Congenital Diaphragmatic Hernia: Maximizing Survival

Mark F. Weems, MD,* Tim Jancelewicz, MD, MA,† Hitesh S. Sandhu, MBBS‡

Divisions of *Neonatal-Perinatal Medicine, †Pediatric Surgery, and ‡Critical Care, Department of Pediatrics, University of Tennessee Health Science Center, Le Bonheur Children’s Hospital, Memphis, TN.

Education Gaps

1. Overall mortality for patients with diaphragmatic hernia remains nearly 30% but can be greatly reduced by following a standardized protocol focused on lung-protective strategies.

2. Early repair before or during extracorporeal membrane oxygenation support may benefit patients with severe pulmonary hypertension.

Abstract

Congenital diaphragmatic hernia occurs when a portion of the fetal diaphragm is absent, allowing abdominal contents to enter the thorax, and is associated with impaired pulmonary development. Although overall mortality is near 30%, a mortality rate less than 15% may be possible by following a standardized multidisciplinary care plan. Fetal diagnosis and evaluation can improve coordination of care, but there is no clear role for fetal intervention. After birth, gentle ventilation with permissive hypercapnia supports the infant while minimizing lung injury. Appropriate cardiovascular support, treatment of pulmonary hypertension, and extracorporeal membrane oxygenation may benefit some patients. Timing of surgical repair depends on disease severity. All patients should have close follow-up after discharge.

Objectives After completing this article, readers should be able to:

1. Describe fetal development, assessment, and interventions for diaphragmatic hernia.

2. Define gentle ventilation and its role in the management of diaphragmatic hernia.

3. Demonstrate the recommended preoperative stabilization of patients with diaphragmatic hernia.

4. Recognize the value of extracorporeal membrane oxygenation for patients with diaphragmatic hernia.

5. Discuss surgical planning for diaphragmatic hernia repair.

AUTHOR DISCLOSURE Drs Jancelewicz and Sandhu have disclosed no financial relationships relevant to this article. Dr. Weems disclosed that he is a consultant to the American Academy of Pediatrics, as associate editor of Pediatrics in Review. This commentary does contain a discussion of an unapproved/investigative use of a commercial product/device.
INTRODUCTION

Congenital diaphragmatic hernia (CDH) is an uncommon and complex condition that carries a high mortality rate. Over the past 20 years, overall survival has improved gradually from 63% to more than 70%. (1) Further advancement remains elusive because clinical trials and universally accepted standards of care for CDH management are lacking. However, implementation and adherence to a CDH protocol may improve outcomes. (2) Management at centers reporting survival of 85% to 90% features several common elements, including gentle ventilation, permissive hypercapnia, cardiovascular support, early use of extracorporeal membrane oxygenation (ECMO), and delayed surgical repair. (2)(3)(4)(5) However, it must be remembered that the survival rate is a function of the denominator that is used. Case series from tertiary centers do not include the sickest infants who die in utero, in the delivery room, or soon after admission but before transfer to a tertiary center. (6)

Although survival rates have improved, patients with CDH are at risk for long-term morbidity. Long-term follow-up is recommended to monitor neurodevelopmental delay, hearing loss, pulmonary and gastrointestinal complications, and CDH recurrence. (7)

EPIDEMIOLOGY AND FETAL DEVELOPMENT

The estimated prevalence of CDH varies between 2.4 and 4.1 per 10,000 births. The European Surveillance of Congenital Anomalies (EUROCAT) data from 1980 to 2009 show an isolated CDH prevalence of 1.6 per 10,000 births and a total (including isolated cases) nonsyndromic CDH prevalence of 2.3 per 10,000 births. These data exclude multiple births, but include all other pregnancies of more than 20 weeks of gestation. The prevalence of CDH has risen slowly over time, but the rate of therapeutic abortion has increased, resulting in a dramatically decreased incidence among live births. (8)

The diaphragm begins as the septum transversum and 2 triangular pleuroperitoneal folds (PPFs) separate the pleural cavity from the peritoneal cavity. The mesodermal PPFs migrate across the septum transversum and give rise to muscle connective tissue fibroblasts to form the connective tissue structure of the diaphragm. Somatic muscle precursor cells then migrate across the muscle connective fibroblasts to complete muscularization of the diaphragm by embryonic day 16.5 in the mouse model (correlating with the 10th week of human gestation). (9)

In the case of CDH, mutated PPF-derived muscle connective tissue fibroblasts prevent muscularization in specific areas adjacent to fully muscularized regions. The relatively weak nonmuscularized area eventually fails under pressure, allowing viscera to enter the thorax (Fig 1). The physical presence of abdominal contents inhibits lung growth and leads to pulmonary hypoplasia. (9) A 2-hit hypothesis has also been proposed, suggesting that genetic mutations leading to CDH may directly inhibit lung growth, but this is less clearly described.

ASSOCIATED ANOMALIES

Isolated CDH occurs in 58% to 64% of antenatally diagnosed CDH cases. (8)(10) EUROCAT data show that chromosomal anomalies occur in 7.2%, genetic syndromes occur in 3.5%, and nonsyndromic associated anomalies occur in 25% of singleton CDH cases. Among the chromosomal anomalies, the most common are trisomy 18 (4.2%), trisomy 13 (1.1%), and trisomy 21 (0.9%). (8)

Fryns syndrome is the most common nontrisomy genetic syndrome associated with CDH; it is found in at least 0.5% of CDH cases. Other syndromes associated with CDH include Pallister-Lillian, Wolf-Hirschorn, and Cornelia de Lange. (8)

Nonsyndromic anomalies are common, occurring in up to 42% of CDH pregnancies. Described anomalies include cardiac (most common), urinary, musculoskeletal, and neurologic. Genetic syndromes and other anomalies confer a poor prognosis and increased mortality. (8)(10)

BENEFITS OF COORDINATED CARE

Individual cases vary widely with regard to severity of illness, size of defect, degree of pulmonary hypoplasia, and response to pulmonary vasodilators. As such, there are many different opinions about appropriate CDH treatment, and management varies from center to center. Despite these differences, several recent studies have shown the benefits of standardized care (Table 1). The details of each protocol differ, but they generally describe gentle ventilation, permissive hypercapnia, cardiovascular support, early use of ECMO, and delayed surgical repair. (2)(3)(4)(5)

PRENATAL MANAGEMENT

Diagnosis

Recent data from the CDH Study Group revealed that 68% of 4,029 live-born infants with CDH were diagnosed antenatally. (11) Fetal ultrasonography is part of routine prenatal
obstetric care, but its usefulness in diagnosing CDH is variable. Diagnostic sensitivity has regional variation and depends on operator experience, defect laterality (left is easier to identify than right CDH), “late” herniation of viscera, and the presence of other anomalies. In theory, it is possible to diagnose CDH any time after completion of diaphragmatic development and return of the intestines to the abdominal cavity, which occurs before the end of the first trimester. However, many cases may not be diagnosed until after 24 weeks of gestation, which could exceed the latest legal fetal age for pregnancy termination. (6)

Diagnostic features of CDH on ultrasonography include primary signs such as viscera in the chest and secondary signs such as mediastinal shift, polyhydramnios, and cardiac malposition or abnormal cardiac axis. Fluid-filled viscera, most commonly the stomach, may be identified at the level of the 4-chamber heart view. Once CDH is identified, magnetic resonance imaging (MRI) can more reliably determine liver herniation, provide 3-dimensional (and potentially more accurate) visualization of the lungs, and detect associated anomalies. (6) However, acquisition early in pregnancy may yield images with inadequate resolution.

Once the diagnosis of CDH is made, multidisciplinary consultation with maternal-fetal medicine, pediatric surgery, and neonatology should be arranged to establish a plan for further evaluation, surveillance, delivery, and postnatal management.

Markers of Severity

In the fetus with CDH, the prognosis is largely determined by gestational age, degree of lung hypoplasia, and the presence or absence of other anomalies. In addition to detection of congenital anomalies, prenatal imaging enables CDH severity to be estimated by directly measuring the size of the lungs or by assessing surrogate variables that indirectly quantify the amount of functional lung that will be available at birth.

A large diaphragmatic defect results in more lung compression and lung hypoplasia, leading to pulmonary hypertension (PHTN) and severe disease. Prenatal identification of liver in the chest (“liver up”) implies a large defect and thus represents a more severe subset of CDH, but it can be difficult to distinguish between lung and liver on ultrasonography. (6) In addition, some “liver up” patients may have good outcomes. (12) In general, liver position is not as accurate in mortality prediction as other measures, though volume of herniated liver measured with MRI may provide a better survival estimate. (13)

### TABLE 1. Successful Diaphragmatic Hernia Protocols

<table>
<thead>
<tr>
<th>AUTHOR</th>
<th>YEAR</th>
<th>PRE-PROTOCOL SURVIVAL</th>
<th>PROTOCOL SURVIVAL</th>
<th>P-VALUE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bagolan et al (3)</td>
<td>2004</td>
<td>50%</td>
<td>86%</td>
<td>0.02</td>
</tr>
<tr>
<td>Tracy et al (4)</td>
<td>2010</td>
<td>52%</td>
<td>85%</td>
<td>0.006</td>
</tr>
<tr>
<td>Antonoff et al (5)</td>
<td>2011</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All CDH</td>
<td></td>
<td>67%</td>
<td>88%</td>
<td>0.015</td>
</tr>
<tr>
<td>CDH on ECMO</td>
<td></td>
<td>20%</td>
<td>82%</td>
<td>0.002</td>
</tr>
<tr>
<td>van den Hout et al (2)</td>
<td>2011</td>
<td>67%</td>
<td>88%</td>
<td>0.004</td>
</tr>
</tbody>
</table>

CDH=congenital diaphragmatic hernia; ECMO=extracorporeal membrane oxygenation.
First reported in 1996, lung-to-head ratio (LHR) is a ratio of the contralateral area of the 2-dimensional lung to the head circumference, as measured with ultrasonography. LHR is the most widely validated marker of CDH severity, and is most reliable between 22 and 26 weeks of gestation. Observed/expected (O/E) LHR is preferred because the LHR will change over time due to disparate growth rates of the lung and head during gestation. (14) Ultrasoundography operator dependence and interobserver variability can hamper the predictive value of LHR. An O/E LHR less than 25% portends less than 30% survival and an O/E LHR greater than 46% is associated with greater than 85% survival. (15)

MRI may afford better visualization of the lung and liver than ultrasonography, and is less dependent on maternal and fetal positioning. (16) Serial MRI can accurately monitor CDH with less operator dependence than ultrasonography. (14) Currently, MRI is the most accurate way to calculate total lung volume, and use of O/E total lung volume has been shown to have the best predictive value for mortality in a study comparing several common predictors. (16) For fetuses with an O/E total lung volume less than 25%, survival is less than 15%, and for those with O/E total lung volume greater than 35%, survival may be greater than 80%. (13)

**Fetal Intervention**

Prenatal therapy for CDH has included both surgical and nonsurgical approaches, with invasive measures typically undertaken only for those fetuses with severe CDH (low LHR and liver herniation). Various pharmacologic treatments and stem cell therapy have been studied, but no definitive survival benefit has yet been demonstrated.

Although open fetal repair of the diaphragm is possible, it has fallen out of favor because it failed to improve mortality. Over time, prospective, randomized, controlled trials of fetal tracheal occlusion have shown increasing promise for select populations of patients with CDH, despite the findings of the original trial that outcomes were equivalent to those of standard management. (17) This procedure, now performed using a small instrument that percutaneously delivers a removable balloon to the fetal trachea, accelerates lung growth and appears to ameliorate the effects of the CDH on lung development. A randomized European study demonstrated 50% survival with tracheal occlusion compared to 4.8% survival with standard management among fetuses with severe isolated CDH. (18) An ongoing international randomized trial, the Tracheal Occlusion To Accelerate Lung growth (TOTAL) trial, may provide further evidence supporting the use of percutaneous tracheal occlusion for severe CDH. However, currently such therapy remains experimental and is only being undertaken in the context of clinical trials.

**DELIVERY AND RESUSCITATION**

Patients with CDH who are born at a high-volume center using a resuscitation protocol may have a survival advantage. Grushka et al report that patient risk factors were equal in both high- and low-volume centers, but the survival was improved in centers delivering more than 6 patients with CDH annually. (19) The mode of delivery, vaginal versus caesarian, does not seem to affect survival and should be determined based on maternal indications. (20)

There are no data to determine best practices for delivery room resuscitation of patients with CDH. Most published protocols recommend immediate intubation with gentle ventilation, oro- or nasogastric decompression, and avoidance of mask ventilation. (4)(5)(21) The purpose of these steps is to minimize the amount of swallowed air (Fig 2) that will inflate the thoracic bowel and limit lung expansion. The 2015 update to the CDH EURO Consortium Consensus suggests that spontaneous breathing could be offered to low-risk patients, but it is unclear which population might benefit from this practice. (22)

Delayed cord clamping is appropriate for most term and preterm infants, but it cannot currently be recommended for patients with CDH because it would interfere with the goal of immediate intubation.

Surfactant therapy has frequently been used in these patients, but supporting data are controversial. Retrospective data from the CDH Study Group show that surfactant therapy is associated with worse outcomes. Of 522 term infants, those who received surfactant therapy were less likely to survive (57.3% vs 70.0%, \( P = .0033 \)), more likely to receive ECMO (69.8% vs 50.6%, \( P = .04 \)), and more likely to develop chronic lung disease (59% vs 47.6%, \( P = .0066 \)). However, it should be recognized that this was not a randomized controlled trial, and a significant selection bias may have skewed the findings. (23) Similarly, surfactant use in preterm infants (mean, 34 weeks) was associated with a significantly greater odds of death than controls (odds ratio \( [OR] = 2.17; 95\% \text{ confidence interval } [CI] = 1.5–3.2; P < .01 \)). After controlling for gestational age and Apgar score, there was no benefit associated with surfactant use (OR = 1.58; 95% CI = 0.99–2.52; \( P = .05 \)). (24) Thus, routine use of surfactant therapy cannot be recommended for patients with CDH.
Vascular access should be established early to provide fluids, nutrition, and medications. Umbilical venous catheters (UVCs) are commonly placed in neonates, but CDH anatomy is distorted, making radiographic evaluation of UVC position challenging (Fig 2). Alternative central venous access is preferred over placement of UVCs in patients with CDH. If possible, an umbilical arterial catheter should be placed; arterial access is helpful for measuring blood gases and monitoring blood pressure in critically ill patients with CDH.

**RESPIRATORY SUPPORT**

Before the widespread acceptance of gentle ventilation for patients with CDH, ventilator-induced lung injury was very prevalent, and nearly all nonsurvivors had significant lung injury. In what was the largest study of autopsy findings from CDH nonsurvivors, 91% of infants with CDH on whom autopsies were performed had evidence of diffuse alveolar damage, 65% had evidence of air-leak, and 50% had evidence of pulmonary hemorrhage, with destruction of the alveolar-capillary interface. It has been estimated that 25% of CDH deaths occur due to the adverse effects of aggressive care. (26)

Wung et al first championed gentle ventilation with permissive hypercapnia for neonates with PHTN in 1985. They successfully applied this strategy to patients with CDH; other studies have since supported the association between gentle ventilation and improved survival. (27)(28) The specifics of gentle ventilation are loosely defined. For conventional mechanical ventilation (CMV), many recommend limiting the peak inflation pressure to 25 cm H₂O or less with positive end-expiratory pressure 3 to 5 cm H₂O. Respiratory rate is generally recommended between 40 and 60 breaths per minute. Volume-targeted ventilation is gaining popularity in neonatal medicine, but data suggesting optimal tidal volume in the CDH population are limited. Smaller-than-normal tidal volumes are often targeted due to presumed pulmonary hypoplasia associated with CDH. Te Pas et al report that patients with CDH with spontaneous respirations have a mean tidal volume of 3.8 ± 1.9 mL/kg. Sharma et al documented a mean tidal volume requirement of 4.6 mL/kg to achieve mean partial pressure of arterial carbon dioxide (PaCO₂) of 46 mm Hg (6.1 kPa), similar to tidal volumes in infants without diaphragmatic hernia. They pointed out that the metabolic carbon dioxide production in infants with CDH is no different from that in other infants of a similar size, and therefore it is not surprising that they should require similar alveolar minute ventilation. In our practice, we target a tidal volume of 4 mL/kg and increase to 6 mL/kg if needed to achieve a goal partial pressure of carbon dioxide (PaCO₂) of 50 to 65 mm Hg (6–8.6 kPa).

Many have proposed high-frequency oscillatory ventilation (HFOV) as a means of improving oxygenation with a lower risk of alveolar damage, but observational data on HFOV in patients with CDH are conflicting. To date, the VICI Trial is the only randomized, prospective, multicenter trial comparing CMV to HFOV. One hundred seventy-one patients were randomized to receive either CMV or HFOV, and the remainder of each patient’s treatment followed guidelines set by the CDH EURO Consortium. Baseline characteristics were similar, and there was no difference in the primary outcome of death or bronchopulmonary dysplasia. Secondary outcomes favored CMV (Table 2), suggesting that CMV may be associated with improved hemodynamics.
compared to HFOV, as used in the VICI trial, in patients with CDH. (31) We recommend starting with CMV, but HFOV remains a reasonable option for those patients who require excessive peak inflation pressure on CMV.

Very little literature is available on the role of high-frequency jet ventilation (HFJV) in patients with CDH, but it may be a reasonable alternative to HFOV, because HFJV is associated with improved hemodynamics and lower airway pressures compared with HFOV. Kuluz et al demonstrated that HFJV is an acceptable mode of ventilation with patients with CDH, but no data are available that directly compare HFJV to other modes. (32)

In addition to limiting peak inflation pressure, the second focus of gentle ventilation is permissive hypercapnia. Historically, induced respiratory alkalosis was standard treatment for patients with CDH to control PHTN. (27) This strategy has since been associated with several negative outcomes. In the lungs, respiratory alkalosis leads to increased lung injury, because of the substantially higher minute ventilation required to drive down the PaCO₂, bronchoconstriction, pulmonary edema, intrapulmonary shunting, and increased alveolar-to-arterial oxygen gradient. In other organs, including the brain and myocardium, respiratory alkalosis worsens tissue injury by decreasing oxygen delivery and increasing metabolic demand. (33) In contrast, hypercapnia increases spontaneous respiratory effort, improves V/Q mismatch, increases cardiac output, improves oxygen delivery, and may attenuate pulmonary inflammation and injury because smaller tidal volumes are required. (34) Permissive hypercapnia is now preferred over induced respiratory alkalosis, and most experts feel comfortable allowing PCO₂ values as high as 60 to 70 mm Hg (8–9 kPa). (3)(4)(22)(26)(35) In our practice, we target PCO₂ values of 50 to 65 mm Hg (6–8.6 kPa) if the pH values are greater than 7.20. However, acidosis is known to increase pulmonary vascular resistance, and in some infants, adequate oxygenation may not be achieved until a more normal pH is established.

Optimal oxygen delivery in patients with CDH has not been defined. Because oxygen is an effective pulmonary vasodilator, delivery of 100% oxygen was once used to treat PHTN. However, hyperoxia and 100% oxygen should be avoided because it increases pulmonary vascular resistance by increasing oxidative stress, increasing pulmonary vascular contractility, and blunting the response to nitric oxide. (36) Most recent reports recommend targeting oxygen saturation to 85% to 95%. (3)(4)(5)(27)(37) However, the EURO Consortium has taken an even stronger stand against hyperoxia and now recommends targeting preductal oxygen saturation greater than 70% in the first 2 hours after birth followed by target saturation of 80% to 95%. (22)

**PULMONARY HYPERTENSION**

PHTN is one of the most important prognostic factors in the survival of patients with CDH. PHTN in CDH has 2 components. The first is a structural or fixed component due to pulmonary hypoplasia with decreased airway branching and alveolar development. This is associated with underdevelopment of the pulmonary vascular bed and hypertrophy of vascular smooth muscle that can take weeks to
months to overcome. The second is a reversible component due to multiple factors, including imbalanced innervation of the smooth muscles, increased reactivity to noxious stimuli, ventilator-induced lung injury, metabolic derangements, and decreased response to endogenous and exogenous vasodilators. (37)

Assessment of Pulmonary Hypertension

The presence of PHTN is clinically assessed by the pre- and postductal saturation gradient. The difference indicates shunting of blood from the pulmonary artery (PA) across the patent ductus arteriosus to the aorta due to suprasystolic PA pressure. The absence of pre-/postductal gradient suggests that the PA pressure is less than systemic pressure, but that may not be the case if the ductus arteriosus is no longer patent.

Echocardiography should be used to assess cardiac anatomy and to screen for PHTN. Doppler echocardiography defines significant PHTN as PA pressure greater than two-thirds of systemic pressure with possible decreased right ventricular function in the absence of a shunt. Detailed protocols using echocardiographic indices such as PA size and the McGoon index may predict long-term prognosis, but they require further validation. The absence of tricuspid regurgitation in 30% to 60% of echocardiograms can limit the use of this modality to quantify PHTN (37); the degree of PHTN is then deduced by subjective parameters such as septal wall position and right ventricular volume or function.

Management

The evidence for medical management of PHTN in CDH is mostly derived from subgroup analyses of PHTN trials that included patients with CDH. These studies uniformly show that PHTN due to CDH confers a worse prognosis than PHTN alone. Subgroup analyses of several trials show that inhaled nitric oxide does not have a meaningful clinical effect and is associated with a slightly increased risk of requiring ECMO. (38)(39) These results are contrary to the effects of inhaled nitric oxide in patients without CDH, who show improvement in Pao2 and survival. We follow other institutional practices to start inhaled nitric oxide in CDH cases with persistent hypoxemia in an attempt to overcome the reversible component of PHTN; inhaled nitric oxide should be discontinued if there is no improvement in the saturation or Pao2. (21)(35) Although inhaled nitric oxide rarely leads to sustained improvement in oxygenation, the transient benefit that is often seen may be sufficient to stabilize the patient until ECMO can be instituted.

Other pharmacologic agents have been used for non-CDH PHTN with varying degree of success but have not been well studied in the CDH population. The level of evidence for the use of these agents is low; therefore, they cannot be recommended as standard practice. Five case series with a total of 22 patients describe the use of sildenafil, a phosphodiesterase-5 inhibitor that increases cyclic guanosine monophosphate levels in the pulmonary vasculature, increasing nitric oxide activity and vasodilation. In studies by Noori et al and Bialkowski et al, an improvement in oxygenation was noted after starting intravenous sildenafil, and improvement in cardiac output was seen on echocardiography. (40)(41) The EURO Consortium recommends sildenafil in the setting of refractory PHTN with failure of inhaled nitric oxide treatment. (21)

Milrinone, a phosphodiesterase-3 inhibitor, may improve both systolic and diastolic function and has been advocated as potentially beneficial in infants with CDH who often have significant left ventricular hypoplasia and dysfunction. (42) Prostacyclin, prostaglandin E1, and bosentan, an endothelin-1 inhibitor, have each been reported as possible therapeutic options with limited supporting data. (35) If PHTN persists despite gentle ventilation, inhaled nitric oxide, and other PHTN therapy, early use of ECMO is recommended. Milrinone is currently the subject of a clinical trial under way in the Eunice Kennedy Schriver National Institute of Child Health and Human Development Neonatal Research Network.

EXTRACORPOREAL MEMBRANE OXYGENATION

ECMO is a temporizing therapy that supports respiratory and cardiac function during recovery from a reversible cause. In the case of CDH, it is usually refractory PHTN or right ventricular failure that causes the vicious cycle of worsening hypoxia, hypotension, and acidosis despite increasing ventilator and inotropic support. Extracorporeal Life Support Organization (ELSO) data show that over 7,500 patients with CDH have been placed on ECMO with a survival rate of 51%. (43) Despite the introduction of PHTN-specific treatment such as inhaled nitric oxide and sildenafil, ECMO is the only therapy proven to reduce mortality in neonates with PHTN. The role of ECMO in patients with CDH, however, remains controversial. Parallel studies comparing frequent ECMO use (50%) with rare ECMO use (1%) in patients with CDH report similar outcomes. (44)(45) Some nonrandomized studies report increased survival among patients with CDH treated with ECMO, (46) but ELSO data show that ECMO survival among patients with CDH has declined in recent years. (47) It is likely that ECMO offers benefit when used as part of a multipronged lung-protective strategy.
Historically, venoarterial ECMO has been the mode of choice in this population, but both venoarterial and venovenous modes have been used. ELSO data show that 82% of patients were placed on venoarterial ECMO. Adjusted mortality is similar for both venovenous and venoarterial modes, but venoarterial ECMO carries an increased risk of neurologic complications whereas venovenous ECMO is associated with increased risk of renal complications. (48) It is common practice to choose venoarterial ECMO for higher-risk patients with CDH to provide hemodynamic support in addition to respiratory support. Some centers use the ex utero intrapartum therapy strategy in addition to ECMO for high-risk CDH. It involves placing the patient on ECMO immediately after delivery while connected to the placenta. However, Stoffan et al showed no survival benefit to this strategy. (49)

The timing of ECMO for patients with CDH has evolved over the last few decades. ECMO is now applied to overcome refractory PHTN before correcting the defect, with ECMO seldom being necessary after operation. (11) Early ECMO has the additional advantage of decreasing ventilator-associated lung injury. Recent studies have suggested that the best outcomes are from corrective surgery early with ECMO or after the resolution of PHTN and decannulation from ECMO. (50) Duration of ECMO is generally longer than in other neonatal conditions, with an average run time of more than 10 days. (43) CDH accounts for 69% of neonatal cases of ECMO for more than 3 weeks. (51) Increased length of ECMO and second courses are associated with increased complications and poorer outcomes. However, Kays et al report survival rates of 43% and 25% after ECMO durations of 4 and 5 weeks, respectively, and 44% survival after a second course of ECMO. (52) These data indicate that there are no absolute limits for ECMO survival, and ECMO decisions should be made on a case-by-case basis.

ECMO entry criteria are center-specific, with significant variation among centers. ECMO may be considered for a patient with CDH who is unable to stay within goal parameters of a gentle ventilation strategy or who is excessively hypotensive and unresponsive to interventions.

OTHER MEDICAL SUPPORT

Sedation

Minimal stimulation and adequate analgesia are recommended to ensure a calm and soothing environment for the newborn and to minimize adverse physiologic responses during invasive procedures such as intubation or central line placement. Opioids in the form of fentanyl and morphine are the most common choices. (22) Sedation may be augmented with benzodiazepines or other agents according to local practices. Neuromuscular blockade has been associated with increased mortality in patients with PHTN and is generally not recommended for CDH. (22)(53)

Blood Pressure

The goal of an age-appropriate blood pressure is to ensure adequate end-organ perfusion. If hypotension is noted, the first step is to ensure adequate intravascular volume. (22) After hypovolemia is corrected, inotropes may help support decreased left ventricular function, and pulmonary vasodilators may improve right ventricular failure. Inotropic agents have been poorly studied in the CDH population, therefore the choice of therapy is determined by local practice. However, the value of inotropic therapy has been questioned by Buijs et al, who showed that dopamine, norepinephrine, and epinephrine each increased blood pressure but had no effect on the impaired microcirculation of patients with CDH. (54)

Those with catecholamine-resistant hypotension may benefit from the addition of vasopressin and/or hydrocortisone. Acker et al reported improved hemodynamics and gas exchange after starting vasopressin, but hyponatremia was common. (55) Kamath et al reported that patients with CDH with random cortisol level less than or equal to 15 μg/dL had increased severity of illness, but there are no data to suggest that empiric treatment with hydrocortisone improves outcomes in these patients. (56) Hydrocortisone has been shown to decrease the need for inotropes in neonates with refractory hypotension and may be appropriate for patients with CDH with catecholamine-resistant hypotension followed by the use of ECMO. (22)

SURGICAL REPAIR

History and Timing

The surgical management of CDH is characterized by complex decision-making regarding the timing of a conceptually straightforward operation. For clinicians treating infants with severe CDH, there may be great angst over the decision, and there is no definitive evidence for the “ideal” timing of surgical repair. Over time, care has evolved from emergent repair immediately after delivery to delayed repair once pulmonary hypertension has subsided. The hope is that a more stable infant can better tolerate surgery after 48 to 72 hours at most centers. The pendulum may be swinging back; evidence is emerging that earlier repair (before ECMO) for the most severely affected newborns may improve survival. (12) For low-risk infants, delayed repair until stabilization remains the standard of care, but consensus
agreement regarding “stability” is elusive and criteria vary from center to center. (1)

For severe CDH, controversy exists regarding the timing of repair in relation to ECMO, because repair while the infant is receiving ECMO involves a high risk of bleeding and other complications. However, delaying repair until after ECMO may not allow the lungs “room” to improve during ECMO. (52) Evidence exists both for and against operating during ECMO versus after decannulation, and no agreement has yet been reached in the absence of high-quality evidence. A recent systematic review suggests that repair undertaken early during ECMO has better outcomes than late repair. Patients fared poorly when repair was planned after decannulation, but had late repair during ECMO after it was found that they could not be weaned off ECMO. (35) Unfortunately, all these recommendations are based on evidence level 3 to 4, leaving much room for interpretation.

Technique

The basic operative approach to repair CDH has not changed over the past several decades. The defect is closed by primary approximation of the diaphragmatic edges (primary repair) or a prosthetic patch is used when the edges cannot be approximated without tension (patch repair). Most surgeons use a subcostal laparotomy on the side of the defect. Although the choice of material used for patch repair of the defect has been debated, it is probably safest to use an oversized dome-shaped polytetrafluoroethylene patch because this approach has the lowest recurrence rate. (35) Recurrence is always a risk with patch repair because the patch does not grow with the patient. Need for a patch means the defect is large and thus the patient is more likely to be a high-risk patient with CDH requiring protracted care.

The thoracoscopic versus open approach for stable patients with CDH has also been debated, but evidence supports open repair because minimally invasive repair has been associated with increased arterial carbon dioxide levels, lower pH, and higher recurrence rates. (35)

OUTCOMES AND FOLLOW-UP

Long-term follow-up into adolescence is recommended for all patients with CDH because multisystem adverse outcomes are common. (7) Particularly with severe CDH, close surveillance is required in the first months and years after birth to enable timely intervention and prevent significant disability. Problems may be pulmonary, gastrointestinal and nutritional, neurodevelopmental, or surgical. Hearing loss is also common.

PHTN may persist after discharge, requiring supplemental oxygen and pulmonary vasodilators. Long-term survival with significant PHTN is uncommon. Other pulmonary sequelae include pneumonia, bronchospasm, obstructive airway disease, and reactive airway disease, all of which will be more common in patients with severe CDH (such as those who received prolonged intubation, ECMO, and/or supplemental oxygen at discharge). Pulmonary function testing may be persistently abnormal in nearly one-third of children older than 5 years, and in up to 50% of adult survivors. (57)

Gastrointestinal morbidity occurs in the form of symptomatic gastroesophageal reflux and nutritional failure due to oral aversion and feeding intolerance. In a large series, 25% of patients received fundoplication and 31% had a gastrostomy tube placed. (58) Overall, 33% to 50% of patients with CDH may suffer significant growth and nutritional failure. (7)

Neurodevelopmental delay, especially with motor rather than cognitive function, is of great concern in patients who suffered long and difficult hospitalizations. (59) Delay may be mild and may improve with time, but outcomes are inconsistent from center to center; the prevalence of adverse neurodevelopmental outcomes may approach 50%. (7)(59) In addition, treatment-related hearing loss is common, but that may largely reflect the now outmoded hyperventilation approach. Close monitoring and serial developmental testing, along with audiometry, is warranted in patients with severe CDH. (7)

Although the true incidence of hernia recurrence is not known, rates of up to 50% have been reported; patch repair is the single greatest risk factor. (7) Recurrence may happen years later in an otherwise asymptomatic patient who “outgrows” his or her patch. (60) Surgical technique with the use of a large, redundant patch may reduce recurrence risk. (61) Other surgical complications may include bowel obstruction and orthopedic (chest and spinal) deformity in 25% to 50% of patients. (7)(58)(60) All CDH survivors should be followed up annually, and clinic visits should include chest radiography to monitor for CDH recurrence.

CONCLUSIONS

Treatment of infants with CDH remains difficult due to widely variable disease severity and limited evidence to guide practice. With adherence to a standard protocol and a multidisciplinary commitment to lung-protective strategies, survival can be greater than 85%. After surgical repair
and improvement of PHTN, patients with CDH should receive close follow-up to monitor for recurrence of herniation or PHTN, failure to thrive, neurodevelopmental delay, and other consequences of their condition.

ACKNOWLEDGMENT

The authors would like to thank Dr Hugh Allen for his review of this article.

American Board of Pediatrics Neonatal—Perinatal Content Specifications

- Plan appropriate therapy for an infant with extrapulmonary causes of respiratory distress
- Plan the ventilatory therapy for infants with respiratory failure of different etiologies
- Know the indications for and techniques of high-frequency ventilation
- Know the indications, techniques, effects, and risks of extracorporeal membrane oxygenation (ECMO)

References


1. A term infant with prenatally diagnosed congenital diaphragmatic hernia (CDH) is admitted to the NICU. The surgical team is consulted. The patient is receiving mechanical ventilation. Which of the following practices has been associated with centers that have higher survival rates for patients with CDH?
   A. Later use of extracorporeal membrane oxygenation.
   B. Early surgical repair.
   C. Permissive hypercapnia.
   D. Birth at smaller, nonsurgical center with subsequent transfer to higher level of care.
   E. Early aggressive ventilation with maximal settings for peak inspiratory and end-expiratory pressures.

2. A woman presents late for prenatal care at the clinic at an estimated 28 weeks’ gestational age. Ultrasonography reveals CDH. Which of the following statements regarding diagnosis and incidence of CDH is correct?
   A. The estimated prevalence of CDH is between 2.4 and 4.1 per 1,000 live births.
   B. Even for those women who receive prenatal care, the antenatal diagnosis rate for CDH is less than 50%.
   C. Generally, left-sided CDH is harder to diagnose antenatally than right-sided CDH.
   D. Secondary signs such as mediastinal shift, polyhydramnios, and cardiac malposition or abnormal cardiac axis may aid in diagnosis.
   E. Ultrasonography is preferred to other imaging modalities, such as magnetic resonance imaging, for the purpose of identifying liver herniation.

3. A woman undergoing routine ultrasonography at 20 weeks of gestation is noted to have a fetus with CDH. A meeting with a multidisciplinary team is scheduled to discuss the options for management and prognosis. Which of the following statements concerning prognosis is correct?
   A. Liver herniation into the chest is the most accurate prediction of mortality.
   B. Lung-to-head ratio on the contralateral area of the 2-dimensional lung to the head circumference measured by ultrasonography is a validated marker of CDH severity and is most reliable between 22 and 26 weeks of gestation.
   C. Although magnetic resonance imaging can provide better visualization of the lungs than ultrasonography, it is highly dependent on maternal and fetal positioning.
   D. The lung-to-head ratio should stay consistent over time, because it is not dependent on gestational age.
   E. An observed to expected lung-to-head ratio of less than 65% is almost always associated with fetal death or early neonatal death.

4. A fetus is diagnosed as having CDH on ultrasonography at a prenatal visit during the 22nd week of gestation. Which of the following factors is accurately described in the context of management for this condition?
   A. Tracheal occlusion in the fetus has demonstrated efficacy in producing higher lung volumes for moderate and severe CDH, but no differences in mortality have ever been demonstrated in any trials.
   B. Open fetal repair of the diaphragm has shown benefit for neonatal survival in several trials and is the current preferred fetal therapy, but is not widely offered due to increased risk of uterine bleeding in the mother.
   C. For those receiving postnatal treatment without fetal intervention, the level of care of the NICU and the number of patients with CDH cared for in the NICU does not appear to have an impact on outcomes.
D. The mode of delivery, vaginal versus cesarean, does not appear to have an impact on neonatal survival, and should be based on maternal indications.

E. The current best practice for immediate management of CDH after delivery, regardless of severity, is to attempt noninvasive, “regular baby” practices, such as delaying cord clamping, avoiding intubation, and refraining from vascular access until explicitly necessary.

5. A term male infant with left-sided CDH is born after cesarean delivery. He undergoes intubation in the delivery room and is transported to the NICU. He is given mechanical ventilation. Sensors demonstrate a pre- and postductal oxygen saturation gradient. You suspect pulmonary hypertension (PHTN). Which of the following statements regarding this patient is correct?

A. Unlike in non-CDH cases, PHTN in CDH is only associated with a structural or fixed component of PHTN, and is not a reversible component.

B. The pre-/postductal gradient is indicative of a closed ductus arteriosus, with lack of ability of adequate “normal” shunting during the transition from in utero to the newborn period.

C. The absence of tricuspid regurgitation on echocardiography can be used to diagnose PHTN.

D. PHTN in the presence of CDH has a worse prognosis compared to PHTN alone.

E. Inhaled nitric oxide should be used in all cases of CDH combined with PHTN, even in milder cases, to avoid the need for extracorporeal membrane oxygenation.
**Congenital Diaphragmatic Hernia: Maximizing Survival**

Mark F. Weems, Tim Jancelewicz and Hitesh S. Sandhu

*NeoReviews* 2016;17:e705

DOI: 10.1542/neo.17-12-e705

<table>
<thead>
<tr>
<th>Updated Information &amp; Services</th>
<th>including high resolution figures, can be found at: <a href="http://neoreviews.aappublications.org/content/17/12/e705">http://neoreviews.aappublications.org/content/17/12/e705</a></th>
</tr>
</thead>
<tbody>
<tr>
<td>References</td>
<td>This article cites 58 articles, 5 of which you can access for free at: <a href="http://neoreviews.aappublications.org/content/17/12/e705.full#ref-list-1">http://neoreviews.aappublications.org/content/17/12/e705.full#ref-list-1</a></td>
</tr>
<tr>
<td>Subspecialty Collections</td>
<td>This article, along with others on similar topics, appears in the following collection(s): Pediatric Drug Labeling Update <a href="http://classic.neoreviews.aappublications.org/cgi/collection/pediatric_drug_labeling_update">http://classic.neoreviews.aappublications.org/cgi/collection/pediatric_drug_labeling_update</a></td>
</tr>
<tr>
<td>Permissions &amp; Licensing</td>
<td>Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at: <a href="https://shop.aap.org/licensing-permissions/">https://shop.aap.org/licensing-permissions/</a></td>
</tr>
<tr>
<td>Reprints</td>
<td>Information about ordering reprints can be found online: <a href="http://classic.neoreviews.aappublications.org/content/reprints">http://classic.neoreviews.aappublications.org/content/reprints</a></td>
</tr>
</tbody>
</table>