Appendix 1 (as supplied by the authors):
The Canadian Congenital Diaphragmatic Hernia Collaborative
Evidence and Consensus-Based National Clinical Management Guideline

The Canadian CDH Collaborative

Short Title: Canadian CDH Collaborative Guidelines

Key Words: congenital diaphragmatic hernia, consensus guidelines, evidence review, management

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I. Introduction

Congenital diaphragmatic hernia (CDH), which has a birth prevalence of approximately 1 per 3,300 live births (1), is a congenital defect in the diaphragm which allows herniation of abdominal viscera into the thorax. The resulting abnormal lung development causes pulmonary hypoplasia and persistent pulmonary hypertension of varying severity, which are the primary determinants of post-natal morbidity and mortality. Within the last 3 decades, mortality from CDH has decreased from 50% to approximately 20% due to improvements in neonatal care, however these rates have remained unchanged for the past decade (2). Moreover, it has become evident that improvements in survival have been offset by the substantial disability burden experienced by survivors of severe neonatal disease. Indeed, contemporary, long-term follow-up studies have demonstrated that CDH patients and their families experience morbidity burdens comparable to other chronic diseases, and include poor growth and pulmonary health as well as neuromotor and cognitive disabilities that extend across the lifespan into adulthood (3). In addition to the quality of life impact on CDH children and their families, the financial costs of caring for CDH, during the birth hospitalization and in the long term are significant. A 2006 Canadian study estimated national health care costs (for the birth hospitalization only) for CDH infants at $10 million annually (3). These figures grossly underestimate the overall cost burden associated with CDH because they do not address the long term direct costs associated with long term inpatient and outpatient care, nor the indirect societal costs associated with lost productivity of families caring for a disabled child with CDH, who becomes an adult with economically limiting disabilities.

Another defining attribute of CDH is its requirement for integrated multidisciplinary care across three distinct phases (a) prenatal, (b) perinatal/postnatal and (c) childhood/adolescent morbidity

surveillance and treatment. Each phase of care is resource-intensive and requires health service delivery from a variety of subspecialties (maternal-fetal medicine, neonatal and pediatric intensive care, pulmonology, general pediatrics, cardiology, surgery, and anesthesia) as well as nursing, respiratory therapy, physio/occupational therapy and other allied health services. The complex interplay of roles between specialists and the lack of evidence informing "best practices" across the various phases of care leads to significant practice and outcome variation within and between children's hospitals in Canada (4). This *unwanted* variation in clinical care contributes to suboptimal outcomes and inefficiencies in healthcare resource utilization. The need to improve care and outcomes for CDH in Canada, and lend sustainability to our healthcare system through efficient use of resources, was the major impetus for this collaborative, multidisciplinary goal to standardize care for CDH in Canada. This project engaged representation from all clinical disciplines that participate in CDH care, as well as stakeholders, policy makers and families. The AGREE-II guidelines development framework was utilized to create best practice recommendations for CDH across the health service continuum, from prenatal diagnosis to long term follow-up.

II. Scope and Purpose

Our overall objective was to provide guidance on the optimal health care and health surveillance for CDH patients from the time of prenatal diagnosis, during the birth hospitalization, and throughout childhood. The guideline addresses the following specific questions :

1. What are the preferred methods of antenatal diagnosis, and with what prognostic criteria should antenatal counselling be conducted?

2. What is the current role for fetal intervention for antenatally diagnosed CDH?

3. At what gestation and by what route should CDH infants be delivered?

4. What precautions should be taken for women with CDH pregnancies at risk for premature delivery?

5. When should mechanical ventilation be instituted after an antenatally diagnosed CDH is delivered?

6. What is the role of pharmacologic sedation and paralysis after delivery?

7. What ventilation parameters and blood gas targets should be used to guide cardiopulmonary stabilization?

8. What ventilatory "rescue therapies" should be used when conventional ventilation fails to achieve desired targets?

9. What is the role of surfactant therapy in CDH?

10. What physiologic monitoring, fluid therapy and medications should be used for the optimization of hemodynamic status?

11. When should echocardiography be performed and what functional indices should be trended?

12. What pharmacologic therapies targeting pulmonary hypertension should be used in CDH?

13. What is the therapeutic role of extracorporeal life support (ECLS) in CDH?

14. If ECLS is required, when should surgery be performed?

15. What criteria should be used to determine readiness for surgery?

16. What is the optimal material for patching large diaphragmatic defects not amenable to primary repair?

17. What is the role of minimally invasive surgery (MIS) in CDH treatment?

18. What is recommended for treatment of gastroesophageal reflux (GER) associated with CDH?

19. What are the recommendations for long term followup?

III. Target Population to whom guideline applies

This guideline is applicable to all antenatally diagnosed CDH pregnancies and to liveborn infants with or without an antenatal diagnosis. Infants not diagnosed within 4 weeks of birth are excluded.

IV. Recommendations and Discussion of Evidence

1. Prenatal Diagnosis, Risk Stratification and Optimal Delivery

- **1.1 Ultrasound measurement of Observed/Expected lung head ratio (O/E LHR) by the tracing method (5) should be used between 22 and 32 weeks of gestational age to predict the severity of pulmonary hypoplasia in isolated CDH. (Level of Evidence B-NR)**

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Discussion: Pulmonary hypoplasia is the main cause of morbidity and mortality in isolated congenital diaphragmatic hernia (CDH). The prediction of pulmonary hypoplasia aids in antenatal counselling of CDH pregnancies. The sonographic lung-head ratio (LHR) was first described by Metkus (6) and has been used to assess fetal lung volume using thresholds of 0.6, 1.0 or 1.4 to predict outcome (6-13). Comparison of three commonly used methods to measure LHR (longest perpendicular axis method, anteroposterior diameter method and trace method (5)) indicates that the manual tracing method is most accurate (14, 15). As such, the CCC

recommends the use of the tracing method for the calculation of LHR.

LHR should be measured between 22-32 weeks of gestational age since this range provides improved survival prediction metrics (16). Unlike LHR, multiple studies have demonstrated the utility of observed/expected (O/E) LHR measurements across a broad spectrum of gestational ages (18-38 weeks) (14, 17) and performs well in the prediction of survival in CDH patients (12, 16, 18-21).

1.2 In left-sided CDH, an Observed/Expected (O/E) Lung Head Ratio (LHR) <25% predicts poor outcome. (Level of Evidence B-NR).

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Discussion: Studies have demonstrated that an O/E LHR threshold of ≤25% is predictive of poor outcome (17, 22), and thus should be used as a prenatal counselling guidepost indicating severe pulmonary hypoplasia.

- **1.3 In right-sided CDH, an O/E LHR <45% may predict poor outcome (Level of Evidence B-NR)**

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Discussion: The validation of prenatal outcome predictors in right-sided CDH has been difficult. One study identified an O/E LHR <45% as an indicator of severe pulmonary hypoplasia (14). This finding was supported by a more recent study of 19 fetuses with right-sided CDH in which survival rates of 17% and 0% were observed with O/E LHR values ≤45% and ≤30%, respectively (23).

- **1.4 Fetal magnetic resonance imaging (MRI) should be used (where available) for the assessment of lung volume and liver herniation in moderate and severe CDH. (Level of Evidence B-NR)**

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Discussion: Current evidence has supported the role of fetal MRI for outcome prediction in CDH. The most commonly studied parameter, the O/E total fetal lung volume (TFLV), has performed well for survival prediction in CDH, with AUC's ranging from 0.786-0.89 in several studies (17, 21, 24-26). While fetal MRI may be performed at any time after 20 weeks gestational age, Coleman and Hagelstein found that the O/E TFLV performed better later in gestation (25, 27).

Comparisons of survival prediction between prenatal MRI and US have demonstrated conflicting results. For example, Alfaraj et al., in a retrospective study of 72 fetuses with CDH, identified better survival prediction with US-based O/E LHR when compared to O/E TFLV measured by MRI (17). To the contrary, Bebbington et al. found that survival prediction appeared better with MRI in a more recent study of 85 CDH fetuses (19). An additional advantage of antenatal MRI is the identification of liver herniation (LH). Ruano et al. showed that LH expressed as a percentage (%LH) or as the liver intra-thoracic ratio (LiTR) both performed well in predicting mortality (21). Moreover, when used in combination with MRI O/E TFLV, the predictive ability of %LH and the LiTR is slightly better (21, 28).

While there is conflicting data regarding the "best" investigation for CDH risk stratification and survival prediction, ultrasound assessment of O/E LHR is likely sufficient and accurate. MRI may have additional value where available, especially in those cases where US-based O/E LHR demonstrates moderate or severe CDH.

- **1.5 The antenatal evaluation of a fetus with CDH should include a fetal echocardiogram; chromosomal evaluation (through karyotyping, quantitative fluorescent polymerase chain reaction [QF-PCR] and/or microarray) should also be offered. (Level of Evidence B-NR*)**

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Discussion: Multiple studies have found that the presence of associated anomalies affects the prognosis of infants with CDH. A meta-analysis by Skari et al., (29) found a significant increase in mortality when major anomalies were present. These findings have been supported by more recent population-based data from Australia (30). Moreover, the recently developed CDH Study Group postnatal clinical prediction model, which includes the presence of cardiac and genetic anomalies (31), effectively discriminates between low, intermediate and high-risk CDH infants.

- **1.6 Infants with CDH <u>should not</u> be delivered electively before 38+0 weeks gestational age. (Level of Evidence B-NR)**

- **1.7 There is no evidence to support routine caesarean section. (Level of Evidence B-LD)**

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Discussion: Controversy exists regarding the optimal timing and mode of delivery in CDH. McIntire, et al., in a retrospective cohort study over 18 years found that neonatal morbidity (transient tachypnea, ventilator-treated respiratory distress, intubation in the delivery room, grade 1 and 2 intraventricular hemorrhage) was significantly increased at 34, 35, and 36 weeks compared to later births (32). Indeed, additional studies have now established that late pre-term delivery (34-36+6/7 weeks GA) in otherwise normal infants is associated with worse outcomes when compared to delivery at full term (>38+6/7 weeks) (33, 34). While a CAPSNet study (35) found that gestational age segregated categorically (<37 weeks, 37-38 weeks, >39 weeks) had no effect on mortality rates in CDH infants, Danzer et al. recently identified poorer neurodevelopmental outcomes in CDH survivors of preterm and near-term births compared to births >39 weeks (36). This same CAPSNet study also found that delivery mode (vaginal vs. caesarean section) had no effect on outcome, supporting an earlier CDH Study Group report

(37).

- **1.8 Women who are at risk of delivery prior to 37 weeks gestation and who have not previously had a course of antenatal steroids should receive a single course of antenatal steroids. (Level of Evidence B-R)**

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Discussion: Evidence for the use of antenatal corticosteroids in CDH is limited. An underpowered and prematurely terminated randomized trial from the CDH Study Group attempted to address this issue but failed to discern any benefit (38). As a result, the authors recommended that the established National Institutes of Health guidelines for the maternal administration of antenatal steroids for delivery <34 weeks be followed (39). Recently, in a multicentre randomized control trial involving 1427 neonates, Gyamfi-Bannerman et al. found that the administration of betamethasone to women at risk for late preterm delivery (<37 weeks GA) experienced significantly reduced rates of neonatal respiratory complications (transient tachypnea of the newborn, surfactant use, bronchopulmonary dysplasia) (40).

2. **Ventilation**

- **2.1 All newborns with CDH who require respiratory support should be intubated (for assisted ventilation) immediately after birth to avoid the risk of intestinal insufflation by bag-valve-mask ventilation. (Level of Evidence C-EO)**

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- **2.2 All newborns with CDH should have an oro- or nasogastric tube inserted at birth and left on low suction until after the hernia has been repaired. (Level of Evidence C-EC)**

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Discussion: The Neonatal Resuscitation Guidelines from the American Heart Association and the American Academy of Pediatrics (41) support the use of immediate endotracheal intubation for neonates with a known diagnosis of CDH, which also implies the strict avoidance of bag-valve-mask ventilation for these patients. Concomitantly, a naso- or orogastric tube should be inserted to reduce gaseous distension of herniated bowel.

- **2.3 Sedation should be provided to all mechanically ventilated newborns with CDH; deep sedation and neuromuscular blockade should be avoided. (Level of Evidence B-NR)**

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Discussion: Most mechanically ventilated infants benefit from sedation and this is particularly true in newborns at risk for pulmonary hypertension. As such, judicious sedation based on local institutional guidelines is recommended for newborns with CDH requiring mechanical ventilation. The routine use of deep sedation and muscle relaxation has been shown to impair respiratory function in newborns with CDH, resulting in higher (i.e. worse) oxygenation indices (42). Furthermore, a cohort study by Murthy et al. compared lung function studies in 15 CDH patients (including six who had undergone fetal tracheal occlusion) before, during and after neuromuscular blockade (43) and found lung compliance was further impaired following the use of neuromuscular blockade. Therefore, the depth of sedation should be carefully monitored and muscle relaxation avoided unless ventilation targets cannot be met.

- **2.4 Gentle intermittent mandatory ventilation (IMV) should be the initial mode of ventilation for all newborns with CDH requiring respiratory support (Level of Evidence B-R)**

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Discussion: Historically, newborns with congenital diaphragmatic hernia (CDH) were subjected to chemical and ventilator-induced alkalosis to control pulmonary hypertension (44). Mortality was high and long-term morbidity significant (45). In 1995, Wung, et al., reported improved results using permissive hypercapnia to reduce ventilator-induced lung injury in a cohort of newborns with CDH (46). This approach has been expanded to include less stringent oxygenation targets and has been labelled "gentle ventilation". Retrospective studies have consistently shown that gentle ventilation improves survival from 50% to 75-95% (47). Autopsy data support the theory that high peak airway pressures damage the lungs, and an association has been demonstrated between the degree of hypocarbia in the neonatal period and long-term cognitive dysfunction in survivors of CDH (3, 48).

- **2.5 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 breath onwards in all newborns with CDH. (Level of Evidence B-NR)**

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Discussion: A peak inspiratory pressure (PIP) above 28 cm H_2O is strongly associated with ventilator-induced lung injury and guidelines for newborn resuscitation support a PIP below 25 cm H_2O to reduce this (49). In general, newborns with CDH often require higher peak pressures (closer to 25 cm H_2O) and there is less room for error. The use of a T-piece or mechanical ventilator in the delivery room and during patient transport may help avoid inadvertent over-distension of the lungs.

- **2.6 An arterial pCO_2 between 45-60 mm Hg and a pH between 7.25-7.40 should be targeted in all newborns with CDH. (Level of Evidence B-NR)**

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Discussion: The concept of permissive hypercapnia was further validated by Boloker et al. in their report on 120 consecutive CDH infants using this strategy (50). Overall survival in this series was reported to be 76% and only 2 discharge survivors required oxygen. A subsequent systematic review further underscored the safety and favorable outcomes of this ventilator strategy in its analysis of several single-centre retrospective studies, each of which demonstrated surprisingly similar pCO_2 targets (47) consistent with the current CCC recommendations.

- **2.7 Supplemental oxygen should be titrated to a preductal oxygen saturation below 95% in newborns with CDH (Level B-EO).**

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Discussion: Pulmonary hypertension (PHTN) in CDH infants results from a reduction in the number of pulmonary arteries that are also abnormally thickened due to the proliferation of smooth muscle cells into the intra-acinar regions of the pulmonary arterioles. As a result, elevated pulmonary vascular resistance (PVR) leads to right-to-left shunting after birth, hypoxemia, and a pre- to post-ductal oxygen saturation gradient.

General guidelines for the resuscitation of newborns recommend beginning with room air and administering oxygen only when required (51). Because of the risk of pulmonary hypertension, an antenatal diagnosis of CDH may lead to the routine use of supplemental oxygen immediately after intubation. While hypoxia itself worsens pulmonary vasoconstriction thereby exacerbating hypoxemia (52), exposure to high oxygen concentrations does not reduce PVR and instead results in free-radical injury (53). Thus, more modest pre-ductal oxygen saturation targets (90-95%) are likely beneficial in the management of CDH infants with pulmonary hypertension. However, if the neonate is otherwise hemodynamically stable and without evidence of

significant pulmonary hypertension, an oxygen saturation of 80% may be acceptable, particularly in the first few hours of life (50). If supplemental oxygen is used at resuscitation, it should be rapidly titrated to a specific preductal oxygen saturation target thereafter (54).

- **2.8 The minimum acceptable preductal oxygen saturation in newborns with CDH is 85% in most cases, but lower values may be tolerated under certain conditions (Level of Evidence B-EO)**

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    Discussion: Ventilation of term newborns with CDH should target a preductal oxygen saturation of at least 85% when achievable. There is ongoing disagreement regarding tolerance of lower preductal saturation targets if clinical and laboratory measures of global perfusion and oxygen delivery are adequate, particularly during the first few hours after birth when the pulmonary vascular resistance is changing rapidly. Furthermore, there was strong consensus amongst the CCC that preductal oxygen saturations as low as 70% during the first two hours after delivery, and as low as 80% thereafter, could be accepted as long as there was strong clinical evidence that systemic perfusion and oxygen delivery were improving over time.

- **2.9 High frequency oscillatory ventilation (HFOV) or high frequency jet ventilation (HFJV) should be used as rescue therapy when the peak inspiratory pressure (PIP) required to control hypercapnia using IMV exceeds 25 cm H_2O. (Level of Evidence B-R)**

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    Discussion: Both high-frequency oscillatory ventilation (HFOV) and high-frequency jet ventilation (HFJV) have been used successfully in newborns with CDH (55, 56). These modes achieve efficient CO_2 removal despite very small tidal volumes, and use mean airway pressure to keep alveolar units open while avoiding damaging peak inspiratory pressures. There are

important differences between these two modes but no direct comparison between HFOV and HFJV has been performed in newborns with CDH; the choice of a high-frequency mode appears to be based on institutional experience and local expertise.

HFOV (with or without inhaled nitric oxide) has most commonly been used as a "rescue" mode of ventilation in CDH with some studies describing a reduced need for extracorporeal life support (ECLS) after its initiation (57, 58). While there are also multiple reports of improved outcome when high frequency ventilation has been added to a "bundle" of clinical care practices (59-67) it is difficult to discern the specific impact of HFOV in these series. Furthermore, the use of high-frequency modes, particularly HFJV for air leaks, is also equivocal (68).

The VICI trial was the first randomized control study comparing conventional mechanical ventilation (CMV) and HFOV as the initial ventilation strategy in infants with CDH (69). While the study was terminated prematurely and did not reach the predicted sample sizes, several important observations were noted. First, no statistical difference in the combined incidence of mortality and bronchopulmonary dysplasia, the primary study outcome, was observed between groups. Second, infants managed with CMV had shorter durations of ventilation and inotropic support than those on HFOV. Finally, the use of ECLS was significantly less in the CMV group. Taken together, the authors supported the use of CMV over HFOV as the first-line ventilation strategy for infants with CDH.

- **2.10 Intra-operative ventilation should be guided by the same principles that determine ventilation before and after the procedure. (Level of Evidence C-EO)**

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Discussion: Regardless of surgical approach, the reduction of herniated contents is associated with decreases in cerebral oxygenation as measured by near-infrared spectroscopy (70-72).

While both HFOV and HFJV have been used successfully in the operating room during CDH repair, reductions in cerebral oxygenation are more profound and of longer duration with HFOV when compared to conventional ventilator modes (72). The impact of HFJV on cerebral oxygenation is unknown.

- **2.11 We recommend against the routine administration of exogenous surfactant in newborns with CDH. (Level of Evidence B-EC)**

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  Discussion: While it has been hypothesized that hypoplastic lungs from CDH produce less surfactant than normal lungs, the human evidence for this is mixed (73, 74). Observational data from the Congenital Diaphragmatic Hernia study group failed to show any benefit to the use of surfactant in both term and preterm infants with CDH (75, 76).

3. **Fundamentals of hemodynamic support**

- **3.1 In the context of poor perfusion (i.e. capillary refill >3 seconds, lactate >3mmol/L, urine output <1 mL/kg/h) and blood pressure below norms for age, initial treatment should include the judicious administration of crystalloids, generally not exceeding 20mL/kg and the administration of inotropic agents such as dopamine and/or epinephrine. If poor perfusion continues, assessment of cardiac function (i.e. echocardiogram, central venous saturation) should be performed. (Level of Evidence B-NR)**

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- **3.2 Hydrocortisone should be used to treat hypotension that responds inadequately to intravenous volume and vasopressor therapy. (Level of Evidence B-NR)**

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Discussion: In infants with CDH, hemodynamic compromise is frequently encountered. Ventricular dysfunction, reduced ventricular compliance and increased vascular resistance may contribute to reduced cardiac output. Hemodynamic stabilization minimizes right-to-left shunting and aids in the treatment of pulmonary hypertension. Continuous hemodynamic monitoring using central venous and arterial pressures as well as echocardiography, arterial and mixed venous saturation is essential. As the left ventricle has been reported to be smaller and less compliant in cases of CDH, excessive fluid administration may lead to pulmonary edema (77, 78). Therefore, judicious fluid resuscitation to normalize physiologic parameters is indicated since excessive increases in systemic blood pressure may reverse right-to-left shunting and worsen cardiac dysfunction. The most frequently used inotropic agents include dopamine, dobutamine, epinephrine and norepinephrine. No randomized control trial (RCT) has specifically compared the effects of these catecholaminergic agents in CDH. In a small cohort study, dopamine, epinephrine and norepinephrine were found to improve the macrocirculation without affecting the microcirculation (79). In another case series, milrinone reduced afterload to improve right and left ventricular dysfunction with some effect (80).

Hydrocortisone has been shown to be effective in increasing mean arterial pressure in critically ill term and preterm neonates (81). While evidence supporting the routine administration of hydrocortisone for all CDH patients is lacking, reports of low cortisol levels (82) as well as altered expression of corticotropin binding protein and its receptor in neonates with pulmonary hypertension (83) suggest a specific role for hydrocortisone in CDH infants with refractory hypotension.

4. Echocardiography

- **4.1 A minimum of two standardized echocardiograms, one in the early (<48h) postnatal period and one at 2-3 weeks of life, is needed to assess pulmonary vascular resistance as well as left ventricular (LV) and right ventricular (RV) function. Additional studies may be conducted as clinically indicated (e.g. pre-surgery or pre-discharge). (Level of Evidence C-LD)**

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Discussion: There was consensus amongst CCC participants that a complete echocardiogram (structural and functional) be performed within the first 48 hours of life. However, there was neither evidence nor group consensus on the need for routine echocardiography prior to planned surgical repair in the absence of a specific clinical indication (e.g. suspicion of a closing ductus arteriosus as the explanation for a resolving pre- to post-ductal oximetry gradient). Given that the persistence of pulmonary hypertension beyond 14 days (IQR 8, 21 days) in CDH infants predicts death, the need for ECMO, as well as the number of ventilator days, repeat echocardiography at this time is considered clinically important (84, 85). Moreover, standardized echocardiographic assessment of pulmonary hypertension, right and left ventricular function and performance as well as pulmonary artery size are important for the evaluation of treatment response as well as prognostication (84-96). Additional echocardiograms may be indicated in the following situations: (a) to assess clinical deterioration; (b) if the clinical trajectory of the patient failed to follow a reasonable timeline of recovery; and (c) when pulmonary hypertension required prolonged therapy with pulmonary hypertension targeted medications after discharge.

5. **Use of Prostaglandin E_1 to re-open or maintain patency of the ductus arteriosus in CDH infants**

- **5.1 PGE_1 infusions should be used if pulmonary or systemic blood flow is dependent on patency of the ductus arteriosus, or in the presence of a concomitant anatomical cardiac lesion, until a management plan for the cardiac lesion is made. (Level of Evidence B-NR)**

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- **5.2 PGE_1 infusions may be useful to maintain ductus arteriosus patency in patients with CDH in the presence of suprasystemic right ventricular pressures, right ventricular failure, or if right to left ductal shunting exceeds left to right shunting. (Level of Evidence C-LD)**

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- **5.3 PGE_1 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. (Level of Evidence C-EO)**

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Discussion: There is a strong physiological rationale and widespread use of PGE_1 to maintain ductal patency in infants with congenital heart disease and duct-dependent systemic or pulmonary circulations (97-100). There are at least 10 reports detailing the use of PGE_1 in more than 50 neonates with CDH (93-96, 101-106). Preoperative continuous right-to-left or bidirectional ductal shunting in patients with CDH may predict a subgroup with a high mortality (95). There is good rationale to delay surgical intervention until the shunt is predominantly left to right and/or other signs of pulmonary hypertension and right ventricular failure (tricuspid valve regurgitation, septal position, right to left shunt at atrial level) have resolved (106).

Inamura, et al. suggested that CDH infants treated with PGE_1 had an improvement in left ventricular indices at day two when compared with infants who did not receive or did not require PGE_1 therapy according to their local treatment protocol (93, 94). However, comparisons of iNO and PGE_1 in neonates with CDH suggested that the group treated with iNO reached local criteria for surgical repair sooner than those receiving PGE_1 treatment (96).

While PGE_1 has been used to open a closed or restrictive ductus arteriosus in CDH infants with right heart failure or clinical deterioration, the initiation of PGE_1 to maintain a patent ductus arteriosus is less clear. Decisions should be guided by the clinical condition of the patient, particularly if there is echocardiographic evidence of constriction in the presence of a right-to-left or bidirectional shunt in an unstable patient or in whom right ventricular function has yet to recover.

The effect of PGE_1 on ductal endothelium may interfere with its ability to close completely, and thus echocardiographic surveillance to confirm ductus closure following any therapeutic use of PGE_1 seems intuitive (107, 108). A widely patent ductus arteriosus will maintain systolic pulmonary artery pressures at systemic levels and delay or prevent pulmonary vascular remodelling with the added hemodynamic burden of a left-to-right shunt. Continued left-to-right shunt through an unrestrictive ducts arteriosus leads to high output cardiac failure, pulmonary edema, prolonged ventilator requirement, resting tachypnea and failure to thrive. Failure of ductal closure in the context of symptomatic left-to-right shunt should be dealt with by surgical ligation, especially if the infant is more than 2-3 months of age since spontaneous closure is unlikely after this age.

6. **Use of "Targeted" pulmonary vasodilators (iNO, milrinone, sildenafil, prostanoids, bosentan)**

- **6.1 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. (Level of Evidence C-EO)**

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- **6.2 Milrinone should be used to treat cardiac dysfunction, particularly if it is associated with pulmonary hypertension. (Level of Evidence B-NR)**

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- **6.3 The use of sildenafil may be considered in patients with refractory pulmonary hypertension (i.e. unresponsive to iNO) or as an adjunct when weaning iNO. (Level of Evidence B-R).**

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Discussion:

Inhaled nitric oxide significantly improves the oxygenation index, increases the PaO_2 and reduces the need for ECMO in non-CDH populations with pulmonary hypertension (109-111). However, a Cochrane review of the 2 largest randomized controlled studies where the CDH sub-group could be examined showed statistically insignificant improvement in PaO_2 and oxygenation index, as well as an increased need for ECMO in those patients treated with iNO (112).

Milrinone may synergistically enhance pulmonary vasodilation in infants that are unresponsive to iNO (113). Milrinone may also improve the oxygenation index by reducing systemic vascular resistance and improving left ventricular function. Only one case series has assessed the use of milrinone in CDH, noting improvement in the oxygenation index without impacting systemic blood pressure (80). In non-CDH neonates with pulmonary hypertension, McNamara et al. reported a transient decrease in blood pressure with milrinone use (114). A Cochrane review that only included two case series could not establish the efficacy or safety of milrinone in the treatment of persistent pulmonary hypertension on the newborn (115).

Two retrospective case series in CDH patients, one using an oral formulation of sildenafil (116) and the other an intravenous preparation (117), demonstrated an improvement in oxygenation. A systematic review, including five randomized controlled trials of oral sildenafil in patients with persistent pulmonary hypertension of the newborn or premature infants with BPD in a resource limited setting where iNO was not available demonstrated an improved oxygenation index and reduced mortality in the sildenafil group. However, these results could not be extrapolated to areas where iNO and high-frequency ventilation were available (118). Additional trials assessing the dosing, safety, and efficacy of sildenafil are needed to further elucidate its benefit in CDH. Other vasodilators have been proposed for the treatment of persistent pulmonary hypertension but there is insufficient clinical evidence to support their routine use. Experience with prostanoids such as epoprostenol (119) and treprostinil (120) have only been reported in case reports or small case series. Bosentan, an endothelin-1 (ET-1) antagonist acting on ET-A and ET-B receptors, has been used in adults and children with pulmonary hypertension (121, 122). While studies in neonates with persistent pulmonary hypertension are scarce, ET-1 plasma levels were found to be higher in CDH non-survivors suggesting a role of ET-1 in the pathobiology of

CDH (92). In a small randomized controlled study, bosentan was shown to improve oxygenation index in patients with pulmonary hypertension (123). However, when used as adjunct therapy, bosentan failed to demonstrate any additive effect (124).

7. **Role of Extracorporeal Life Support (ECLS) in CDH**

- **7.1 The possibility of extracorporeal life support (ECLS) should be discussed during prenatal counselling for CDH. This discussion should disclose the fact that the available evidence does not suggest a short or long term survival benefit to ECLS use (Level of Evidence B-R)**

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- **7.2 In circumstances where ECLS is used as a rescue therapy in CDH, the usual contraindications to its use should apply, including irreversible lung disease. (Level of evidence C-EO)**

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Discussion: The specific role of ECLS in CDH remains unclear despite its mortality benefit for most types of severe neonatal respiratory failure (125). However, ECLS continues to be used in CDH with approximately 300 cases occurring per year in North America since the 1990's (126). While Morini et al. (127) concluded that ECLS provided some short-term but minimal long-term mortality benefit in CDH in their systematic review, these results should be interpreted with caution. The retrospective data analyzed in this report was confounded by the wide timespan of included studies, inconsistent criteria for ECLS deployment as well as variable CDH management strategies involving ventilator care (i.e. aggressive hyperventilation vs. "gentle ventilation") and pulmonary vasodilator therapy (i.e. inhaled nitric oxide). Furthermore, it is difficult to draw any firm conclusions from the meta-analysis of the prospectively collected data

in this study due to the small numbers of patients involved (n=39; mortality in ECLS 13/20 vs. conventional mechanical ventilation 17/19; 95%CI 0.54-0.98). Finally, the recently published VICI trial also failed to demonstrate any difference in CDH outcome between ECLS and non-ECLS centres, further questioning its true role in CDH (69).

In contemplating their recommendations, the CCC also took into consideration current ECLS practice patterns in Canada. Only 38 infants (6.7%) within the CAPSNet registry, across five centres, were treated with ECLS between 2005-2015. Despite the infrequent use of ECLS, the overall survival of liveborn CDH infants across Canada is comparable to other published reports (128-130). Thus, the exact role of ECLS in CDH remains to be defined. It should be discussed during prenatal counselling and may be considered as a therapeutic option in those centres that offer it.

8. Surgical "Readiness" Criteria

- **8.1 The following criteria should be met prior to surgery: urine output >1 mL/kg/hr, FiO2<0.5, preductal oxygen saturation between 85-95%, normal mean arterial pressure for GA, Lactate <3 mmol/L, and estimated pulmonary artery pressures less than systemic (Level of Evidence C-LD)**

  ★★☆☆

- **8.2 A recommendation for optimal timing of surgery cannot be made based on current evidence (Level of Evidence B-R)**

  ★★★★

- **8.3 All treatment options, including surgery or palliation, should be reconsidered if a patient fails to meet surgical readiness criteria after two weeks (Level of Evidence C-LD).**

  ★★★★

Discussion: The evidence behind the move from early, emergent surgery to delayed repair in the early 1990s consisted of multiple small cohort studies that used historical controls to demonstrate improved survival with delayed repair (131, 132). The broader acceptance of "gentle ventilation" strategies that occurred concurrently with the strategy of delayed surgery likely contributed to the observed improved outcome. However, additional studies, including two randomized controlled trials, failed to demonstrate an advantage to either early or late surgery (133, 134). For this reason, the CCC does not recommend a strategy of either early or late surgery. This is in keeping with the recommendations of the American Pediatric Surgical Association published in 2015 (135). Counter to current common practice, one center in Florida has documented good survival with a strategy of early surgery for "high risk" patients, while delaying surgery for "low risk" patients (136). This approach is in need of further study and thus cannot be widely endorsed at this time.

There is also very little evidence to support any specific set of preoperative "readiness" criteria. Practices have become more liberal over the years, accepting higher oxygen requirements and less ideal physiologic parameters at the time of surgery (60, 67, 137). Our recommendations are in keeping with published protocols associated with improved outcome, particularly when compared to historical care strategies, as well as those recently updated by the CDH EUROConsortium (78, 138). Importantly, the CCC has added the preoperative requirement of infra-systemic pulmonary arterial pressure. The addition of this criterion is based on its inclusion in several protocols with published effectiveness, as well as level C evidence demonstrating that the control of preoperative pulmonary hypertension may actually improve survival (59, 67, 86). The use of rigid preoperative readiness criteria should select those infants most likely to survive. However, failure to offer surgery for those who do not fulfill these criteria may ensure mortality

in a group where meaningful survival might be achievable. Indeed, early surgical repair of severe diaphragmatic defects may allow for improved pulmonary function in the highest risk patients (136). There have been several studies, including two Canadian population-based reports, which highlight the difficulty in reliably identifying the non-salvageable CDH patient (137, 139, 140). Based on this uncertainty, and the fact that non-repair leads to 100% mortality, consideration to pursue surgical repair should be given to patients who fail to meet operative criteria after medical stabilization has been attempted for 2 weeks. An equally important consideration at this time is the role of palliation, which should be based on interdisciplinary and parental input. Two weeks was chosen somewhat arbitrarily in an attempt to balance potential improvements in pulmonary hypertension with the risks of ongoing pulmonary injury associated with prolonged ventilation.

9. **Patch Repair**

- **9.1 For diaphragmatic defects not amenable to primary repair, oversized and tension-free polytetrafluoroethylene (PTFE)/Goretex™ patches should be used. (Level of Evidence C-LD)**

  ★★★★

- **9.2 Porcine small intestinal submucosal (SIS) patches alone should not be used for diaphragmatic patching (Level of Evidence C-LD)**

  ★★★☆

Discussion: There were no prospective or multicenter studies evaluating the use of patch repair in CDH. Nine were comparative cohort studies using either historical (prior to a change in practice) or concurrent controls, and one study was a case series of patients treated with a composite synthetic patch. Six of nine studies compared polytetrafluoroethylene (Teflon™ Dupont, Wilmington, DE; Gore-tex ™ WL Gore and Associates Inc, Newark, DE) with a variety

of synthetic and biomaterial patches, including porcine small intestinal submucosa (Oasis wound matrix™ Smith and Nephew, London, UK), and porcine dermal collagen (Permacol™, Medtronic, Minneapolis, MN). There was marked variability between reporting institutions with respect to overall recurrence rates (19 to 46%), duration of follow-up, the need for ECLS and survival. PTFE/Gore-tex™ patches accounted for 50% of all patches used, with a reported recurrence rate ranging from 5 to 40%.

The largest study from Grethel et al. (n=72) reported no difference in recurrence or rates of small bowel obstruction between patients who had either a Gore-tex™ or SIS patch (141). Jancelewicz et al. reported on 54 patients who received either Gore-tex™, SIS or composite SIS/Gore-tex™ patches (142). In this study, SIS patches had a significantly higher recurrence rate compared to the other groups, while the composite patch demonstrated a trend towards lower rates of recurrence. Another study compared recurrence rates of 37 patients requiring either Gore-tex™ (29) or Permacol™ (8) patches and demonstrated no recurrences amongst the Permacol™ group after 20 month follow-up (143). Two other studies compared a variety of synthetic and biologic patch materials, but demonstrated no difference in recurrence rates (144, 145). Two studies included autologous split abdominal wall muscle flaps. Barnhart et al. reported a significantly lower recurrence rate among patients treated with a muscle flap when compared to Gore-tex™ or unspecified biopatch repairs (146). Contrarily, a study by Nasr et al. involving 51 patients of whom 19 received a split muscle flap showed no difference in rates of recurrence, small bowel obstruction or development of chest wall deformity in comparison to other patch materials (147). A case series of 28 consecutive patients who received a composite prosthetic patch consisting of Gore-tex™ on the abdominal aspect and Marlex™ (CR Bard, Inc, Murray Hill, NJ) on the thoracic side demonstrated a low recurrence rate of 4% after a median 4-year follow-up (148). A

comparative cohort series (Gore-tex™ versus SIS patches), demonstrated a Gore-tex™ recurrence rate of 5% amongst 35 patients with a mean 9-year follow-up (149). Finally, a study by Loff et al. reported on the recurrence rates of Gore-tex™ repairs configured into three different states: "taut", "loose" or "cone" (150). Recurrence rates were lowest in the patients who had either a "loose" or "cone" repair.

The level of evidence from all studies considered was Level C, and was felt to be of fair to poor quality. Comparative cohorts were either convenience samples (reflecting preferences of individual surgeons) or retrospective, reflecting a temporal change in practice. Despite the poor level and quality of evidence, the CCC supported the use of PTFE/Goretex™ due to its widespread used. Although evidence is lacking, experience suggests that the use of SIS patches for large defects (i.e. diaphragm agenesis) provides insufficient autologous tissue ingrowth thereby leading to high observed rates of CDH recurrence.

10. Type of Repair

- **10.1 A minimally invasive surgical (MIS) approach/technique should not be used in the repair of neonatal CDH (Level of Evidence B-NR)**

★★★★

Discussion: Since the first case series in 2003 (151), multiple publications have illustrated the feasibility of repair using minimally invasive surgery (MIS) techniques, with purported advantages that include reduced perioperative pain, a decrease in resource utilization and a reduction in long-term complications. Disadvantages of the MIS approach include the potential for an increased recurrence rate as well as intra-operative physiologic derangements due to carbon dioxide insufflation.

Between 2003 and 2015, nine non-comparative case series were identified that included both neonates and older children whose diaphragmatic hernia was repaired via MIS techniques (151-159). Together, these reports consisted of retrospective single institution experiences totalling 479 patients (range: 7 patients (151, 159) to 311 (153)), 196 of which were repaired outside of the neonatal period. The overall conversion rate was 12.3% (n=59), which did not improve significantly over time; the largest and most recent case series indicated a conversion rate of 12% (153). While only 6 recurrences are reported overall (1.2%) there was considerable variability in follow-up and reporting standards across series.

Eleven comparative papers that used historical controls were identified between 2009-2015 (median n=45.5 patients/study, range 24-109)(160-170). Of 505 included patients, 259 had an MIS repair. A 2012 study by Jancelewicz, et al., compared 23 MIS repairs to 136 open repairs after a concerted practice change to minimize recurrences through multiple technical modifications (171). Nonetheless, the recurrence rate of MIS repair was 39% versus 10% by conventional open procedures. By far, the largest single investigation of surgical technique originates from the CDH Study Group (172). This paper reviewed the in-hospital outcomes of neonatal CDH repairs by MIS (159 [3.4%]) to 4239 open repairs. While MIS repair was performed in only 21.5% of all participating centres, an improved survival was associated with this technique (98.7% MIS vs. 82.9% open). This survival advantage is a reflection of selection bias, as only the most stable patients would have been subjected to MIS repair. Patients undergoing MIS repair had an in-hospital recurrence rate of 7.9% as compared to 2.6% in the open group. This increased risk persisted despite attempting to control for confounders, including gestational age, birth weight, need for ECLS and the need for patch repair. Four additional studies summarized available comparative literature through a systematic review process,

calculating either a risk ratio (173-175) or an odds ratio (176) of recurrence; each study confirmed an increased risk of recurrence with MIS repair.

Recently, several publications have investigated intra-operative physiologic changes occurring as a result of thoracic CO_2 insufflation during MIS CDH repair. One pilot randomized trial reported pCO_2 ranges in excess of 100 torr during MIS repair (70); several others have reported intra-operative acidosis (70, 166, 177, 178). The clinical significance of these findings remains unclear, but the potential for adverse outcomes attributable to the physiological effects of acidosis and hypercapnea on the labile pulmonary vasculature in CDH cannot be altogether ignored.

The purported advantages of the MIS approach for CDH have been poorly documented. A pilot study of pain after CDH repair (n=10) demonstrated *increased* discomfort after MIS repair (179). While several investigations document bowel obstruction after CDH repair, the majority of these are associated with recurrence and bowel incarceration which has been demonstrated in multiple prior systematic reviews to be more frequent in MIS patients. No study has compared chest wall abnormalities after MIS and open repair, nor has any paper rigorously investigated cosmesis and/or satisfaction after surgery.

In summary, there exists considerable and consistent evidence that the MIS approach for CDH repair subjects the neonatal patient to an increased risk of recurrence without any demonstrable concomitant benefit. Thoracoscopy may also be associated with ventilation and acid-base disturbances of unclear clinical consequence. As such, the repair of neonatal CDH using MIS techniques should only be performed within the context of a trial and only after full disclosure of the known increased risk of recurrence, as well as the potential for risks not yet appreciated, due to the limited experience and follow-up with MIS repair.

11. Surgery on Extracorporeal Life Support (ECLS)

- **11.1 Surgical repair of CDH should preferentially be delayed until the ECLS run is completed (i.e. after decannulation). (Level of Evidence C-LD)**

  ★★★★

- **11.2 If unable to wean off ECLS, consideration should be given for either surgery or palliation as appropriate. (Level of Evidence C-LD)**

  ★★★★

Discussion: The role of extracorporeal life support (ECLS) in the management of patients with CDH remains controversial (see topic 7). When a patient is committed to ECLS, further controversy exists regarding the role and timing of surgical repair.

The proponents of CDH repair during ECLS cite potential advantages to this approach, including the reduction of the mass effect produced by visceral contents within the thoracic cavity and the availability of the ECLS circuit to help support the patient during post-operative cardiovascular and renal perturbations that often occur after repair (180). Several small retrospective studies have demonstrated the feasibility of CDH repair during ECLS (181-187). Significant bleeding (and mortality) complicated these early attempts (186, 187). The use of fibrinolytics such as aminocaproic acid (188) and tranexamic acid (189) helped to significantly reduce these complications. Many centres now use antifibrinolytic therapy as a standard part of pre-surgical preparation when CDH repair during ECLS is considered (190, 191).

A few studies have attempted to define the role and timing of surgical repair during ECLS. Given that bleeding complications have been effectively reduced using antifibrinolytic therapy, surgical repair during ECLS continues to be considered advantageous by some (180, 192). Dassinger, et al., (192) assessed the outcomes and bleeding complications in 34 CDH infants

repaired on ECLS within 72 hours of cannulation from 1993-2007. They compared their outcomes with historical data from the Extracorporeal Life Support Organization (ELSO) registry over the same time period. Despite the significant limitations regarding selection bias and the lack of a "true" control group for comparison in this study, the authors concluded that CDH repair during ECLS had acceptable outcomes and complication rates, and that early surgery avoided body wall edema that could complicate the repair if performed later. In a more recent single-centre study, Fallon et al. (180) compared the outcomes of infants undergoing repair during ECLS at three different time points: <72 hours after ECLC cannulation (early), >72 hours after ECLS cannulation (late) or after decannulation (delayed). "Early" ECLS repair demonstrated a slight improvement in survival (73% vs. 50%; p=0.27) compared to "late" repair and did lead to significantly fewer ECLS days (12 vs 18; p=0.01) and circuit changes (27% vs. 72%; p=0.03). While comparisons of the "early" and "late" repair groups failed to demonstrate any major differences in length of stay, intubation days, or major or minor bleeding complications, there was a trend towards larger transfusion requirements (712 vs. 323 mL; p=0.07) in the "early" group. Despite acknowledged study limitations, the authors concluded that the "early" surgical repair during ECLS was advantageous since it led to reduced time on ECLS and fewer ECLS -related complications. In a recent retrospective single-centre study, the outcomes of 87 severe CDH infants (i.e. left liver up) who required ECLS were evaluated (136). Survival was 92% (23/25) in infants who were repaired before ECLS. Twenty-two of these infants were repaired at a mean 20 hours (+/- 10 hours) after birth (survival 22/22), while an additional 3 infants were repaired at approximately 5 days of life (survival 2/3). Most interestingly, infants who arrived at ECLS unrepaired and who ultimately underwent delayed repair after ECLS had significantly reduced survival (65%; p=0.018). The authors did not

identify any differences in demographics between infants requiring ECLS who underwent either "early" or "delayed" repair. Moreover, "early" surgical patients were not exposed to the bleeding risks of surgery on ECLS.

The CCC's recommendation that surgery be delayed until after weaning from ECLS is based predominantly on a report from the Congenital Diaphragmatic Hernia Study Group (CDHSG) (193). Using prospectively collected registry data, the outcomes of infants repaired either "on" (n=348) or "after" (n=208) ECLS were compared (1995-2005). Using Cox proportional hazards analyses, the authors identified an increased hazard ratio for mortality (1.41; 95%CI 1.03-1.92) if the repair was conducted on ECLS. While this is currently the best "quality" evidence to date due to prospective data collection and improved external validity, it still has limitations, including the fact that 172 patients who were repaired during ECLS were not included for analysis due to missing data. Moreover, there may have been significant variability in the management of these infants between centres. Nonetheless, these findings were supported by a more recent retrospective single centre study by Partridge et al. who found that repair after decannulation from ECLS was associated with improved survival and reduced operative morbidity (194).

The clinical situation involving infants who cannot be readily weaned from ECLS is difficult. At present, there are no pre-ECLS criteria that reliably predict survival after cannulation. However, an unwillingness to repair the diaphragmatic defect in CDH infants who fail to reach "stability" criteria (i.e. wean from ECLS) is associated with 100% mortality (139). The CCC suggests that in this specific scenario, consideration should be given to proceed either with surgery or palliation as deemed appropriate by interdisciplinary discussions and parental input, particularly

if weaning has failed over 2 weeks. More information regarding "early" repair, either before or during ECLS, is needed before definitive recommendations regarding this strategy can be made.

12. Treatment of Gastroesophageal Reflux (GER)

- **12.1 Routine fundoplication is not indicated during CDH repair (Level of Evidence B-R)**

★★★★

Discussion: One prospective, single center trial (195) randomized 79 patients to either standard CDH repair alone (n=43) or combined with fundoplication (n=36). Patients were followed at 6, 12 and 24 months with a chest radiograph and a questionnaire inquiring about symptoms of reflux. The only difference between groups was a lower occurrence of reflux symptoms at 6 months in the fundoplication group. Two additional prospective case series have shown that fundoplication at the time of CDH repair is only beneficial in "high-risk" infants (196, 197). In the first, 2 groups of patients were prospectively followed: 17 who underwent a fundoplication at the time of CDH repair, and 19 who had only CDH repair (196). They observed an advantage to simultaneous fundoplication only in patients who were found to have an intra-thoracic liver at the time of repair and/or those who required a patch. In the second study, high-risk CDH was defined by the anatomy as assessed by the surgeon intra-operatively (e.g. intra-thoracic gastro-esophageal junction, obtuse angle of His and small vertical stomach) (197). There was no control group in this study, but the authors based their recommendation for simultaneous anterior fundoplication at the time of CDH repair on the fact that 10/13 of these patients were discharged on full oral feeds (197). Importantly, several case series have described a greater incidence of complicated GER in more severe forms of CDH(198-203). While these reports beg the question of whether a concomitant fundoplication could be considered in the subset of patients considered "high-risk", such a question could only be answered by a properly designed RCT.

13. Long-term Follow-up

- **13.1 We recommend standardized multi-disciplinary follow-up for children with CDH to provide surveillance and screening, optimal and timely diagnosis and clinical care adjusted to the level of risk. (Level of Evidence B-NR)**

  ★★★★

- **13.2 We recommend subset identification of CDH survivors at high risk for long-term morbidity as those infants and children requiring ECLS support, repaired with a patch or who required respiratory support at 30 days of life. (Level of Evidence B-NR)**

  ★★★★

Discussion: With improved prenatal diagnosis and risk stratification, and advancements in cardiopulmonary stabilization and lung protection, CDH survival rates have improved significantly over the past two decades. Hence, the focus of outcome improvement in CDH has expanded from mortality prevention to prevention, early diagnosis and treatment of survivor morbidity. In support of this trend is the increasing evidence that adverse outcomes in CDH survivors are common, frequently multiple and usually evident within the first few years of life. Reported adverse outcomes were categorized as cardiopulmonary (204, 205), gastrointestinal/nutritional (206, 207), neurodevelopmental (36, 208, 209), musculoskeletal (210), hearing loss (211, 212), complications requiring surgical intervention (142), and child and family unit well being (213).

Since the late 1990s, there has been an increase in the number of pediatric centers in North America and Europe that have established routine, multi-disciplinary follow-up for CDH survivors (214). Through systematic follow-up, these centers have established the burden of survivor morbidity, and have encouraged integration and standardization of the provision of

multi-disciplinary care. Although there is no evidence for the clinical effectiveness of

multidisciplinary clinics in altering survival outcomes, it is intuitive that timely screening leading

to early detection of morbidity, such as hearing loss and neurodevelopmental impairment, can

only help the child and family in receiving care that could offer impact mitigation.

In alignment with an earlier policy statement which proposed an algorithm for developmental

surveillance and screening of infants and children with developmental disorders (215), the

American Academy of Pediatrics has published guidelines for the follow-up of CDH survivors,

with explicit recommendations for growth and oral feeding surveillance, cardiopulmonary

functional testing, neuroimaging, hearing evaluation, developmental screening,

neurodevelopmental testing and musculoskeletal evaluation (216). These recommendations can

be best implemented through a multi-specialty clinic with subspecialist expertise as well as an

allied health team to assess feeding, growth and neurodevelopment and provide social support.

This clinic model which aggregates multi-specialty assessment around the family has been

shown to improve family experience scores and offers the potential for health system efficiencies

and cost savings (217). Within Canada, the practice model for the delivery of multispecialty

follow up care for CDH patients varies between centers and reflects, at least in part, the volume

of patients seen. Not surprisingly therefore, some of the larger centres utilize dedicated,

multispecialty CDH clinics, while in smaller centres, the pediatric surgeon or specialty

pediatrician is responsible for the overall coordination of decentralized follow-up with the

various disciplines, usually within a children's hospital (218).

While the concept of scheduled follow-up for all CDH survivors is appropriate, the systematic

review addressed whether a subset of patients at increased risk for adverse outcome, as a

consequence of their disease severity or treatment intensity would benefit from more intensive

screening. The most frequently cited predictors of severity of survival morbidity include the need for pulmonary support at 30 days of age (209, 219, 220), need for patch repair (142, 209, 221) and need for ECLS (209, 222). It is recommended that these CDH survivors be offered screening, including standardized neurodevelopmental testing at standard ages. Lower risk CDH patients who are easily stabilized without substantial cardiopulmonary support, undergo primary diaphragmatic repairs, and have an uncomplicated postoperative course without the need for invasive supportive therapy require less intensive screening which can occur closer to home.

14. Fetal Interventions for High Risk CDH

While our discussion identified a number of topics for a research agenda (out of scope), the CCC felt that some discussion of fetal intervention should be included. Although not currently offered in any Canadian center as clinical care, the procedure is available in a number of North American Centers (including one in Canada) for fetuses with "high risk" CDH, either as an innovative procedure offered on compassionate grounds, or in the context of a randomized controlled trial. The CCC felt it was important to discuss this as a treatment option, since it could be available to families considering all options of treatment for their fetus deemed at high risk of mortality based on antenatal risk stratification.

- **14.1 In the management of CDH, experimental therapies should ONLY be considered in the context of a well-designed clinical study. Currently these include, but are not limited to, fetal endoscopic tracheal occlusion (FETO), antenatal sildenafil administration, and ex-utero intra-partum treatment [EXIT]-to-ECLS delivery. (Level of Evidence C-EO)**
  ★★★☆

Discussion: The survival of the most severely affected fetuses with CDH (LHR < 1.0 and liver herniation; o/e LHR <25%) is associated with extremely poor survival despite maximal therapy. Several "experimental" therapies have been investigated to improve these outcomes. Fetal endoscopic tracheal occlusion (FETO) was first described in 1995 (223) and was clinically applied as a percutaneous procedure in 2004 (224). Tracheal occlusion has been shown to stimulate lung growth while release of the balloon allows for pulmonary maturation (225). Despite increasing acceptance, the role of FETO is still debated. A recent meta-analysis of 5 studies (4 prospective, 1 RCT) involving 110 FETO and 101 control patients (226) demonstrated significantly improved survival outcomes in the FETO group (OR 13.32, 95%CI 5.40-32.87) for infants with LHR<1.0 and a "liver up" position. An international, multi-institutional trial (Tracheal Occlusion To Accelerate Lung (TOTAL) Growth Trial for Severe Pulmonary Hyperplasia; NCT01240057) involving centres across Europe and North America is currently underway.

Early experience with an EXIT-to-ECLS strategy for severe CDH showed some benefit but a more recent study from the same institution failed to identify a clear survival advantage to this approach. (227, 228). Additional studies are needed before any further recommendations can be made.

While nitrofen-based animal models of CDH (229, 230) and a few small retrospective case series (116, 117) have demonstrated some efficacy with the antenatal and post-natal administration of sildenafil, respectively, there is currently no clinical experience with the use of antenatal sildenafil in CDH.

V. Appendices:

<u>a. The Canadian CDH Collaborative:</u>

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Robert Baird, Pediatric Surgery, Montreal Children's Hospital

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*Canadian CDH Collaborative Steering Committee

In addition, a neonatology trainee and a content expert, non-voting process observer from the United States participated in the face to face consensus discussions.

b. Acknowledgements

The Canadian CDH Collaborative thanks Dr. Brian Kavanagh (Hospital for Sick Children (Toronto), Pediatric Intensive Care/Pediatric Anesthesia) for his participation in the development of these guidelines and Alison Butler, CAPSNet coordinator for her organizational and logistical support of the guidelines development process.

c. Conflicts of Interest/Commitment

All members signed COI/COC forms. There was one disclosure: Pramod Puligandla – Member of Advisory Board of Ikaria Canada Inc. for one-time meeting participation regarding inhaled nitric oxide use in children and adults (honorarium)

d. Guideline Development Group and Patient/Family Stakeholders

The guideline has been developed by the Canadian CDH Collaborative (Appendix a): a geographically representative group of specialists from across Canada with expertise in the fields of maternal-fetal medicine, pediatric surgery, pediatric anesthesia, neonatal intensive care, neonatal follow-up, pediatric intensive care, and pediatric cardiology. In preparing these guidelines, consideration has been given to the views and preferences of parental advisory/advocacy groups (Rare Disease Foundation, Canadian Family Advisory Network). The target users for these guidelines include maternal-fetal medicine specialists (antenatal diagnosis and parental counselling), the multi/interdisciplinary critical care teams involved throughout the birth hospitalization, including neonatologists, pediatric subspecialists (surgeons, cardiologists, critical care physicians, anesthesiologists), respiratory technologists, and the neonatal followup specialists and a wide array of pediatricians and pediatric subspecialists who provide ongoing care and active CDH-related morbidity surveillance for CDH survivors and their families.

e. Evidence Review Process: Data Sources, Selection and Extraction

For each evidence review subject, Medical Subject Heading (MeSH) terms were created to identify articles within existing literature databases (e.g. PubMed, Google Scholar, CINHAL, MEDLINE, Cochrane, Web of Science and EMBASE) for the period 1990 to 2015. Using bibliography management software, duplicates were removed that left a master list of manuscript titles. Evidence selection criteria dictated inclusion or exclusion: *A priori*, animal or experimental studies, case reports involving <3 patients, non-neonatal CDH, non-English language articles as well as review articles and opinion pieces/editorials were excluded. Included

articles subsequently underwent abstract review to confirm relevance after which all remaining full length manuscripts were evaluated as part of the formal evidence review. Selected articles were appraised and their level of evidence graded according to the taxonomy scheme shown in Appendix d.

f. Consideration of Existing Guidelines

The steering committee used the CDH Euro-Consortium (CDH EURO) recommendations published in 2010 and 2016 (78, 138) and the recently published recommendations on the management of pulmonary hypertension by the American Heart Association and American Thoracic Society (231) (AHA/ATS) as existing recommendations to be considered by our consensus-building group.

A questionnaire was sent to each contributor asking if they would "accept," "modify" or "reject" the baseline recommendations from the existing CDH EURO and AHA/ATS guidelines using the following decision framework:

1. **Accept**: This recommendation may be adopted into practice without a formal discussion.
2. **Modify**: While worthy of consideration, the recommendation is not acceptable as written but is important enough that it should be included for discussion in the face-to-face consensus meeting.
3. **Reject**: This implies that the recommendation is either wrong, out of date, or so unimportant as to not require recognition as a guideline or recommendation.

   It was decided *a priori* that any recommendation accepted by >80% of the participants would be adopted and excluded from further discussion in the face-to-face consensus meeting. All other acceptable recommendations not achieving 80% endorsement, along with prioritized subject areas, would be discussed and were the focus of the literature review and discussion. A few recommendations were adopted *a priori* and are presented, with source acknowledgement, in the recommendation section. The level of evidence for each of these is denoted as C-EC (CDH EURO) or E-ATS (AHA/ATS).

g. Evidence Appraisal and Modified Delphi Consensus Methods

The evidence appraisal tool used is shown in Table 1. The process for determining consensus using the anonymized audience response tool (Poll Everywhere™) is shown in Figure 1. The completed searches and PRISMA flow diagrams can be provided on request.

Table 1:

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

h. Formulation of Recommendations

The CCC face-to-face consensus meeting was held over two days with 17 participants, including an experienced guidelines facilitator, a record-keeper and a non-voting observer. A modified Delphi technique was used (Figure 1). The participants were organized into multidisciplinary working groups, each tasked with creating visual, summarized evidence discussions and recommendations for consideration by the group at large.

The facilitator ensured fidelity of the work plan and adherence to a timeline for discussion. A "parking lot" was created for issues or questions that required further discussion. Once the recommendations and evidence were presented, real-time, anonymous electronic voting occurred with 15 participants (excluding the neutral observer and the record-keeper) using the live audience participation system *Poll Everywhere*® (www.polleverywhere.com). If the predetermined target of 80% consensus was not met, the recommendation was modified through discussion, and a second vote was held. If consensus could still not be reached, the recommendation was placed in the "parking lot" for later discussion.

At the completion of the meeting, the wording of the recommendations was subsequently finalized and distributed to participants who then provided written evidence summaries to

support the publication of the final CCC guideline. Committee members then reviewed the manuscript prior to final submission.

Figure 1:

Modified Delphi Consensus Framework

1) Strongly agree
2) Somewhat agree
3) Neither agree or disagree
4) Somewhat disagree
5) Strongly disagree

★★★★★ ....STRONG AGREEMENT WITH RECOMMENDATION: >80% #1 OR #5
★★★★☆ ....GOOD AGREEMENT WITH RECOMMENDATION: >80% OF #1 + #2 OR #4 + #5 BUT >50% OF THE VOTES AS #1 OR #5
★★☆☆☆ ....WEAK AGREEMENT WITH RECOMMENDATION: >80% OF #1 + #2 OR #4 + #5 BUT <50% OF THE VOTES AS #1 OR #5
☆☆☆☆☆ ....NO CONSENSUS
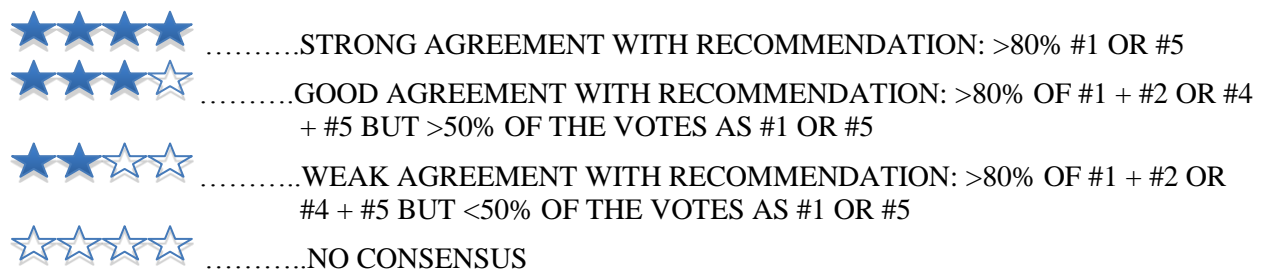
i. Strengths and Limitations of the Body of Evidence

The body of evidence in support of the guideline is of relatively low level and variable quality. The majority of studies tended to be comparative cohort studies, often comparing historical to contemporary cohorts after an instituted practice change. Much of the literature related to surgical timing and technique is limited to case series. A strength of the process was the a priori consensus framework and the use of an audience response tool which ensured participant anonymity in expressed opinion.

j. Expert Reviewers

The guidelines have been sent to two experts:

i) Dr. Marjorie Arca, Professor of Surgery, University of Wisconsin. Dr. Arca is the former Chair of the Outcomes and Evidence-Based Practice Committee of the American Pediatric Surgical Association (APSA). She is currently the Chair of the APSA Education Committee.

ii) Dick Tibboel, MD, PhD, Departments of Intensive Care and Pediatric Surgery, Erasmus MC; Sophia Children's Hospital, Rotterdam, The Netherlands. Professor Tibboel was a senior author of the Euro-Consortium CDH guidelines.

k. Procedure for Updating the Guideline

The Steering Committee members (Offringa, Puligandla, Skarsgard) will be responsible for leading an evidence renewal review every 3 years, effectively making this a "living guideline". Ad hoc membership to the renewal review committee will be informed by the need for content expertise according to new literature.

l. Tools and Resources Necessary for Implementation

The guidelines have been distributed to the professional societies of the clinical groups involved in CDH care. These include the Society of Obstetricians and Gynaecologists of Canada (SOGC), the Fetus and Newborn Committee of the Canadian Pediatric Society and the Canadian Association of Pediatric Surgeons (CAPS). In collaboration with the Executive Committees of each of these societies, a preferred knowledge mobilization (KM) strategy will be identified. In collaboration with the Canadian Neonatal Network, electronic decision support tools will be created and made available to all 15 participating NICUs in the Canadian Pediatric Surgery Network. The Canadian Association of Paediatric Health Centres (CAPHC) will be approached as a KM partner, leveraging the infrastructure of the Knowledge Exchange Network (e.g. webinars).

m. Facilitators and Barriers to Guideline Utilization

A facilitator of the launch and utilization of the guidelines are the existing collaborative clinical and research communities in perinatal and neonatal medicine and surgery. Three perinatal networks (Canadian Neonatal, Canadian Perinatal and the Canadian Pediatric Surgery Networks) have established, integrated infrastructure for knowledge creation and dissemination. Each of the 15 children's hospitals that care for CDH in Canada have surgical and neonatal site investigators who will have oversight for guidelines implementation. A checklist will be created and shared with all sites that will ensure that guidelines are used during daily rounds. This checklist will also capture variances from the guidelines, and their justification. Barriers to

facilitation will be local practices and biases, especially when a specific recommendation as at variance with the historical practice at that institution, or if specific recommendations cannot be complied with due to a lack of availability of a specific therapy at an individual institution (e.g. availability of ECLS).

n. Audit Criteria/Quality Assurance

A guidelines audit tool will be developed that will capture, for individual patients, compliance with the recommendations. Where variances occur, every effort will be made to capture why a variance has occurred. A guideline "process measures" checklist will allow quantitative assessment of compliance on individual patients, and an overall guidelines compliance score will be reported for individual NICUs in the CAPSNet Annual Report. Our patient/family partners will be engaged in the development of compliance tools to be used in the NICU.

o. Funding Bodies and Guideline Content Integrity

External funding for CAPSNet comes from CIHR (project-based) and from the Canadian Association of Pediatric Surgeons. Neither external funder introduce any bias into the creation of these guidelines.

p. Evidence Maps

HEMODYNAMIC SUPPORT AND PULMONARY VASODILATION

Abstracts imported from Medline through several searches using the key words CDH and pulmonary hypertension; CDH and pulmonary vasodilators; CDH management; CDH and blood pressure; CDH and adrenal insufficiency; CDH and NO; CDH and sildenafil; CDH and dopamine, dobutamine, milrinone, epinephrine, vasopressin;
Languages used were French and English
Animal studies were excluded
Reviews were included to ensure that we did not miss any important citations
(n=284)

⬇

Citations identified for review and only the ones that were systematic reviews, cohort studies, case series, consensus and comment
(n=90)   ➡   Citations Excluded(n=194)

⬇

Articles retrieved(n=26)   ➡   Articles Excluded(n=64)

Systematic Review or RCT (n=5)

Cohort study with concurrent controls (n=3)

Cohort study with retrospective controls (n=7)

Case Series (n=9)

Comment (n=1) Consensus (n=1)

1. **Antenatal Imaging Articles Selection:**

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┌─────────────────────────┐        ┌─────────────────────┐
│ Citations identified for│───────▶│ Citations           │
│ review (n=72)           │        │ Excluded(n=520)     │
└─────────────────────────┘        └─────────────────────┘
              │
              ▼
┌─────────────────────────┐        ┌─────────────────────┐
│ Articles retrieved(n=20)│───────▶│ Articles Excluded(n=52)│
└─────────────────────────┘        └─────────────────────┘
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| Cohort study with retrospective controls (n=19) | Cohort study with concurrent controls (n=1) | Abstracts identified through medline (n=284) | Case Series (n=0) |
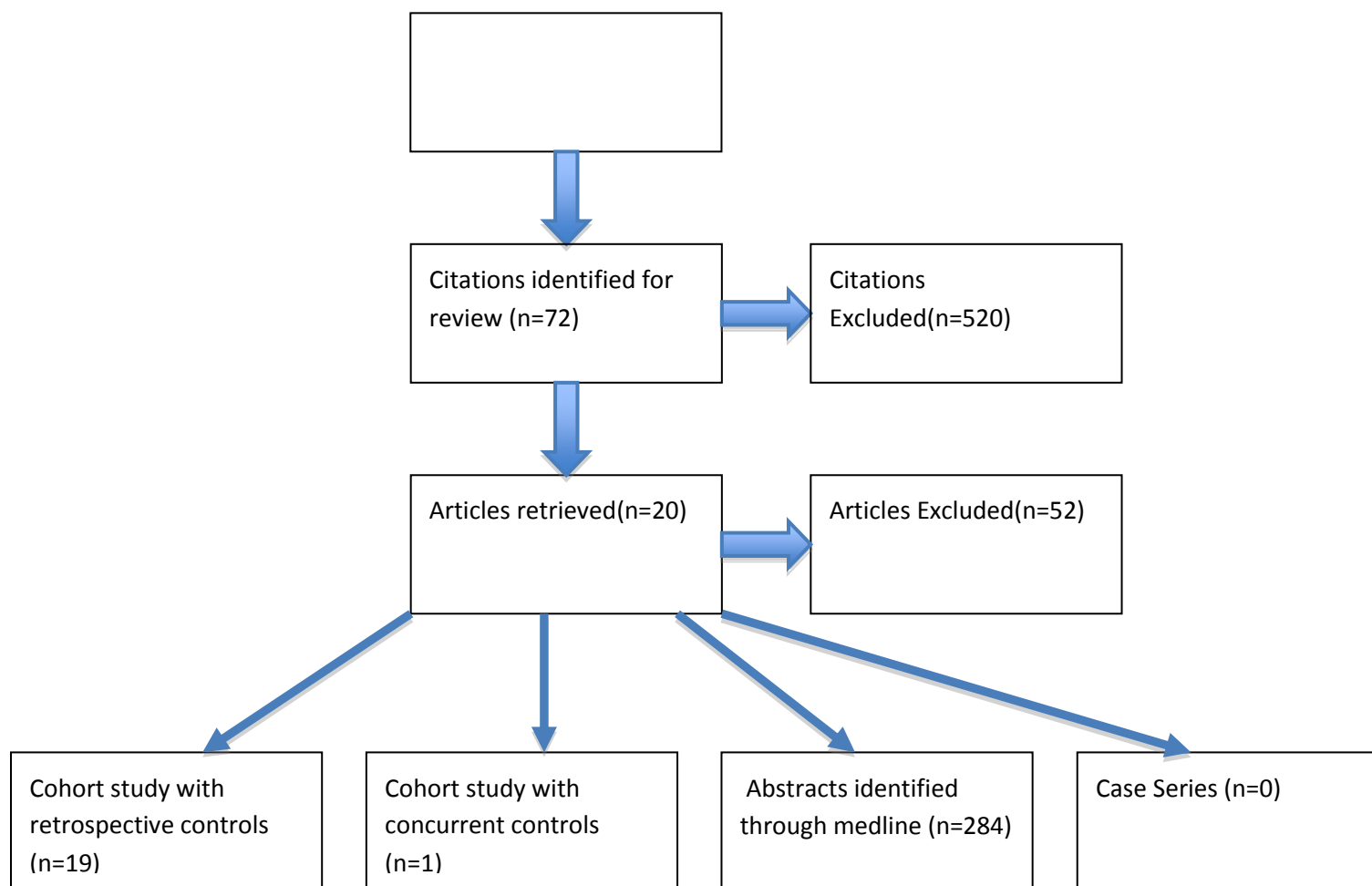
Ventilation Article Selection Process:

Abstracts imported from Medline (n=530)

↓

Citations identified for review (n=530) → Citations Excluded (n=455)

↓

Articles retrieved (n=75) → Articles Excluded (n=6)

Systematic Review or RCT (n=8)

Cohort study with concurrent controls (n=3)

Cohort study with retrospective controls (n=47)

Case Series (n=11)
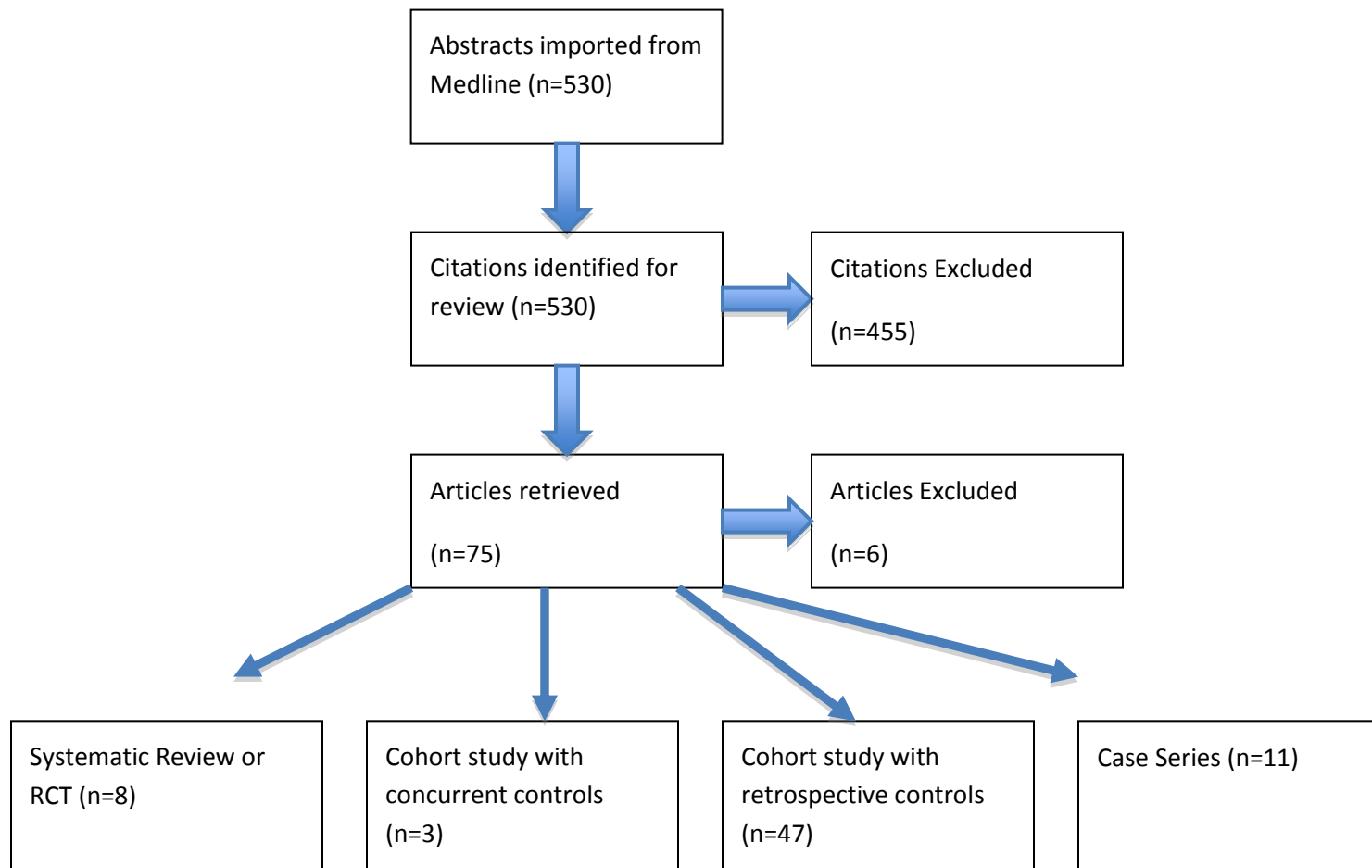
Echocardiography in CDH Articles Selection Process:

Abstracts imported from Medline (n=19)

Citations identified for review (n=19)

Citations Excluded(n=0)

Articles retrieved(n=19)

Articles Excluded(n=8)

Systematic Review or RCT (n=0)

Cohort study with concurrent controls (n=1)

Cohort study with retrospective controls (n=0)

Case Series (n=10)

Prostaglandin in CDH to Keep Ductal Patency Article Selection Process:

Abstracts imported from Medline (n=32)

Citations identified for review (n=32)

Citations Excluded(n=0)

Articles retrieved(n=32)

Articles Excluded(n=21)

Systematic Review or RCT (n=0)

Cohort study with concurrent controls (n=0)

Cohort study with retrospective controls (n=1)

Case Series (n=10)

ECLS and CDH Article Selection Process:


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┌─────────────────────────┐
│ Abstracts imported from │
│ Medline (n=988)         │
└─────────────────────────┘
              │
              ▼
┌─────────────────────────┐        ┌─────────────────────────┐
│ Citations identified for│───────▶│ Citations               │
│ review (n=219)          │        │ Excluded(n=121)         │
└─────────────────────────┘        └─────────────────────────┘
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┌─────────────────────────┐        ┌─────────────────────────┐
│ Articles retrieved(n=98)│───────▶│ Articles Excluded(n=46) │
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| | Cohort study with concurrent controls (n=0) | Cohort study with retrospective controls (n=0) | Case Series (n=47) |

Timing and Readiness Criteria For Surgery in CDH:

Abstracts imported from Medline (n=)

Citations identified for review (n=456)

Citations Excluded(n=373)

Articles retrieved(n=83)

Articles Excluded(n=41)

Systematic Review or RCT (n=6)

Cohort study with concurrent controls (n=7)

Cohort study with retrospective controls (n=15)

Case Series (n=14)

Method of Surgical Repair in CDH Article Selection Process:

Abstracts imported from Medline (n=232)

Citations identified for review (n= 56)

Citations Excluded (n=176) Concerned FETENDO, Morgagni Hernia, basic science, duplicates...

Articles retrieved (n=28)

Articles Excluded (n=29) Case reports, review articles

Systematic Review or RCT (n=5) 4=SR, 1=RCT

Cohort study with concurrent controls (n=1)

Cohort study with retrospective controls (n=13)

Case Series (n=9)

Best CDH Patch Article Selection Process:

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┌─────────────────────────┐
│ Abstracts imported from │
│ Medline (n=393)         │
└─────────────────────────┘
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┌─────────────────────────┐          ┌─────────────────────────┐
│ Citations identified for│ ───────▶ │ Citations Excluded(n=371)│
│ review (n=22)           │          │                         │
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┌─────────────────────────┐          ┌─────────────────────────┐
│ Articles retrieved(n=22)│ ───────▶ │ Articles Excluded(n=12) │
└─────────────────────────┘          └─────────────────────────┘
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| Systematic Review or RCT (n=0) | Cohort study with concurrent controls (n=5) | Cohort study with retrospective controls (n=4) | Case Series (n=1) |

Repair of CDH on ECLS Article Selection Process:

Abstracts imported from Ovid, PubMed and Google Scholar (n=206)

Citations identified for review (n=15)

Citations Excluded(n=191)

Articles retrieved(n=12)

Articles Excluded(n=3)

Systematic Review or RCT (n=2)

Cohort study with concurrent controls (n=2)

Cohort study with retrospective controls (n=4)

Case Series (n=4)

Management of GERD in CDH Article Selection Process:

Abstracts imported from Medline (n=592)

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Citations identified for review (n=72) → Citations Excluded(n=520)

↓

Articles retrieved(n=20) → Articles Excluded(n=52)

Systematic Review or RCT (n=0)

Cohort study with concurrent controls (n=1)

Cohort study with retrospective controls (n=19)

Case Series (n=0)

Sedation in CDH Article Selection Process:

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┌─────────────────────┐
│ Abstracts imported  │
│ from Medline        │
│ (n=56)              │
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┌─────────────────────┐      ┌─────────────────────┐
│ Citations identified│─────▶│ Citations           │
│ for review (n=4)    │      │ Excluded(n=52)      │
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┌─────────────────────┐      ┌─────────────────────┐
│ Articles retrieved  │─────▶│ Articles            │
│ (n=4)               │      │ Excluded(n=0)       │
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| Systematic Review or RCT (n=2) | Cohort study with concurrent controls (n=0) | Cohort study with retrospective controls (n=0) | Case Series (n=2) |

Long-term Surveillance in CDH Article Selection Process:

Abstracts imported from Medline (n= 481)

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Citations identified for review (n= 117) → Citations Excluded (n= 364)

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Articles retrieved (n=104) → Articles Excluded (n=13)

Systematic Review or RCT (n= 3)

Cohort study with concurrent controls (n= 12)

Cohort study with retrospective controls (n= 0)

Longitudinal cohort study without controls (n= 89)

Hemodynamic Support and Pulmonary Vasodilator Therapy Article Selection Process:

Articles identified through Medline

(N-284)

Citations identified for review and only the ones that were systematic reviews, cohort studies, case series, consensus and comment (n=90)

Citations Excluded(n=194)

Articles retrieved(n=26)

Articles Excluded(n=64)

Cohort study with retrospective controls (n=7)

Case Series (n=9)

Systematic Review or RCT (n=5)

Cohort study with concurrent controls (n=3)

Comment (n=1)

Consensus (n=1)

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