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

Puligandla P, *et al. Arch Dis Child Fetal Neonatal Ed* 2024; 109:239–252. doi: 10.1136/archdischild-2023-325865

				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

		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

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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

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				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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