centre retrospective study to determine if total ventilatory time (VT) for non-ECMO treated patients affect neurodevelopmental outcomes		BSID-III scores correlated negatively with length of VT in all 3 domains (language, motor, cognitive) with ROC curve showing VT predictive of delay in motor and cognitive scales. The VT "cut off" for delay outcomes was 9 days.	C-LD
Danzer (2017)[93]	CDH infants (n=35)	Single centre retrospective review of CDH patients tested at 5 years for cognition, visual/motor, academic and behavioural scores	Non-CDH infant controls	More CDH patients scored borderline or extremely low in at least 1 domain compared to controls despite the cohort mean scores being in the normal/expected range for cognitive tests. CDH patients had significantly lower visual/motor	C-LD

				testing and behavioral scores; also higher incidence of autism among CDH patients than population incidence. Worse cognitive outcomes at age 5 correlated with more severe physiology (longer LOS, prolonged intubation, PH, hearing impairment, developmental delays and autism identified in early infancy.	
Gunn-Charlton (2019)[94]	CDH survivors (n=83)	Retrospective review of the use of MRI neuroimaging with ND assessments in CDH survivors		83 patients had ND assessments at age 2 y (n=48), 5 y n=32) and 8 y (n=29) but only 65 had MRI's while 119 had head US. Low ND < 1SD associated with severe CDH and abN head US correlated with lower motor and cognitive scores. No correlation between working memory testing and US imaging abN. MRI documented changes in white matter and myelination changes correlated with lower motor, language scores at age 2 y. No imaging findings correlated	C-LD

				with ND outcomes at age 5 and 8 y-correlated with clinical risk factors.	
Van der Veeken (2021)[95]	CDH neo	Meta-analysis of neurodevelopmental outcomes for CDH		4 studies met inclusion criteria. ND delay identified in 16% (3-34%)-motor 13%, cognitive 5%, hearing loss 3%. ND delay lower in isolated CDH compared to CDH patients with other diagnoses.	B-BR
Aydin (2019)[96]	CDH survivors (n=98)	Retrospective study of MSK morbidity among left-sided CDH survivors		MSK changes present in all risk categories (defect size, prenatal risk stratification) and repair group (primary repair, patch repair, muscle flap repair) but patch/muscle flap repair had highest rate of MSK change for scoliosis and scoliosis + pectus excavatum respectively. Delayed closure of laparotomy incision also associated with MSK defects.	C-LD
Burgos (2017)[97]	CDH late deaths (n=251)	Retrospective single-centre study of "late deaths"		Overall and in total-49 (20%) deaths. Deaths before d/c (36, 14%) vs. 13 (5%) after d/c differed in the cause of death- "early" mortality from cardiorespiratory causes but "late"	C-LD

				(age > 1year, n=7) due to GI complications (n=3) or progression of cardiopulmonary morbidity (n=4). Recurrent CDH was a common finding among late mortality patients (3/7) but recurrence or GI deaths did not correlate with CDH severity but were affected by developmental issues and more likely to have other congenital anomalies.	

*11 papers were excluded due to lack of relevance relating to CDH and LFTU. 4 studies were excluded at the discretion of the steering committee due to relevance. 1 paper was excluded as it was a review paper.

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Table 15: Evidence summary regarding pain, analgesia and neuromuscular blockade management in CDH

Author	Population	Intervention	Comparison	Outcome	Class of Evidence
Weems (2023)[98]	1063 infants with CDH from CHNC registry	Descriptions of opiod, sedative and NM paralytic agent use (no doses or durations)	3 groups: All patients (1063) ECMO (315) No ECMO (748) Subgroups: pre and post repair	Survival, need for ECMO Inter-center variability for duration of use of opioid, benzo, paralytic	B-NR
Abiramalatha (2019)[99]	Neonates requiring 24-48h of mechanical ventilation	Open label RCT wih fentanyl as CI vs IB	100 neonates (53 CI, 47 IB)	Pharmacokinetics (peaks and troughs) more favorable with CI. Pain scores, adverse events comparable	B-R
Ancora (2019)[100]	Term, preterm infants requiring mechanical ventilation. Evidence review 1986-2017) GRADE				B-NR
Ohlsson (2016)[101]	Use of paracetamol in newborns undergoing painful procedures or as part of postop analgesia	9 trials w low risk of bias (728 infants)	Treatment/outcomes varied widely between groups	For postoperative care following major surgery, total opioid dose administered over 48h less in paracetamol group	B-NR
Baarslag (2018)[102]	Infants undergoing non-cardiac major surgery	Implementation cohort of postoperative paracetamol (n=75) based on findings of previous RCT PMID 23299606	No comparison group	Opioid sparing effect noted (similar to previous RCT) with lower pain scores vs RCT cohort	C-LD

Grabski (2022)[103]	Infants undergoing CDH repair	Multi-modal intervention targeting reduced opioid use post-CDH repair 1.IV acetaminophen 2.Education 3.Standardized pain handover	3 groups: pre (n=18), peri (n=6), post (n=21) intervention	Main outcomes (intervention cohort): -Significantly reduced total opioid use -equivalent pain/sedation scores -reduced postop intubation duration	B-NR

*One article (McPherson et al) was excluded as it was a review article ineligible for data abstraction. 2 articles were excluded due to relevance.

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CDH Guidelines Update Supplementary Material - Search Strategy

For ease of use, the following updates are shown once. All search updates were run from January 1, 2017 to August 30, 2022. Specific updates were run on May 22, 2020 June 17, 2021 and August 30, 2022. For the full original numbers, please contact the author.

Cochrane [Wiley] (August 30, 2022)

#1	((congenital* and hernia*) and (diaphragm* or repair* or defect*)):ti,ab,kw	272
#2	((congenital* or neonat* or neo-nat* or newborn* or new-born* or birth* or maternal* or fetal or fetus* or fetu or feto or foet* or prenatal* or pre-natal* or antenatal* or ante-natal* or trimester* or pregnan* or uter* or preterm* or pre-term* or premature* or pre-mature* or preemie*) NEAR/5 diaphragm* NEAR/5 (hernia* or defect*)):ti,ab,kw	229
#3	((bochdalek* or morgagni*)):ti,ab,kw	8
#4	((agene*) AND (hernia* or hemidiaphragm* or diaphragm*)):ti,ab,kw	3
#5	#1 OR #2 OR #4 OR #4	278
#6	#1 OR #2 OR #4 OR #4 *with Cochrane Library publication date from January 2017 to Sep 2022*	31

Embase [Ovid] (August 30, 2022)

Embase Classic+Embase 1947 to 2022 August 29

1	congenital diaphragm hernia/	6979
2	diaphragm hernia/ or bochdalek hernia/ or diaphragm eventration/ or hiatus hernia/ or traumatic diaphragmatic hernia/	27883
3	exp congenital disorder/	1690056
4	newborn intensive care/	27170
5	neonatal intensive care unit/	18019
6	exp prenatal diagnosis/	122716
7	exp pregnancy complication/	174876
8	exp child/	3339660
9	(infan* or child* or adolesc* or paediatr* or pediatr* or baby* or babies* or toddler* or kid or kids or boy* or girl* or nicu or preterm* or pre-term* or premature* or pre-mature* or preemie*).tw,kf.	3473192
10	2 and (or/3-9)	8947
11	(agene* adj2 (hemidiaphragm* or diaphragm* or ((unilat* or hern*) adj1 diaphragm*))).tw,kf.	125
12	((bochdalek* or morgagni*) adj2 (hernia* or defect*)).tw,kf.	1754
13	((congenital* or neonat* or neo-nat* or newborn* or new-born* or birth* or maternal* or fetal or fetus* or fetu or feto or foet* or prenatal* or pre-natal* or antenatal* or ante-natal* or trimester* or pregnan* or uter* or preterm* or pre-term* or premature* or pre-mature* or preemie*) adj5 (posterolateral* or substernal*) adj2 hernia*).tw,kf.	109
14	((congenital* or neonat* or neo-nat* or newborn* or new-born* or birth* or maternal* or fetal or fetus* or fetu or feto or foet* or prenatal* or pre-natal* or antenatal* or ante-natal* or trimester* or pregnan* or uter* or preterm* or pre-term* or premature* or pre-mature* or preemie*) adj2 diaphragm* adj2 (hernia* or defect*)).tw,kf.	7414
15	(congenital* and hernia* and diaphragm*).tw,kf.	8482
16	(or/2-8) and (hernia* and diaphragm*).tw,kf.	14236
17	1 or (or/10-16)	21805
18	limit 17 to yr="2017 -Current"	1569

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19	(exp animal/ or exp juvenile animal/ or adult animal/ or animal cell/ or animal experiment/ or animal model/ or animal tissue/ or nonhuman/) not human/	7933232
20	((animal or animals or canine* or cat or cats or dog or dogs or feline or hamster* or lamb or lambs or mice or monkey or monkeys or mouse or murine or pig or pigs or piglet* or porcine or primate* or rabbit* or rats or rat or rodent* or sheep* or veterinar*) not (human* or patient*)).ti,kf,jx.	3087095
21	18 not (19 or 20)	1478
22	remove duplicates from 21	1469
23	limit 22 to (conference abstract or conference paper or "conference review")	316
24	22 not 23	1153

Medline [Ovid] (August 30, 2022)

Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily <1946 to August 29, 2022>

1	Hernias, Diaphragmatic, Congenital/	5346
2	Hernia, Diaphragmatic/	11621
3	limit 2 to yr="2010 - 2014"	1063
4	hernia, diaphragmatic/ or hernia, diaphragmatic, traumatic/ or hernia, hiatal/	17046
5	exp "congenital, hereditary, and neonatal diseases and abnormalities"/ or exp congenital abnormalities/	1334598
6	Intensive Care, Neonatal/ or Intensive Care Units, Neonatal/	22231
7	exp Prenatal Diagnosis/	79719
8	exp Pregnancy Complications/	463429
9	exp child/ or exp infant/	2706885
10	(infan* or child* or adolesc* or paediatr* or pediatr* or baby* or babies* or toddler* or kid or kids or boy* or girl* or nicu or preterm* or pre-term* or premature* or pre-mature* or preemie*).tw,kf.	2569376
11	4 and (or/5-10)	6405
12	(agene* adj2 (hemidiaphragm* or diaphragm* or ((unilat* or hern*) adj1 diaphragm*))).tw,kf. [((agenesis or ageneses) adj2 (hemidiaphragm* or hemi-diaphragm or (unilateral adj1 diaphragm*))).tw,kf.]	86
13	((bochdalek* or morgagni*) adj2 (hernia* or defect*)).tw,kf.	1333
14	((congenital* or neonat* or neo-nat* or newborn* or new-born* or birth* or maternal* or fetal or fetus* or fetu or feto or foet* or prenatal* or pre-natal* or antenatal* or ante-natal* or trimester* or pregnan* or uter* or preterm* or pre-term* or premature* or pre-mature* or preemie*) adj5 (posterolateral* or substernal*) adj2 hernia*).tw,kf.	78
15	((congenital* or neonat* or neo-nat* or newborn* or new-born* or birth* or maternal* or fetal or fetus* or fetu or feto or foet* or prenatal* or pre-natal* or antenatal* or ante-natal* or trimester* or pregnan* or uter* or preterm* or pre-term* or premature* or pre-mature* or preemie*) adj2 diaphragm* adj2 (hernia* or defect*)).tw,kf.	5717
16	(congenital* and hernia* and diaphragm*).tw,kf.	6272
17	(or/5-9) and (hernia* and diaphragm*).tw,kf.	7177
18	1 or 3 or (or/11-17)	11010
19	limit 18 to yr="2017 -Current"	706
20	(Animals/ or Models, Animal/ or Disease Models, Animal/) not ((Animals/ or Models, Animal/ or Disease Models, Animal/) and Humans/)	5007892
21	((animal or animals or canine* or cat or cats or dog or dogs or feline or hamster* or lamb or lambs or mice or monkey or monkeys or mouse or murine or pig or pigs or piglet* or	2533086

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	porcine or primate* or rabbit* or rats or rat or rodent* or sheep* or veterinar*) not (human* or patient*)).ti,kf,jw.	
22	19 not (20 or 21)	662
23	remove duplicates from 22	657

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