

# Diagnosis and management of congenital diaphragmatic hernia: a clinical practice guideline

The Canadian Congenital Diaphragmatic Hernia Collaborative\*

\*The complete list of authors appears at the end of the article.

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*CMAJ* Podcasts: author interview at <https://soundcloud.com/cmajpodcasts/170206-guide>

**C**ongenital diaphragmatic hernia (CDH), which occurs in about 1 in 3300 live births, is a congenital defect in the diaphragm that allows herniation of abdominal viscera into the thorax.<sup>1</sup> The resulting abnormal lung development leads to pulmonary hypoplasia and pulmonary hypertension, which are the primary determinants of morbidity and mortality for these patients. An unintended consequence of advances in neonatal care, which have improved survival from 50% to almost 80% over the past three decades,<sup>2</sup> has been the frequency and severity of morbidity among survivors. The health and economic impact of morbidity related to CDH on patients and families has been equated to that of other chronic diseases. The financial cost and personal toll of prolonged, variably intense use of the health system by the surviving child with CDH-specific disability is augmented by the reduced productivity of families caring for these children, with the result being a marked reduction in quality of life for patients and their families.<sup>3</sup>

A defining attribute of CDH is its requirement for integrated multidisciplinary care across three distinct phases: prenatal, perinatal/postnatal and childhood/adolescent. The complex interplay of roles between specialists and the lack of evidence informing “best practices” across the phases of care leads to substantial practice and outcome variation within and between children’s hospitals in Canada.<sup>4</sup> This unwanted variation in clinical care contributes to suboptimal outcomes and inefficiencies in use of health care resources.

The Canadian CDH Collaborative sought to develop an evidence-based guideline to standardize CDH care practices across Canada and improve outcomes. This abridged document summarizes the methodology used in developing the guideline, as well as the most pertinent recommendations for practice. The complete guideline is available in Appendix 1 (available at [www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.170206/-/DC1](http://www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.170206/-/DC1)).

## Scope

The purpose of this project was to produce an evidence-based and consensus-driven national guideline for the health surveil-

## KEY POINTS

- The severity of congenital diaphragmatic hernia (CDH) can be estimated prenatally using observed-to-expected lung-head ratios (by ultrasound) and total fetal lung volumes (by magnetic resonance imaging), as well as fetal liver position.
- Infants with CDH require intensive cardiopulmonary support after birth, including immediate endotracheal intubation and “gentle ventilation,” as well as judicious fluid and inotropic support.
- Pulmonary hypertension, as assessed by echocardiography, may require the use of pulmonary vasodilators and other medical adjuncts (e.g., prostaglandin E<sub>1</sub>, milrinone) or, in severe cases, extracorporeal life support, if available.
- Open surgical repair of the diaphragmatic defect should usually be delayed until physiologic stability has been achieved, but a failure to perform surgery within the first two weeks of life should prompt a team discussion of priorities with the family.
- Infants with CDH should undergo long-term, multidisciplinary surveillance that includes standardized neurodevelopmental testing, especially if they are considered high risk (i.e., needing pulmonary support at 30 days, needing a patch repair or requiring extracorporeal life support).

lance and care of patients with CDH from prenatal diagnosis through to long-term follow-up (see Appendix 1 for full statement of purpose). The guideline is intended for specialty and primary care providers whose clinical practice includes pre- or postnatal care of patients with CDH. The desired outcome is overall improvement in the quality of health care delivery for these patients, leading to optimized health and quality of life for them and their families. This guideline is applicable to all pregnancies with antenatally diagnosed CDH and live-born infants with CDH with or without an antenatal diagnosis. Infants not given a diagnosis of CDH within four weeks of birth are excluded, based on a substantially reduced severity of disease at presentation.

## Methods

### Guideline panel composition

This guideline was developed by the Canadian CDH Collaborative, a panel 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. The steering committee invited participants during the planning stages of the project, with a goal of achieving a panel of 22 individuals that was balanced in terms of both practitioner specialty and geographic representation.

### Guideline development

A three-member steering committee (PP, ES, MO) was formed to oversee the guideline development process, to finalize membership of the collaborative and contributors to the literature reviews, to appraise critically all materials generated during the process, chair teleconferences, and convene and lead a two-day face-to-face meeting. Teleconferences were organized to establish and prioritize literature review topics, working group assignments and timelines.

For each evidence review subject, Medical Subject Heading (MeSH) terms were created to identify articles within existing literature databases (e.g., PubMed, Google Scholar, CINAHL, MEDLINE, Cochrane, Web of Science and Embase) for the period from 1990 to 2015. Evidence selection criteria dictated inclusion or exclusion a priori. Animal or experimental studies, case reports involving fewer than three patients, studies on non-neonatal CDH, non-English language articles, review articles, opinion pieces and editorials were excluded. Included articles subsequently underwent abstract review by the members of specific working groups created for the literature reviews: prenatal diagnosis, risk stratification and optimal delivery (GR, TO-O); ventilation (SD, DM, MT); fundamentals of hemodynamic support (TP, BP); echocardiography and pulmonary hypertension management (including sedation, the use of prostaglandin and extracorporeal life support) (IA, AC, RK, TP, BP, TP); surgery (including “readiness criteria,” patch repair, type of repair and surgery on extracorporeal life support) (MB, RB, ES, PP); and long-term surveillance and the management of gastroesophageal reflux (HF, PC, AS, SPR, JAMB). Selection of full-length manuscripts to include was based on clinical relevance and working group consensus. The steering committee (PP, ES, MO) deliberated over any disagreements related to inclusion of articles. Selected articles were appraised using tools obtained from the Oxford Centre for Evidence-Based Medicine.<sup>5</sup> The participants in each work group initially appraised and graded the evidence. Their evidence summaries were then reviewed by the group at large for consensus. Final grading was provided by the steering committee. The final level of evidence was graded according to the taxonomy scheme shown in Box 1.<sup>6</sup> The Appraisal of Guidelines for Research & Evaluation (AGREE) II instrument<sup>7</sup> was applied throughout the compilation of the guideline (Appendix 2, available at [www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.170206/-/DC1](http://www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.170206/-/DC1)).

In preparing the current guideline, the panel reviewed existing guidelines published by the CDH EURO Consortium (CDH

EURO)<sup>8,9</sup> and the American Heart Association and American Thoracic Society.<sup>10</sup> We used pre-established consensus criteria to accept, modify or reject these baseline recommendations in the guideline-finalization process described below.

The face-to-face meeting was held over two days with 17 participants, including an experienced guideline facilitator, a record-keeper and a nonvoting observer. The participants had been organized into working groups (the same working groups that did the literature reviews) before the meeting, each tasked with creating visual, summarized evidence maps and recommendations for consideration by the group at large. After the working groups presented the evidence maps and recommendations, real-time, anonymous electronic voting occurred with 15 participants (excluding the neutral observer and the record-keeper; the facilitator also voted as a content expert), using the live audience participation system Poll Everywhere ([www.pollerywhere.com](http://www.pollerywhere.com)).

We established consensus using a modified Delphi technique (Box 2). If the predetermined target of 80% consensus was not met, the recommendation was modified through discussion, and a second vote was held. If consensus still could not be reached, the recommendation was placed in the “parking lot” for later discussion. After the meeting, written evidence summaries in support of the final recommendations were submitted by the working groups responsible. These summaries, along with the final recommendations, were edited by the steering committee (PP, ES, MO) and then returned to the working groups for feedback. All participants reviewed the completed manuscript before submission.

### Management of competing interests

Members of the collaborative performed their tasks voluntarily. Travel stipends to the face-to-face consensus meeting were supported by discretionary research funding from the Canadian

#### Box 1: Taxonomy scheme for grading of evidence<sup>6</sup>

##### Level A

- High-quality evidence from more than one randomized controlled trial (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 one or more RCTs
- Meta-analyses of moderate-quality RCTs

##### Level B-NR (nonrandomized)

- Moderate-quality evidence from one 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
- Physiologic or mechanistic studies in human participants

##### Level C-EO (expert opinion)

- Consensus of expert opinion based on clinical experience

Pediatric Surgery Network, a national surgical birth defects registry and research network with foundational funding from the Canadian Institutes of Health Research. All members of the collaborative completed competing interest and commitment declarations. The one member who revealed a potential competing interest (PP) was deemed eligible to participate because the conflict was isolated to a single meeting that focused exclusively on the use of inhaled nitric oxide in adults and thus had no influence on the development of the current guideline.

## Recommendations

The most pertinent recommendations for clinical practice evidence supporting these recommendations are discussed below (Table 1).

### Prenatal diagnosis and risk stratification

*Ultrasound measurement of observed-to-expected lung-head ratio should be used between 22 and 32 weeks of gestational age to predict the severity of pulmonary hypoplasia in isolated CDH (strength of recommendation: ●●●●; level of evidence: level B, nonrandomized [B-NR]).*

The prediction of pulmonary hypoplasia aids antenatal counselling in CDH pregnancies. The observed-to-expected lung-head ratio accurately predicts CDH survival across a broad spectrum of gestational ages (18–38 w).<sup>11</sup> However, measurement of the lung-head ratio using the manual tracing method<sup>12</sup> has been shown to best assess fetal lung volumes in order to predict outcome.<sup>13,14</sup> The lung-head ratio should be measured between 22 and 32 weeks of gestational age, as this range provides improved survival prediction metrics.<sup>15</sup>

*In left-sided CDH, an observed-to-expected lung-head ratio < 25% predicts poor outcome; in right-sided CDH, an observed-to-expected lung-head ratio < 45% may predict poor outcome (strength of recommendation: ●●●○; level of evidence: B-NR).*

Studies have shown that an observed-to-expected lung-head ratio threshold of  $\leq 25\%$  in left CDH is predictive of a 25% survival rate,<sup>11</sup> and survival rates for right CDH tend to be lower at various thresholds of observed-to-expected lung-head ratio.<sup>16</sup> The observed-to-expected total fetal lung volume has performed well

for survival prediction in CDH, with areas under the curve ranging from 0.79 to 0.89.<sup>17–19</sup>

*Fetal magnetic resonance imaging (MRI) should be used (where available) for the assessment of lung volume and liver herniation in moderate and severe CDH (strength of recommendation: ●●●●; level of evidence: B-NR).*

Comparisons of survival prediction between prenatal MRI for total fetal lung volume estimation and ultrasound imaging to measure lung-head ratio have shown conflicting results.<sup>11,20</sup> However, an advantage of antenatal MRI is the identification and quantification of liver herniation which, when combined with observed-to-expected total fetal lung volume, improves prediction characteristics.<sup>17</sup> Thus, MRI may have additional value where available, especially in those cases where the observed-to-expected lung-head ratio on ultrasound shows moderate or severe CDH.

### Ventilation

*Newborns with CDH who have immediate respiratory distress should be preferentially intubated at birth; bag-valve-mask ventilation should be avoided (strength of recommendation: ●●●●; level of evidence: level C, expert opinion [C-EO]).*

The neonatal resuscitation guideline from the American Heart Association and the American Academy of Pediatrics<sup>21</sup> supports immediate endotracheal intubation for neonates with a known diagnosis of CDH, and thus the strict avoidance of bag-valve-mask ventilation for these patients.

*Sedation should be provided to all mechanically ventilated newborns with CDH. Deep sedation and neuromuscular blockade should be provided selectively to those with greater ventilation or oxygen requirements (strength of recommendation: ●●●●; level of evidence: B-NR).*

The routine use of deep sedation and muscle relaxation has been shown to impair respiratory function and lung compliance in newborns with CDH, resulting in higher oxygenation indices.<sup>22</sup>

*A T-piece should be used with the ventilator to avoid a peak inspiratory pressure > 25 cm H<sub>2</sub>O (strength of recommendation: ●●●●; level of evidence: B-NR).*

High peak inspiratory pressures above 28 cm H<sub>2</sub>O are strongly associated with ventilator-induced lung injury and recommendations for newborn resuscitation support the use of peak inspiratory pressures below 25 cm H<sub>2</sub>O.<sup>23</sup> Because newborns with CDH often require higher peak pressures (closer to 25 cm H<sub>2</sub>O), the use of a T-piece or mechanical ventilator in the delivery room and during patient transport may help avoid inadvertent overdistension of the lungs.

*An arterial pCO<sub>2</sub> between 45 and 60 mm Hg and a pH between 7.25 and 7.40 should be targeted in all newborns with CDH (strength of recommendation: ●●●●; level of evidence: B-NR).*

*Supplemental oxygen should be titrated to achieve a preductal saturation of at least 85%, but not > 95% (strength of recommendation: ●●●●; level of evidence: B-EO).*

#### Box 2: Modified Delphi consensus framework

- Strong agreement with recommendation  
> 80% of the votes were strongly agree OR strongly disagree
- Good agreement with recommendation  
> 80% of the votes were strongly/somewhat agree OR strongly/somewhat disagree  
AND > 50% of these votes were either strongly agree or disagree
- Weak agreement with recommendation  
> 80% of the votes were strongly/somewhat agree OR strongly/somewhat disagree  
AND < 50% of these votes were either strongly agree or disagree
- No consensus

**Table 1 (part 1 of 2): Abridged recommendations for diagnosing and managing congenital diaphragmatic hernia**

Recommendation	Strength of recommendation*	Level of evidence†
<b>Prenatal diagnosis</b>		
Ultrasound measurement of O/E LHR should be used between 22 and 32 w of gestational age to predict the severity of pulmonary hypoplasia in isolated CDH.	●●●●	B-NR
In left-sided CDH, an O/E LHR < 25% predicts poor outcome. In right-sided CDH, an O/E LHR < 45% may predict poor outcome.	●●●○	B-NR
Fetal magnetic resonance imaging should be used (where available) for the assessment of lung volume and liver herniation in moderate and severe CDH.	●●●●	B-NR
<b>Ventilation</b>		
Newborns with CDH and immediate respiratory distress should be preferentially intubated at birth. Bag-valve-mask ventilation should be avoided.	●●●●	C-EO
Sedation should be provided to all mechanically ventilated newborns with CDH. Deep sedation and neuromuscular blockade should be provided selectively to those with greater ventilation or oxygen requirements.	●●●●	B-NR
A T-piece should be used with the ventilator to avoid a peak inspiratory pressure > 25 cm H <sub>2</sub> O.	●●●●	B-NR
An arterial pCO <sub>2</sub> between 45 and 60 mm Hg and a pH between 7.25 and 7.40 should be targeted in all newborns with CDH.	●●●●	B-NR
Supplemental oxygen should be titrated to achieve a preductal saturation of at least 85%, but not > 95%.	●●●●	B-EO
Gentle, intermittent mandatory ventilation should be the initial ventilation mode for newborns with CDH who require respiratory support. High-frequency oscillatory ventilation or high-frequency jet ventilation should be used when the peak inspiratory pressure required to control hypercapnia using intermittent mandatory ventilation exceeds 25 cm H <sub>2</sub> O.	●●●●	B-NR
<b>Hemodynamic support</b>		
Treatment of poor perfusion (capillary refill > 3 s, lactate > 3 mmol/L, urine output < 1 mL/kg/h) and blood pressure below norms for age should include: <ul style="list-style-type: none"> <li>• judicious administration of crystalloid, generally not exceeding 20 mL/kg;</li> <li>• inotropic agents such as dopamine or epinephrine; and</li> <li>• hydrocortisone.</li> </ul> If poor perfusion continues, assessment of cardiac function (i.e., echocardiogram, central venous saturation) should be performed	●●●●	B-NR
<b>Echocardiography</b>		
Two standardized echocardiograms, one within 48 h of birth and one at 2–3 w of life, are needed to assess pulmonary vascular resistance, as well as left ventricular and right ventricular function. Additional studies may be conducted as clinically indicated.	●●●●	C-LD
<b>Management of pulmonary hypertension</b>		
<b>iNO</b> is indicated for confirmed suprasystemic pulmonary arterial hypertension without left ventricular dysfunction, provided lung recruitment is adequate. In the absence of clinical or echocardiographic response, iNO should be stopped.	●●●○	C-EO
<b>Sildenafil</b> should be considered in patients with refractory pulmonary hypertension (i.e., unresponsive to iNO) or as an adjunct when weaning iNO.	●●●○	B-R
<b>Milrinone</b> should be used to treat cardiac dysfunction, particularly if it is associated with pulmonary hypertension.	●●●●	B-NR
<b>Prostaglandin E<sub>1</sub></b> can be used to maintain ductus arteriosus patency and reduce right ventricular afterload in patients with pulmonary hypertension with right ventricular failure, or in the presence of a closing ductus.	●●●○	C-LD
<b>Extracorporeal life support</b>		
The possibility of extracorporeal life support should be discussed during prenatal counselling for CDH, and should disclose that available evidence does not suggest a survival benefit to its use.	●●●○	B-R

**Table 1 (part 2 of 2): Abridged recommendations for diagnosing and managing congenital diaphragmatic hernia**

Recommendation	Strength of recommendation*	Level of evidence†
<b>Surgery</b>		
The following physiologic criteria should be met before surgery: <ul style="list-style-type: none"> <li>• urine output &gt; 1 mL/kg/h</li> <li>• FiO<sub>2</sub> &lt; 0.5</li> <li>• preductal oxygen saturation between 85% and 95%</li> <li>• normal mean arterial pressure for gestational age</li> <li>• lactate &lt; 3 mmol/L</li> <li>• estimated pulmonary artery pressures less than systemic pressure.</li> </ul> Failure to meet these criteria within 2 w should prompt consideration of either attempted repair or a palliative approach.	●●○○	C-EO
<b>Patch repair:</b> For diaphragmatic defects that are not amenable to primary repair, oversized, tension-free polytetrafluoroethylene/GORE-TEX patches should be used.	●●●●	C-LD
<b>Open repair v. minimally invasive surgery:</b> A minimally invasive surgical approach or technique should not be used in the repair of neonatal CDH because of the high rates of recurrence.	●●●●	B-NR
<b>For patients on extracorporeal life support:</b> Surgery should be avoided until after decannulation. If the patient cannot be weaned off extracorporeal life support, consideration should be given for either surgery or palliation, as appropriate.	●●●●	C-LD
<b>Long-term follow-up</b>		
• We recommend standardized multidisciplinary follow-up for children with CDH to provide surveillance and screening, optimal and timely diagnosis and clinical care adjusted to the level of risk.	●●●●	B-NR
• We recommend identifying the subset of CDH survivors at high risk for long-term morbidity as comprising those infants and children who require extracorporeal life support, who have been repaired with a patch or who required respiratory support at 30 days of life.	●●●●	B-NR
Note: CDH = congenital diaphragmatic hernia, iNO = inhaled nitric oxide, O/E LHR = observed-to-expected lung-head ratio. *Strength of recommendation: the number of circles represents the level of expert consensus during creation of recommendations (see Box 2). †Level of evidence: evidence supporting the recommendation (see Box 1).		

The concept of permissive hypercapnia was validated by Boloker and colleagues in their report on 120 consecutive infants with CDH using this strategy.<sup>24</sup> Overall survival in this series was 76% and only two of those discharged required oxygen. A subsequent systematic review<sup>25</sup> further supported a strategy of permissive hypercapnia as a means of achieving improved survival with minimization of lung injury. Because of the risk of pulmonary hypertension, routine administration of supplemental oxygen in CDH is often considered. However, exposure to high oxygen concentrations in neonates results in free radical injury to the lungs; thus, more modest oxygenation targets are likely beneficial.<sup>26</sup>

*Gentle, intermittent mandatory ventilation should be the initial ventilation mode for newborns with CDH who require respiratory support. High-frequency oscillatory ventilation or high-frequency jet ventilation should be used when the peak inspiratory pressure required to control hypercapnia using intermittent mandatory ventilation exceeds 25 cm H<sub>2</sub>O (strength of recommendation: ●●●●; level of evidence: B-NR).*

The VICI trial (Ventilation in Infants with Congenital diaphragmatic hernia: an International randomized clinical trial) was the first randomized controlled study to show that conventional mechanical ventilation should be the first-line strategy for

infants with CDH.<sup>27</sup> This study showed similar rates of mortality and bronchopulmonary dysplasia, the primary study outcome, between groups with conventional mechanical ventilation and groups with high-frequency oscillatory ventilation. Infants who were managed with conventional mechanical ventilation also had shorter durations of ventilation, reduced inotrope requirements and lower rates of extracorporeal life support. Although high-frequency oscillatory ventilation and high-frequency jet ventilation have been used successfully as a primary ventilation strategy,<sup>28,29</sup> these should be considered “rescue” modes in infants with CDH who do not meet ventilatory targets with initial conventional mechanical ventilation.

### Hemodynamic support

*Treatment of poor perfusion (capillary refill > 3 s, lactate > 3 mmol/L, urine output < 1 mL/kg/h) and blood pressure below norms for age should include the judicious administration of crystalloid, generally not exceeding 20 mL/kg; inotropic agents (e.g., dopamine, epinephrine); and hydrocortisone. If poor perfusion continues, assessment of cardiac function (i.e., echocardiogram, central venous saturation) should be performed (strength of recommendation: ●●●●; level of evidence: B-NR).*

Hemodynamic instability, a frequent occurrence in infants with CDH, requires prompt detection, interpretation of cause and

effective treatment to optimize perfusion and attenuate the effects of severe pulmonary hypertension. As the left ventricle may be smaller and less compliant, judicious fluid resuscitation is required to prevent pulmonary edema;<sup>9,30</sup> the absence of a prompt response to fluid usually signals the need for inotropic support. In a small cohort study, dopamine, epinephrine and norepinephrine increased heart rate and mean arterial pressure without improving buccal perfusion (a proxy for the microcirculation).<sup>31</sup> Milrinone, a purported pulmonary vasodilator and inotrope, was shown to reduce both right ventricular dysfunction and oxygenation index substantially.<sup>32</sup> Reports of low cortisol levels,<sup>33</sup> as well as altered expression of corticotropin binding protein and its receptor, in neonates with pulmonary hypertension<sup>34</sup> suggest a specific role for hydrocortisone in infants with CDH who have refractory hypertension.

### Echocardiography

*Two standardized echocardiograms, one within 48 hours of birth and one at 2 to 3 weeks of life, are needed to assess pulmonary vascular resistance, as well as left ventricular and right ventricular function. Additional studies may be conducted as clinically indicated (strength of recommendation: ●●●●; level of evidence: level C, limited data [C-LD]).*

Standardized echocardiography is a critical assessment tool in CDH care. A complete echocardiogram (structural and functional) should be performed within 48 hours of birth to define intracardiac anatomy (given the known association of congenital heart disease) and assess pulmonary artery size, the severity of pulmonary hypertension, presence and direction of ductal and intracardiac shunting, and right and left ventricular function.<sup>35-37</sup> Follow-up echocardiograms are indicated for unexplained hemodynamic instability, but not “routinely” before surgical repair in the absence of a clinical indication (i.e., suspicion of a closing ductus arteriosus). A follow-up echocardiogram is routinely indicated, given that persistence of pulmonary hypertension beyond 14 days predicts death and other adverse outcomes,<sup>35,38</sup> and should be part of the ongoing evaluation of patients with CDH who are maintained on pulmonary hypertension therapy after discharge.

### Management of pulmonary hypertension

*Inhaled nitric oxide is indicated for confirmed suprasystemic pulmonary arterial hypertension without left ventricular dysfunction, provided lung recruitment is adequate. In the absence of clinical or echocardiographic response, inhaled nitric oxide should be stopped (strength of recommendation: ●●●○; level of evidence: C-EO).*

Inhaled nitric oxide significantly improves the oxygenation index, increases the PaO<sub>2</sub> and reduces the need for extracorporeal membrane oxygenation in populations that have pulmonary hypertension.<sup>39-41</sup> However, a Cochrane subgroup analysis of inhaled nitric oxide use in 51 patients with CDH failed to discern similar benefit.<sup>42</sup> Although these results suggest that inhaled nitric oxide may not be effective in CDH, they need to be interpreted cautiously, given the era in which they were obtained (> 15 years ago), the evolution in care over this period, and the limited numbers of patients included in the analysis. Thus, we support the use of inhaled nitric oxide for the treatment of severe pulmonary hypertension (with

preserved left ventricular function and adequate lung recruitment), but recommend its discontinuation if no clinical improvement is observed within 24 hours of beginning treatment.

*Sildenafil should be considered in patients with refractory pulmonary hypertension (i.e., unresponsive to inhaled nitric oxide) or as an adjunct when weaning inhaled nitric oxide (strength of recommendation: ●●●○; level of evidence: level B, randomized [B-R]).*

*Milrinone should be used to treat cardiac dysfunction, particularly if it is associated with pulmonary hypertension (strength of recommendation: ●●●●; level of evidence: B-NR).*

The evidence for the routine use of other pulmonary vasodilators in CDH is sparse. Milrinone<sup>32</sup> and sildenafil<sup>43,44</sup> have shown some efficacy in small case series, but most of the evidence supporting the biological plausibility of their benefit is derived from populations without CDH.<sup>45</sup>

*Prostaglandin E<sub>1</sub> can be used to maintain ductus arteriosus patency and reduce right ventricular afterload in patients with pulmonary hypertension with right ventricular failure, or in the presence of a closing ductus (strength of recommendation: ●●●○; level of evidence: C-LD).*

Preoperative continuous right-to-left or bidirectional shunting in patients with CDH may predict a subgroup of patients with high mortality secondary to pulmonary hypertension or impending right ventricular failure.<sup>46</sup> Case series have suggested that prostaglandin E<sub>1</sub> may be considered to help offload the right ventricle in the context of a closing ductus arteriosus with an exclusive right-to-left shunt.<sup>47</sup>

### Extracorporeal life support

*The possibility of extracorporeal life support should be discussed during prenatal counselling for CDH, and disclose that available evidence does not suggest a survival benefit to its use (strength of recommendation: ●●●○; level of evidence: B-R).*

*In circumstances where extracorporeal life support is considered as rescue therapy, the usual contraindications to its use should apply, including irreversible lung disease (strength of recommendation: ●●●●; level of evidence: C-EO).*

The specific role of extracorporeal life support remains unclear despite its survival benefit for most types of severe neonatal respiratory failure.<sup>48</sup> The recently published VICI trial failed to show any difference in CDH outcome between extracorporeal life support and non-extracorporeal life support centres.<sup>27</sup> Current extracorporeal life support practice patterns in Canada show very low rates of use compared with the United States and Europe, yet CDH outcomes across Canada are comparable with those of published international reports.<sup>49-51</sup> Extracorporeal life support should be discussed during prenatal counselling and may be considered as a therapeutic rescue option in those centres that offer it.

### Surgery

*The following physiologic criteria should be met before surgery: urine output > 1 mL/kg/h; FiO<sub>2</sub> < 0.5; preductal oxygen saturation between 85% and 95%; normal mean arterial pressure for gestational age; lactate < 3 mmol/L; and estimated pulmonary artery*

pressures less than systemic pressure. Failure to meet these criteria within two weeks should prompt consideration of either attempted repair or a palliative approach (strength of recommendation: ●●○○; level of evidence: C-EO).

Two randomized controlled trials and a systematic review failed to show an advantage to either early or late surgery.<sup>52-54</sup> In addition, no studies have shown explicit “readiness for surgery” criteria that optimize outcome.<sup>55-59</sup> Although we recommend that certain physiologic criteria (including intrasystemic pulmonary artery pressures) be met before surgery, we have cautioned that failure to meet these criteria should not prevent surgery, which offers the only hope for survival. We specifically suggest that failure to meet physiologic stabilization criteria within two weeks (estimated to correspond with the time required to achieve optimal improvement in pulmonary hypertension) should prompt consideration of either attempted repair or the adoption of a palliative (nonoperative) approach, in accordance with the family’s wishes.

*For diaphragmatic defects that are not amenable to primary repair, oversized, tension-free polytetrafluoroethylene/GORE-TEX patches should be used (strength of recommendation: ●●●●; level of evidence: C-LD).*

A variety of materials, including permanent (polytetrafluoroethylene), biosynthetic (e.g., small intestinal submucosa, dermal collagen), and composite (e.g., polytetrafluoroethylene and intestinal submucosa) patches, as well as autologous muscle flaps, have been used to repair large diaphragmatic defects that are not amenable to primary repair. The supportive literature for patch use in CDH consists of cohort studies of low quality.<sup>55,56,60-62</sup> We endorse the use of tension-free or cone-shaped polytetrafluoroethylene/GORE-TEX patches, because of the accumulated experience with their use. We specifically advocate against the use of intestinal submucosal patches alone, as they are associated with an unacceptably high rate of recurrence.

*A minimally invasive surgical approach or technique should not be used in the repair of neonatal CDH because of the high rates of recurrence (strength of recommendation: ●●●●; level of evidence: B-NR).*

The minimally invasive surgical repair of CDH was proposed because of its theoretical benefits of reduced perioperative pain, decreased use of resources and reduction in long-term complications.<sup>57</sup> However, despite technical feasibility, studies comparing minimally invasive surgery with open repair have identified a relative risk of recurrence that is three- to four-fold higher with the minimally invasive surgery approach.<sup>58,59,63</sup> Although the clinical implications of intraoperative hypercarbia<sup>64</sup> and acidosis<sup>64,65</sup> during minimally invasive surgical repair are unclear, the potential adverse outcomes attributable to these physiologic derangements in the context of labile pulmonary vascular resistance cannot be ignored. As such, the repair of neonatal CDH using minimally invasive surgical techniques should be performed only within the context of a trial and only after full disclosure of the known increased risk of recurrence and the potential risks associated with hypercarbia and acidosis.

*For patients on extracorporeal life support, surgery should be avoided until after decannulation. If the patient cannot be weaned off extracorporeal life support, consideration should be given for either surgery or palliation, as appropriate (strength of recommendation: ●●●●; level of evidence: C-LD).*

The role of extracorporeal life support in CDH is still being debated (as discussed earlier), but there is further controversy regarding its role with respect to the timing of surgical repair. Proponents of CDH repair during extracorporeal life support cite the potential advantages of reducing the mass effect produced by visceral contents within the thoracic cavity, the availability of the extracorporeal life support circuit to support postoperative cardiovascular and renal dysfunction, and reduced overall duration of extracorporeal life support.<sup>66,67</sup> Moreover, many centres now use perioperative antifibrinolytic therapy to reduce bleeding complications.<sup>68,69</sup> Our recommendation that surgery be delayed until after weaning from extracorporeal life support is based predominantly on a comparative study involving more than 500 infants with CDH from the Congenital Diaphragmatic Hernia Study Group (CDHSG),<sup>70</sup> which showed an increased hazard ratio for mortality (hazard ratio 1.41; 95% confidence interval [CI] 1.03-1.92) if the repair was conducted while patients were on extracorporeal life support. Infants who cannot be weaned from extracorporeal life support within two weeks pose a difficult problem. We suggest that in this specific scenario, the team proceed with surgery while patients are on extracorporeal life support or adopt a palliative approach, in accordance with family wishes.

### Long-term follow-up

*We recommend standardized multidisciplinary follow-up for children with CDH to provide surveillance and screening, optimal and timely diagnosis and clinical care adjusted to the level of risk (strength of recommendation: ●●●●; level of evidence: B-NR).*

*We recommend identifying the subset of CDH survivors at high risk for long-term morbidity as comprising those infants and children who require extracorporeal life support support, who have been repaired with a patch or who required respiratory support at 30 days of life (strength of recommendation: ●●●●; level of evidence: B-NR).*

In recent years, the focus of outcome improvement in CDH has shifted from mortality reduction to the prevention, early identification and timely management of survivor morbidity, including cardiopulmonary,<sup>71</sup> gastrointestinal and nutritional,<sup>72</sup> neurodevelopmental<sup>73</sup> and musculoskeletal issues;<sup>74</sup> hearing loss;<sup>75</sup> and reduced quality of life for the child and the family.<sup>76</sup> The American Academy of Pediatrics has published a set of recommendations for the surveillance of CDH survivors<sup>77</sup> that can effectively be implemented in specialized interdisciplinary clinics. Long-term follow-up of CDH in Canada, however, appears more variable and may be influenced by centre volume, with larger centres having interdisciplinary follow-up clinics and smaller centres providing decentralized surveillance through local pediatric surgeons and subspecialty pediatricians.<sup>78</sup>

In addition to regular surveillance, we recommend intensified screening for patients identified as high risk, which includes those requiring pulmonary support at 30 days of age,<sup>79</sup> who need

patch repair<sup>80</sup> and who need extracorporeal life support.<sup>81</sup> These CDH survivors should be offered screening (e.g., growth, hearing), including standardized neurodevelopmental testing.

### Implementation

This guideline has been distributed to the professional societies of the clinical groups involved in CDH care. These include the Society of Obstetricians and Gynaecologists of Canada, the Fetus and Newborn Committee of the Canadian Paediatric Society and the Canadian Association of Paediatric Surgeons. In collaboration with the executive committees of each of these societies, and in partnership with the Canadian Association of Paediatric Health Centres, a preferred knowledge mobilization strategy is being developed.

Using the existing Canadian Pediatric Surgery Network framework, we are creating decision support tools that will be distributed to all 15 participating neonatal intensive care units, to encourage the use of the guideline on daily rounds of these units. Compliance audits will be built into existing registry data collected at each site, and become part of the benchmarked annual report provided to each Canadian Pediatric Surgery Network site, which currently provides anonymized, risk-adjusted, centre-specific treatment and outcome summaries for CDH. The steering committee will be responsible for leading an evidence renewal review every three years, effectively making this a “living guideline.”

### Other guidelines

Two major guidelines were taken into consideration in creating these recommendations: the CDH EURO Consortium recommendations published in 2010 and updated in 2016,<sup>8,9</sup> and the American Heart Association/American Thoracic Society<sup>10</sup> guideline on pulmonary hypertension management. This guideline differs from previously published guidelines in several respects. First, the controversies related to the timing of CDH repair are dealt with more directly, specifically addressing the not-so-infrequent situation of the neonate who does not meet “ideal” physiological stability criteria. In this situation, meaningful survival can still be expected, but the risks and limitations must be explicitly discussed with the family and care team. As an extension of this, we have also provided a perspective on how to approach an infant with unrepaired CDH who cannot be weaned from extracorporeal life support. Second, we also address the ideal patch material to be used for those infants with CDH that cannot be repaired primarily. Third, we comment on the role of “experimental therapies” and how these treatments should likely only be considered in the context of a well-designed clinical study. Lastly, our guideline makes specific statements regarding the role of long-term, multidisciplinary follow-up, particularly for high-risk CDH infants.

### Gaps in knowledge

The major gaps in knowledge in the creation of this guideline relate to the relatively low level and variable quality of the evidence used to inform the recommendations. Most studies tended to be comparative cohort studies, often comparing his-

torical to contemporary cohorts after an instituted practice change. Furthermore, much of the literature related to surgical timing and technique is limited to case series. Prospective studies would be valuable to reaffirm the clinical care recommendations that we have made.

### Conclusion

This guideline reflects a national, interdisciplinary effort to standardize CDH care across Canada. Using a combination of available evidence, expert consensus and pragmatism, this guideline addresses the phases of CDH care from prenatal diagnosis to acute, in-hospital care and to postdischarge surveillance. Prenatal risk prognostication will help identify infants with severe CDH and aid mobilization of human and material resources for those infants in most need. Cardiorespiratory support should escalate in a stepwise manner, in accordance with the severity of physiologic impairment, but always seeking to minimize iatrogenic lung injury. Echocardiography is critical for characterizing the severity of pulmonary hypertension and myocardial function, and allows for targeted identification of systemic therapies that optimize hemodynamic function or reduce pulmonary vascular resistance. Open surgical repair should generally be delayed until the infant is “stable.” Long-term disability surveillance is essential, especially in the high-risk cohort, and should be managed by interdisciplinary teams of primary care physicians, pediatricians, pediatric subspecialists, pediatric surgeons and other allied health providers.

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**Authors:** Pramod S. Puligandla MD MSc, Erik D. Skarsgard MD MSc, Martin Offringa MD PhD, Ian Adatia MBChB, Robert Baird MDCM MSc, J.A. Michelle Bailey MD MSc, Mary Brindle MD MPH, Priscilla Chiu MD PhD, Arthur Cogswell MBBS, Shyamala Dakshinamurti MD MSc, Hélène Flageole MD MSc, Richard Keijzer MD PhD, Douglas McMillan MD, Titilayo Oluyomi-Obi MD, Thomas Pennaforte MD, Thérèse Perreault MD MSc, Bruno Piedboeuf MD, S. Patricia Riley MDCM, Greg Ryan MD, Anne Synnes MDCM MHS, Michael Traynor MD

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**Affiliations:** University of Alberta and Glenwood Radiology and Medical Centre (Adatia), Edmonton, Alta.; Montreal Children's Hospital (Perreault, Puligandla, Riley), Montréal, Que.; Foothills Medical Hospital (Oluyomi-Obi), Calgary, Alta.; Alberta Children's Hospital (Bailey, Brindle), Calgary, Alta.; The Hospital for Sick Children (Chiu, Kavanagh, Offringa), Toronto, Ont.; British Columbia Children's Hospital (Baird, Cogswell, Skarsgard, Traynor), Vancouver, BC; British Columbia Women's Hospital &

Health Centre (Synnes), Vancouver, BC; Winnipeg Children's Hospital (Dakshinamurti, Keijzer), Winnipeg, Man.; McMaster Children's Hospital (Flageole), Hamilton, Ont.; Mount Sinai Hospital (Ryan), Toronto, Ont.; IWK Health Centre (McMillan), Halifax, NS; Centre hospitalier universitaire Sainte-Justine (Pennaforte), Montréal, Que.; CHU de Québec — Université Laval (Piedboeuf), Québec, Que.

**Canadian CDH Collaborative Steering Committee:** Pramod S. Puligandla (Chair), Erik D. Skarsgard, Martin Offringa.

**Canadian CDH Collaborative:** Ian Adatia, Robert Baird, J.A. Michelle Bailey, Mary Brindle, Priscilla Chiu, Arthur Cogswell, Shyamala Dakshinamurti, Hélène Flageole, Richard Keijzer, Douglas McMillan, Titilayo Oluyomi-Obi, Thomas Pennaforte, Thérèse Perreault, Bruno Piedboeuf, S. Patricia Riley, Greg Ryan, Anne Synnes, Michael Traynor.

**Solicited parental advisory/advocacy groups:** Rare Disease Foundation, Canadian Family Advisory Network.

**External reviewers:** Dr. Marjorie Arca (Professor of Surgery, University of Wisconsin). Prof. Dick Tibboel MD PhD (Departments of Intensive Care and Pediatric Surgery, Erasmus MC; Sophia Children's Hospital, Rotterdam, The Netherlands).

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**Correspondence to:** Pramod Puligandla, pramod.puligandla@mcgill.ca